Proposed Preferred Drug List

with

Clinical Criteria

Proposal for TennCare

August 26, 2008
Responsibilities of the TennCare Pharmacy Advisory Committee

Source: Tennessee Code/Title 71 Welfare/Chapter 5 Programs and Services for Poor Persons/Part 24 Tennessee TennCare Pharmacy Advisory Committee/71-5-2401 through 71-5-2404.

- Make recommendations regarding a preferred drug list (PDL) to govern all state expenditures for prescription drugs for the TennCare program.
  - The TennCare Pharmacy Advisory Committee shall submit to the bureau of TennCare both specific and general recommendations for drugs to be included on any state PDL adopted by the bureau. In making its recommendations, the committee shall consider factors including, but not limited to, efficacy, the use of generic drugs and therapeutic equivalent drugs, and cost information related to each drug. The committee shall also submit recommendations to the bureau regarding computerized, voice, and written prior authorization, including prior authorization criteria and step therapy.
  - The state TennCare pharmacy advisory committee shall include evidence-based research in making its recommendations for drugs to be included on the PDL.
  - The TennCare bureau shall consider the recommendations of the state TennCare pharmacy advisory committee in amending or revising any PDL adopted by the bureau to apply to pharmacy expenditures within the TennCare program. The recommendations of the committee are advisory only and the bureau may adopt or amend a PDL regardless of whether it has received any recommendations from the committee. It is the legislative intent that, insofar as practical, the TennCare bureau shall have the benefit of the committee’s recommendations prior to implementing a PDL or portions thereof.

- Keep minutes of all meetings including votes on all recommendations regarding drugs to be included on the state preferred drug list

- The chair may request that other physicians, pharmacists, faculty members of institutions of higher learning, or medical experts who participate in various subspecialties act as consultants to the committee as needed.
PDL Decision Process

- The primary clinical decision that needs to be made is determining if the drugs within the therapeutic class of interest can be considered therapeutic alternatives.

- **A Therapeutic Alternative** is defined by the AMA as: "drug products with different chemical structures but which are of the same pharmacological and/or therapeutic class, and usually can be expected to have similar therapeutic effects and adverse reaction profiles when administered to patients in therapeutically equivalent doses"\(^1\).

- The Committee should not feel obligated to decide if every drug within the therapeutic class is exactly equal to all other drugs within the class, nor should they feel obligated to decide if every drug within the therapeutic class works equally well in every special patient population or in every disease.

- In special situations (e.g., presence of comorbid conditions) and in special populations (e.g., pediatrics) use of a non-preferred drug might be the most appropriate therapy. These cases can be handled through prior authorization (PA). PA serves as a “safety valve” in that it facilitates use of the most appropriate agent regardless of PDL status.

**LENGTH OF AUTHORIZATIONS:** Dependent upon diagnosis and length of therapy needed to treat. (Most medications are used chronically, and thus would be approved for 1 year.)

1. Is there any reason the patient cannot be changed to a medication not requiring prior approval within the same class?
   - **Acceptable reasons include:**
     - **Allergy** to medications not requiring prior approval
     - **Contraindication** to or drug-to-drug interaction with medications not requiring prior approval
     - **History** of unacceptable/toxic side effects to medications not requiring prior approval

2. The requested medication may be approved if both of the following are true:
   - If there has been a therapeutic failure of at least two medications within the same class not requiring prior approval (unless otherwise specified)
   - The requested medication’s corresponding generic (if a generic is available and preferred by the State) has been attempted and failed or is contraindicated

3. The requested medication may be approved if the following is true:
   - An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or an FDA approved indication exists.

The information provided for each drug class is organized into the following sections, when applicable:

**BACKGROUND:**
- General overview
- Pharmacology
- Therapeutic effect(s)
- Adverse reactions
- Outcomes data
- Place in therapy according to current Treatment Guidelines

**RECOMMENDATION:**
- General recommendation regarding utility and therapeutic equivalence among the agents in the class, as well as requirements for product availability (PDL placement)

\(^1\) AMA Policy H-125.991 Drug Formularies and Therapeutic Interchange
BACKGROUND

- Bacterial conjunctivitis presents with itching, burning eyes with purulent discharge, usually unilaterally. Although self-limiting in most cases, topical antibiotics are applied in many infections in an attempt to prevent the spread of conjunctivitis to others. Serious infection of the eye can rapidly damage important functional structures and lead to permanent vision loss or blindness. Infections that could threaten vision may require broad-spectrum antibiotics. The agents in this category contain various combinations of bacitracin, dexamethasone, gramicidin, hydrocortisone, neomycin, polymyxin B, prednisolone, sulfacetamide and trimethoprim.

- These agents have varying mechanisms of action.
  - Bacitracin inhibits bacterial growth by preventing cell wall subunits from being added to the peptidoglycan chain.
  - Gramicidin increases bacterial cell permeability to inorganic cations by forming a network of channels through the lipid bilayer of the membrane.
  - Neomycin, along with the other aminoglycosides, inhibits protein synthesis by binding to the 30S ribosomal subunit.
  - Polymyxin B increases the permeability of the bacterial cell membrane by interacting with the phospholipid components of the membrane.
  - Folic acid is essential for bacterial transport of one-carbon fragments and for the synthesis of thymidine, purines and certain amino acids. Sulfacetamide inhibits bacterial dihydrofolate synthetase, the enzyme responsible for the conversion of p-aminobenzoic acid (PABA) into folic acid.
  - Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by interfering with folate synthesis.
  - Corticosteroids (dexamethasone, hydrocortisone and prednisolone) work by suppressing the inflammatory response to a variety of agents.

- All of the products containing a corticosteroid are indicated for inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial infection exists. There are no specific indications for the ophthalmic steroids in pediatric patients; however, data are available for patients greater than 2 months of age for prednisolone/sulfacetamide. The FDA-approved indications for the antibiotic agents are as follows:

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<th>Indication</th>
<th>Age Range</th>
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<td>bacitracin</td>
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<tr>
<td>bacitracin/poly B</td>
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<td>Adults</td>
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<td>Adults</td>
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<td>polymyxin B/TMP</td>
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<td>sulfacetamide</td>
<td>Conjunctivitis  &lt;br&gt; Corneal ulcers  &lt;br&gt; Chlamydial conjunctivitis including &lt;br&gt; trachoma and inclusion conjunctivitis</td>
<td>&gt; 2 months</td>
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OPHTHALMIC AGENTS

- The spectrums of action of the agents in this class vary.
  - Bacitracin has broad coverage of gram positive organisms.
  - Polymyxin has broad coverage of gram negative organisms including *P. mirabilis*, *P. aeruginosa*, and *S. marcessens*.
  - Neomycin has mixed gram positive and gram negative activity; however, its gram positive coverage is not as broad as bacitracin, and it lacks some of the gram negative activity of polymyxin, such as *Pseudomonas*.
  - Gramicidin has a spectrum similar to bacitracin, targeting solely gram positive organisms.
  - Sulfacetamide has broad spectrum activity against *E. coli*, *S. aureus*, *S. pneumoniae*, *Streptococcus* (viridans group), *H. influenzae*, *Klebsiella* species and *Enterobacter* species.
  - Trimethoprim has mixed gram positive and gram negative activity, including *Staphylococcus* species, *S. pneumoniae*, *E. coli*, *H. influenzae*, *K. pneumoniae* and *P. mirabilis*.

- The most common adverse effects seen with the non-quinolone ophthalmic antibiotics are localized ocular toxicity and hypersensitivity, lid itching, lid swelling, and conjunctival erythema. Serious hypersensitivity reactions including anaphylaxis and secondary fungal and viral infections have occurred rarely. The steroid component may frequently cause increased intraocular pressure (IOP) which may result in glaucoma. Infrequently optic nerve damage, cataract formation, and delayed wound healing may occur. Secondary fungal infections have been reported as well.
  - The combination products containing a steroid are contraindicated in most viral diseases of the cornea and conjunctiva, in mycobacterial infections of the eye and in fungal diseases of ocular structures.
  - Prolonged use of corticosteroids may result in glaucoma and increased susceptibility to other ocular infections. If an ophthalmic steroid is used for longer than 10 days, it is recommended that IOP be monitored.

- There is very little comparative data of good quality from the US for the medical management of bacterial conjunctivitis due to a large portion of study patients not completing the study period. However *in vitro* susceptibility has been studied.
  - Isolates from clinically symptomatic eyes (n=454) were tested for susceptibility to ciprofloxacin, norfloxacin, ofloxacin, gentamicin, neomycin, tobramycin, bacitracin, erythromycin and chloramphenicol. Results showed the fluoroquinolones were very effective against the gram-negative organisms but were not as effective against the gram-positive organisms such as coagulase-negative *Staphylococcus* and *S. viridans*. Bacitracin and chloramphenicol showed good *in vitro* activity against gram-positive organisms. While no antibiotic demonstrated 100% coverage, results showed the overall *in vitro* efficacy in descending order is as follows: chloramphenicol, ciprofloxacin, ofloxacin, norfloxacin, bacitracin, tetracycline, neomycin, erythromycin, tobramycin and gentamicin.

- Ophthalmic ointments have the longest contact time between the drug and the ocular tissues; however, ointments can act as a physical barrier and impede delivery of other ophthalmic drugs. Ointments are usually most useful in young children as they decrease the loss of drug due to tear production and are often easier to administer. Ophthalmic suspensions less rapidly mix with tears and remain in the cul-de-sac longer than solutions.

- There appears to be a lack of good quality literature comparing antibiotics of any type with placebo for the treatment of acute bacterial conjunctivitis. Treatment guidelines from the American Optometric Association (AOA) state that ideally the treatment of bacterial conjunctivitis would be aimed at the specific causative organism identified by diagnostic testing; however, in the absence of a culture or smear, the etiologic agent should be considered with respect to the patients age, environment and related ocular finding. While the AOA does not recommend an agent of choice, they do state that in most cases, broad-spectrum topical antibiotics are the treatment of choice.
• The American Academy of Ophthalmology (AAO) also recommends a course of broad spectrum antibiotics for empiric therapy for bacterial conjunctivitis. In addition, the AAO recommends bacitracin, as well as cefazolin, vancomycin, moxifloxacin or gatifloxacin, for the treatment of bacterial keratitis in which the causative organisms are gram positive cocci.

• In general the use of an antibiotic/corticosteroid combination drug is indicated where the risk of superficial ocular infection is high or where there is the expectation that dangerous numbers of bacteria will be present in the eye. The AOA guidelines specifically recommend the use of topical antibiotic/steroid combinations in the treatment of herpes zoster conjunctivitis to reduce the risk of secondary bacterial infection and decrease the inflammatory response. While topical steroids are contraindicated in viral conjunctivitis, they do not exacerbate herpes zoster infections. Symptomatic patients with toxic conjunctivitis may benefit from cold compresses and/or topical ophthalmic antibiotic/corticosteroid combinations, and phlyctenular conjunctivitis responds to topical use of an antibiotic/corticosteroid combination. Again, the AOA does not name an antibiotic/corticosteroid combination of choice.

RECOMMENDATION

The non-quinolone ophthalmic antibiotics are often used for the treatment of conjunctivitis and other superficial ocular infections. Current guidelines from the AOA and the AAO state that in most cases, broad-spectrum topical antibiotics are the treatment of choice for bacterial conjunctivitis. All of the products in this category, with the exception of bacitracin, offer broad spectrum coverage of both gram positive and gram negative organisms, and therefore, can be considered therapeutic alternatives for empiric treatment of bacterial conjunctivitis. Based on this information, it is recommended that at least 3 non-quinolone antibiotics be available, two that offer broad spectrum coverage of gram positive and gram negative organisms and bacitracin for gram positive coverage. It is also recommended that there be at least one solution and one ointment dosage form available.

Antibiotic/corticosteroid combination products are indicated for inflammatory conditions where the risk of superficial ocular infection is high or where there is an expectation that dangerous numbers of bacteria will be present in the eye. The AOA specifically recommends these combination products for the treatment of herpes zoster, toxic conjunctivitis and phlyctenular conjunctivitis. The AOA makes no differentiation between the available ophthalmic steroid/antibiotic products in their guidelines. Therefore, it is recommended that at least two combination steroid/antibiotic products be available. In order to allow for patient and provider choice, it is recommended that there be at least one solution and one ointment dosage form available as well.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION
## REREVIEW: OPHTHALMIC ANTIMICROBIALS NON-QUINOLONE AND COMBINATIONS

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### References


## REREVIEW: OPHTHALMIC AMINOGLYCOSIDES AND COMBINATIONS

### BACKGROUND

- Although bacterial conjunctivitis is generally a self-limiting condition, topical antibiotics are applied to lessen the symptoms, duration and chances of recurrence. This category will include gentamicin and tobramycin and the combinations of gentamicin/prednisolone, tobramycin/dexamethasone and tobramycin/loteprednol.
- Aminoglycosides (gentamicin and tobramycin) are broad spectrum ophthalmic antibiotics with activity against a variety of organisms including, but not limited to: S. aureus, S. epidermidis, S. pyogenes, some S. pneumoniae, P. aeruginosa, E. coli, H. influenzae and P. mirabilis.
The aminoglycosides bind to the 30S ribosomal subunit of susceptible bacteria resulting in prevention of bacterial protein synthesis. Corticosteroids (prednisolone, dexamethasone and loteprednol) work by suppressing the inflammatory response to a variety of agents. Loteprednol is an analog of prednisolone resulting in slightly less elevation of intraocular pressure (IOP) compared to prednisolone. Corticosteroids slow the healing process; therefore, they should be given along with an antimicrobial agent if this delayed healing is considered to be clinically significant (e.g., when the risk of infection is high or when there is an expectation that potentially dangerous numbers of bacteria will be present in the eye).

The aminoglycosides are indicated for the treatment of superficial ocular infections involving the conjunctiva or cornea. Tobramycin is indicated for patients over the age of 2 months and the combination of tobramycin/dexamethasone is indicated for those over 2 years. Gentamicin and its combination products do not have any specific indications based on age. The combination products are indicated for ocular conditions in which anti-inflammatory properties are needed and in which a superficial bacterial infection or risk of infection exists.

The most common adverse effects seen with the aminoglycosides are localized ocular toxicity and hypersensitivity, lid itching, lid swelling, conjunctival erythema (less with tobramycin than with gentamicin), bacterial/fungal corneal ulcers, nonspecific conjunctivitis, conjunctival epithelial defects, and conjunctival hyperemia. The steroid component most frequently causes increased IOP. However, studies show that IOP is not increased with loteprednol (2%) to the extent that it is with prednisolone (7%). Optic nerve damage, cataract formation and delayed wound healing may occur infrequently with the use of ophthalmic corticosteroids.

Tobramycin ophthalmic ointment has been shown to produce significantly fewer adverse reactions (3.7%) than gentamicin ophthalmic ointment (10.6%) in clinical trials.

The ophthalmic steroids are contraindicated in most viral or fungal diseases of the cornea and conjunctiva as well as mycobacterial infections of the eye.

Practitioners should be warned that ophthalmic ointments may retard corneal healing. Gentamicin and the corticosteroid combination products are Pregnancy Category C; however, tobramycin is category B. Prolonged use of ophthalmic corticosteroids may cause glaucoma with damage to the optic nerve, defects in visual acuity and field of vision, cataract formation, corneal perforation and secondary ocular infection due to depression of the host immune response. Care should be taken to ensure abrupt discontinuation of the steroid combination products does not occur.

There is very little comparative data of good quality published in the last five years regarding the products in this class.

Two hundred seventy-one patients undergoing cataract surgery in Europe and Brazil were randomized to receive tobramycin 0.3%/dexamethasone 0.1%, dexamethasone 0.1%/neomycin 0.35%/polymyxin B 6,000 units/mL, or control (neomycin 0.35%/polymyxin B 7,500 units/mL/gramicidin 20 mcg/mL) in a prospective, double-blind, parallel-group study. Results showed intraocular inflammation to be similar between the groups using tobramycin/dexamethasone and dexamethasone/neomycin/polymyxin B. Both of the corticosteroid groups had less inflammation on day 8 compared to control (p=<0.05). More allergic reactions resulting in drug withdrawal were reported with neomycin/polymyxin B/gramicidin compared with tobramycin/dexamethasone (p=<0.05).

A double-blind, randomized trial comparing tobramycin/dexamethasone and tobramycin/loteprednol in 40 patients with blepharo-keratoconjunctivitis was performed. Patients received tobramycin/dexamethasone or tobramycin/loteprednol twice daily in the test eye. After 3-5 days, the ocular surface was examined for treatment response. Results showed that tobramycin/dexamethasone significantly decreased clinical signs of ocular inflammation based on a decrease in total ocular surface scores (p=0.002), blepharitis scores (p=0.017), discharge scores (p=0.05) and conjunctivitis scores (p=0.013) compared to tobramycin/loteprednol.
Treatment guidelines from the AOA state that ideally the treatment of bacterial conjunctivitis should be aimed at the specific causative organism identified by diagnostic testing; however, in the absence of a culture or smear, the etiologic agent should be considered with respect to the patient’s age, environment and related ocular finding. While the AOA does not recommend an agent of choice, they do state that in most cases, broad-spectrum topical antibiotics are the treatment of choice.

The AAO also recommends a course of broad spectrum antibiotics, such as tobramycin, gentamicin or cefazolin, for empiric therapy for bacterial conjunctivitis. In addition, the AAO recommends tobramycin or gentamicin for the treatment of bacterial keratitis in which the causative organism is a gram negative rod.

In general the use of an antibiotic/corticosteroid combination drug is indicated for inflammatory conditions where the risk of superficial ocular infection is high or where there is the expectation that dangerous numbers of bacteria will be present in the eye. The AOA guidelines specifically recommend the use of topical antibiotic/steroid combinations in the treatment of herpes zoster conjunctivitis to reduce the risk of secondary bacterial infection and decrease the inflammatory response. While topical steroids are contraindicated in viral conjunctivitis, they do not exacerbate herpes zoster infections. Symptomatic patients with toxic conjunctivitis may benefit from cold compresses and/or topical ophthalmic antibiotic/corticosteroid combinations, and phlyctenular conjunctivitis responds to topical use of an antibiotic/corticosteroid combination. Again, the AOA does not name an antibiotic/corticosteroid combination of choice.

**RECOMMENDATION**

The ophthalmic aminoglycosides represent a reasonable option for the treatment of conjunctivitis and other superficial ocular infections. Current guidelines from the AOA and the AAO state that in most cases, broad-spectrum topical antibiotics are the treatment of choice for bacterial conjunctivitis. Based on their similar spectrums of action and adverse event profiles, tobramycin and gentamicin can be considered therapeutic alternatives to one another. Antibiotic/corticosteroid combination products are indicated for inflammatory conditions where the risk of superficial ocular infection is high or where there is an expectation that dangerous numbers of bacteria will be present in the eye. The AOA specifically recommends these combination products for the treatment of herpes zoster, toxic conjunctivitis and phlyctenular conjunctivitis. The AOA makes no differentiation between the available aminoglycosides or combination products in their guidelines. Therefore, it is recommended that at least one aminoglycoside and at least one aminoglycoside/corticosteroid combination product be available. Given that loteprednol is associated with a lower increase in IOP than other ophthalmic steroids, it should be available for those patients in whom increased IOP is a concern. In order to allow for patient and provider choice, it is recommended that there be at least one solution and one ointment dosage form available.

**COMMITTEE VOTE:**

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<td>TOBRASOL® (tobramycin solution)</td>
<td>ZYLET® (tobramycin/loteprednol suspension)</td>
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Clinical Criteria for Zylet®

Zylet® will be approved if the recipient has a contraindication or intolerance to any two of the preferred ophthalmic steroids, OR if there are concerns over a potential increase in intra-ocular pressure (IOP) with other steroids (i.e. glaucoma, recipient is pre or post cataract surgery and a known steroid-responder, etc.).

COMMITTEE VOTE:

APPROVED   DISAPPROVED  APPROVED with MODIFICATION

References

9. Rhee SS, Mah FS. Comparison of tobramycin 0.3%/dexamethasone 0.1% and tobramycin 0.3%/loteprednol 0.5% in the management of blepharo-keratoconjunctivitis. Adv Ther. 2007;24(1):60-7.

REREVIEW: OPHTHALMIC MACROLIDES

BACKGROUND

- Macrolides are broad spectrum ophthalmic antibiotics with activity against a variety of organisms including but not limited to: H. influenzae, S. aureus, S. pneumoniae, S. pyogenes and C. trachomatis.
- There are two available ophthalmic macrolides, erythromycin and azithromycin. These agents are often used for the treatment of conjunctivitis and other superficial ocular infections.
- The ophthalmic macrolides prevent bacterial protein synthesis by binding to the ribosomal 50S subunit of susceptible bacteria.
- Ophthalmic azithromycin is approved for the treatment of bacterial conjunctivitis in those older than 1 year of age. Ophthalmic erythromycin is FDA-approved for the treatment of superficial ocular infections involving the conjunctiva or cornea and for prophylaxis against ophthalmia neonatorum due to N. gonorrhoeae or C. trachomatis in patients ranging in age from newborn to adult.
• The most common adverse effects seen with the ophthalmic macrolides include eye pain or discomfort, edema, itching and burning. Most of these reactions are associated with local irritation upon instillation; however, rarely allergic sensitization reactions such as itching, swelling and conjunctival erythema may occur. Serious hypersensitivity reactions and fungal or viral infections have been reported.

• Currently there are no head-to-head trials comparing the ophthalmic macrolides, and few comparative clinical trials exist comparing the macrolides to other ophthalmic antibiotics.
  o Azithromycin ophthalmic solution was compared to tobramycin ophthalmic solution in a prospective, randomized, active-controlled, double-masked, phase 3 trial conducted over a 14 month period at 47 sites. Patients with a clinical diagnosis of bacterial conjunctivitis were randomly assigned to either azithromycin 1% (n=365) or tobramycin 0.3% (n=378). Rates of microbial eradication and bacterial infection recurrence were the same in both groups; however, incidence of side effects including eye irritation, conjunctival hyperemia, and worsening bacterial conjunctivitis favored the azithromycin group.
  o Azithromycin 1.5% ophthalmic solution was compared to tobramycin 0.3% ophthalmic solution in the treatment of purulent bacterial conjunctivitis. Patients (n=1043) received either 3 days of azithromycin or 7 days of tobramycin. Clinical cure rates were 87.8% for azithromycin and 89.4% for tobramycin. Both agents had comparable tolerability as well.

• Treatment guidelines from the AOA state that ideally the treatment of bacterial conjunctivitis would be aimed at the specific causative organism identified by diagnostic testing; however, in the absence of a culture or smear, the etiologic agent should be considered with respect to the patient’s age, environment and related ocular finding. While the AOA does not recommend an agent of choice, they do state that in most cases broad-spectrum topical antibiotics are the treatment of choice. Antibiotics can lessen the symptoms, duration and chances of recurrence.

• The AAO also recommends a course of broad spectrum antibiotics for empiric therapy for bacterial conjunctivitis. However, for treatment of chlamydial conjunctivitis, the AAO recommends azithromycin or doxycycline for adults and children >45kg. For children <45 kg, erythromycin ointment is recommended.

RECOMMENDATION
The ophthalmic macrolides represent a useful class of broad-spectrum antibiotics for the treatment of conjunctivitis and other superficial ocular infections. Current guidelines from the AOA and the AAO state that in most cases, broad-spectrum ophthalmic antibiotics are the treatment of choice for bacterial conjunctivitis; however, these guidelines fail to name an agent or class of agents of choice. Both azithromycin and erythromycin have similar spectrums of action and adverse event profiles, and thus can be considered therapeutic alternatives to one another. In order to ensure adequate patient and prescriber choice for the treatment of bacterial conjunctivitis, it is recommended that at least one ophthalmic macrolide be available. In addition, it is recommended that erythromycin ointment be available for young children and neonates with chlamydial conjunctivitis.

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References

REREVIEW: OPHTHALMIC AGENTS

BACKGROUND
- There are five available quinolones for ophthalmic use, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin and ofloxacin.
- DNA gyrase is an essential enzyme involved in replication, transcription and repair of bacterial DNA. Topoisomerase IV plays a key role in the partitioning of the chromosomal DNA during bacterial cell division. The fluoroquinolones exert their antibacterial effects by inhibiting DNA gyrase and topoisomerase IV. Gatifloxacin and moxifloxacin posses an 8-methoxy substitution resulting in enhanced antimicrobial activities which may limit the selection of resistant mutants in pathogens.
- All of the ophthalmic quinolones are FDA approved for the treatment of bacterial conjunctivitis, with the exception of levofloxacin 1.5% solution which is indicated only for the treatment of corneal ulcers. Ciprofloxacin solution and ofloxacin are indicated for both the treatment bacterial conjunctivitis and corneal ulcers. Ciprofloxacin ointment is approved for use in patients ≥ 2 years and levofloxacin 1.5% solution is approved for use in patients ≥ 6 years; all remaining products in this class are approved for use in patients one year or older.
- The susceptibilities of the ophthalmic quinolones vary slightly among the different agents.
  - In general, all quinolones provide excellent activity against the most frequent ophthalmic pathogens including S. aureus, coagulase-negative Staphylococcus, S. pneumoniae, S. viridans and P. aeruginosa.
  - Ciprofloxacin exhibits greater gram-negative activity than the other quinolones.
  - The fourth-generation agents (moxifloxacin and gatifloxacin) exhibit greater activity against gram positive organisms as well as against second-generation fluoroquinolone resistant pathogens (especially S. aureus).
    - Among the fourth generation quinolones, moxifloxacin exhibits better gram-positive coverage while gatifloxacin exhibits better gram-negative coverage.
The most common adverse effects associated with the ophthalmic quinolones include pain or discomfort, edema, foreign body sensation, itching, conjunctival hyperemia and transient burning. Most of these reactions are associated with local irritation upon instillation; however, rarely allergic sensitization reaction such as itching, swelling and conjunctival erythema may occur. Serious hypersensitivity reactions and fungal or viral infections have been reported.

Several head-to-head clinical trials have been performed to compare the ophthalmic quinolones.

- Gatifloxacin 0.3% was compared to ciprofloxacin 0.3% in a randomized, double-masked trial of 104 eyes of 104 patients with bacterial keratitis. The majority of pathogens identified were gram-positive. Results showed significantly more patients in the gatifloxacin group had complete healing compared to those in the ciprofloxacin group (p=0.042). In vitro results demonstrated gatifloxacin was more effective against gram positive cocci (p=<0.001) and produced significantly faster healing rates in patients with gram-positive pathogens (p=0.009). For gram-negative bacteria, the mean healing time and efficacy were similar in both treatment groups.

- Patients (n=167) ages 1-16 years were given either levofloxacin 0.5% or ofloxacin 0.3% every 2 hours on days 1 and 2 and every 4 hours on days 3-5 for the treatment of bacterial conjunctivitis. At the study endpoint (mean of 6.5 days), levofloxacin demonstrated greater microbial eradication than ofloxacin (p=0.032) for children ages 2-11 years only.

- A double-blind, randomized, prospective trial compared healing rates among 35 patients who received moxifloxacin in one eye and gatifloxacin in the other eye following photorefractive keratectomy (PKR). Both eyes healed on the same day in 18 patients (51.4%), while the moxifloxacin-treated eye healed first in 13 patients (37.1%) and the gatifloxacin-treated eye healed first in 4 patients (11.4%). The median healing time for both agents was 4 days (range 3-7 days for moxifloxacin, 3-9 days for gatifloxacin); however, only 69% of gatifloxacin treated eyes had healed by day 4 compared to 80% of moxifloxacin-treated eyes (p=0.001).

- An open-label study involving 46 patients undergoing corneal transplant compared healing rates of moxifloxacin versus gatifloxacin. Results showed that gatifloxacin was associated with smaller epithelial defects at days 4 and 7 compared to moxifloxacin (p=<0.001). In addition, more eyes showed complete reepithelialization of the corneal graft with gatifloxacin after day 4 (statistically significant at days 7 and 14) than with moxifloxacin.

Unlike the other agents in this class, moxifloxacin does not contain a preservative and it is only administered three times daily for conjunctivitis.

Treatment guidelines from the AOA state that ideally the treatment of bacterial conjunctivitis would be aimed at the specific causative organism identified by diagnostic testing; however, in the absence of a culture or smear, the etiologic agent should be considered with respect to the patient’s age, environment and related ocular finding. While the AOA does not recommend an agent of choice, they do state that in most cases, broad-spectrum topical antibiotics are the treatment of choice. Antibiotics can lessen the symptoms, duration and chance of recurrence. The AAO recommends topical broad-spectrum antibiotics to be used initially in the empiric treatment of bacterial keratitis. The initial therapeutic regimen should be modified when the eye shows a lack of improvement or stabilization within 48 hours.
OPHTHALMIC AGENTS

RECOMMENDATION
Despite the slight differences in FDA-approved indications, all products in this class can be used to treat ophthalmic infections involving the conjunctiva or cornea which are caused by susceptible bacteria. The fourth-generation fluoroquinolones (gatifloxacin and moxifloxacin) may provide better coverage for gram-positive and resistant organisms than the third generation (levofloxacin) and second generation (ciprofloxacin and ofloxacin) products. According to current treatment guidelines from the AOA, broad-spectrum topical antibiotics are the treatment of choice in most cases of bacterial conjunctivitis diagnosed without culture or smear. The AAO also recommends broad-spectrum topical antibiotics as initial therapy for the treatment of bacterial keratitis. Neither group suggests one agent over another. Therefore it is recommended that at least two products be available, one of which should be a fourth-generation agent.

COMMITTEE VOTE:
APPROVED   DISAPPROVED  APPROVED with MODIFICATION

REREVIEW: OPHTHALMIC ANTIBIOTICS, QUINOLONES

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References

REREVIEW: OPHTHALMIC NSAIDS

BACKGROUND
- Ophthalmic NSAIDs are most commonly used for ophthalmic surgery. These agents have utility to reduce pain and control inflammation during and after surgery as well as to maintain pupillary dilatation during surgery without a significant effect on IOP.
• The ophthalmic NSAIDs exert their anti-inflammatory and analgesic effects through the ability to inhibit prostaglandin biosynthesis in the eye. Prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased IOP. Prostaglandins also appear to play a role in the miotic response produced during ocular surgery by constricting the iris sphincter.

• FDA approved indications:
  o Bromfenac, diclofenac and nepafenac are indicated for the treatment of post-operative inflammation and pain secondary to cataract extraction. Diclofenac has an additional indication for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.
  o Flurbiprofen is indicated for the inhibition of intraoperative miosis.
  o Ketorolac 0.5% is indicated for the treatment of post-operative inflammation secondary to cataract extraction as well as temporary relief of ocular itching due to allergic conjunctivitis.
  o Ketorolac 0.4% is indicated for the reduction of ocular pain, burning and stinging after corneal refractive surgery.
  o Ketorolac 0.5% preservative-free is indicated for the reduction of ocular pain and photophobia secondary to incisional refractive surgery.

• Common adverse effects associated with the use of ophthalmic NSAIDs include:
  - Continued use of topical NSAIDs may result in severe corneal adverse events, including: corneal thinning, erosion, ulceration or perforation, which may become sight damaging. Therefore, the use of ophthalmic NSAIDs beyond 14 days is not recommended.
  - Bromfenac contains sodium sulfite and is contraindicated in patients with sulfite hypersensitivity.
  - All agents in this class are Pregnancy Category C.
  - Due to the topical administration of the ophthalmic NSAIDs, systemic absorption is minimal; therefore, clinically significant drug interactions are not well defined.

• There are several head to head trials comparing the ophthalmic NSAIDs.
  - Three trials compared diclofenac and ketorolac 0.5% for efficacy and tolerability in a total of 150 post-ocular surgery patients. No difference was found in any of the trials with regards to anti-inflammatory effects or reduction of ocular pain. Adverse effects, including instillation reactions and the incidence of post-operative posterior opacification, were similar between the treatment groups.
  - Ketorolac 0.4% and nepafenac were compared in a randomized, double-blind study of 132 patients undergoing cataract surgery. More patients receiving ketorolac had ocular PGE (2) levels below the level of detection than those receiving nepafenac (61.9% vs. 17.5%, p<0.001). Additionally, active drug concentrations in the eye were significantly higher with ketorolac than with amfenac, the active drug of nepafenac (p<0.001).

• In addition, there are several trials available comparing ophthalmic NSAIDs to ophthalmic steroids post-cataract surgery. In general, the literature shows that NSAIDs provide similar inflammatory control and superior pain control than steroids.
  - One randomized, double-blind study compared prednisolone 1%, rimexolone 1%, and ketorolac 0.5% among 45 patients undergoing cataract extraction. Patients were assigned to one of the topical treatments post-surgery, and assessed for inflammation, best-corrected visual acuity, and IOP. The efficacy of inflammation control did not differ among the treatment groups (p=0.165), nor did visual acuity. However, one patient developed increased IOP with prednisolone, and one patient developed a corneal ulcer with ketorolac.
  - Another randomized, double-blind trial compared ketorolac 0.5%, diclofenac 0.1%, and prednisolone acetate 1% among 58 patients undergoing cataract surgery. No statistically significant differences were observed in flare, cell counts, or intraocular pressure.
A randomized trial involving 40 pediatric patients undergoing strabismus surgery compared topical diclofenac 0.1% to dexamethasone 0.1%. By week 2 post-surgery, patients in the diclofenac group reported less discomfort and had less conjunctival inflammation, edema, and gap than patients in the dexamethasone group (p<0.05). At 4 weeks post-surgery, the difference in patient discomfort and conjunctival gap remained significant. In addition, by 4 weeks post-op, 38% of patients in the dexamethasone group had developed increased IOP, while no increase in IOP was seen in the diclofenac group.

A randomized trial involving 37 patients undergoing posterior segment surgery compared topical diclofenac to dexamethasone. Patients receiving diclofenac reported lower pain scores at days 1 and 15 than those receiving dexamethasone (p<0.05).

Guidelines from the AAO regarding surgical management of cataracts state that there is no established optimal post-operative regimen of topical antibiotics, steroids, and NSAIDs. Therefore, they recommend that it should be the decision of the operating surgeon to use any or all of these products singly or in combination. The AAO guidelines point out that there is no difference in rates of post-capsular opacification (the most common problem encountered post-cataract surgery) between topical steroids and topical NSAIDs. Importantly, the guidelines point out that there is evidence that NSAIDs alone or in combination with steroids are more effective than steroids alone at preventing cystoid macular edema (CME), a serious sight-threatening complication of cataract surgery.

In general, ophthalmic corticosteroids are widely considered first line therapy for the treatment of ophthalmic inflammatory conditions but are commonly associated with increased IOP, which may place some patient populations at risk, including glaucoma patients. Immunosuppressed patients and patients with concerns for wound healing should also avoid the use of corticosteroids. Ophthalmic NSAIDs offer the anti-inflammatory benefits without the risks associated with ophthalmic corticosteroids.

RECOMMENDATION
Ophthalmic NSAIDs are most commonly used for the treatment of inflammation and pain secondary to ophthalmic surgery. Although there are no clinical guidelines which address the appropriate use of ophthalmic NSAIDS, ophthalmic corticosteroids are widely considered first line therapy for the treatment of ophthalmic inflammatory conditions. However, due to adverse effects, certain patient populations should avoid the use of corticosteroids. Ophthalmic NSAIDs offer the anti-inflammatory benefits without the risks associated with ophthalmic corticosteroids in these patient populations. Guidelines from the AAO regarding ophthalmic surgery recommend ophthalmic NSAIDs as an alternative to or in combination with ophthalmic corticosteroids for the treatment of ophthalmic inflammation associated with cataract surgery. The AAO guidelines do not distinguish between the various NSAIDs for use post-cataract surgery. Based on all of this information, it appears that the ophthalmic NSAIDs produce similar anti-inflammatory and pain relieving effects and can thus be considered therapeutic alternatives to one another. In order to maintain costs and ensure appropriate use, it is recommended that ophthalmic NSAIDs be reserved for patients for whom corticosteroid monotherapy is not appropriate.

COMMITTEE VOTE:

| APPROVED | DISAPPROVED | APPROVED with MODIFICATION |

REVIEW: OPHTHALMIC NSAIDS

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Class Step Therapy

Recipients will be approved for an ophthalmic NSAID if any of the following are true:

1. The recipient is using the ophthalmic steroid for pain pre- or post-ocular surgery
2. The recipient has a contraindication, intolerance or adverse reaction to an ophthalmic steroid (i.e. prednisolone, dexamethasone, fluorometholone, etc.). Acceptable reasons for not using an ophthalmic steroid include, but are NOT limited to:
   - Concerns that a potential increase in intraocular pressure (IOP) with ophthalmic steroids would place the patient at risk (i.e., glauna, pre-/post-cataract surgery, etc.)
   - Concerns that the steroid would impair wound healing
   - Concerns that the steroid may cause/induce infection due to immunosuppression.
3. Concomitant use of an ophthalmic steroid and an ophthalmic NSAID is needed to control inflammation

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

References

5. el-Harazi SM, et al. A randomized double-masked trial comparing ketorolac tromethamine 0.5%, diclofenac sodium 0.1%, and prednisolone acetate 1% in reducing post-phacoemulsification flare and cells. Ophthalmic Surg Lasers. 1998; 29(7): 539-44.
BACKGROUND

- Fat malabsorption and protein maldigestion occur when the pancreas loses more than 90% of its ability to produce digestive enzymes, resulting in diarrhea and malabsorption. Pancreatic enzyme preparations contain varying amounts of lipase, protease and amylase.
- Pancreatic enzyme products have a long history of use, some preceding the Federal Food, Drug, and Cosmetic Act of 1938. There are more than three dozen different products being marketed; however, only one product, which is no longer available, has ever received formal FDA approval. The other products continue to be available because of their established use as replacement therapy to treat serious conditions associated with pancreatic insufficiency. In response to variations in drug potency that could significantly affect safety and efficacy, the FDA has mandated that manufacturers of pancreatic enzymes obtain FDA approval by 2010 in order for the products to remain on the market.
- Pancreatic enzymes hydrolyze fats to glycerol and fatty acids, change proteins into peptides and amino acids, and starch into dextrins and maltose which results in re-establishing natural digestive conditions.
- Pancreatic enzymes are indicated for use in patients with pancreatic exocrine deficiency including: chronic pancreatitis, cystic fibrosis, pancreatectomy, pancreatic duct obstruction, pancreatic insufficiency, and steatorrhea.
- The most frequently reported adverse reactions are GI in nature including: nausea, vomiting, bloating, cramping, constipation or diarrhea. Colonic strictures have been reported which may possibly be associated with lipase doses greater than 6,000 units/kilogram/meal.
  - All of the pancreatic enzymes are contraindicated in patients with hypersensitivity to pork proteins, and in patients with acute pancreatitis or acute exacerbations of chronic pancreatitis.
  - Capsules should not be crushed or chewed due to potential for throat irritation. Inhalation of airborne powder can precipitate an asthma attack.
  - Calcium carbonate or magnesium hydroxide may negate the beneficial effect of pancreatic enzymes; however, co-administration may be required to prevent inactivation of pancrelipase especially with use of dosage forms which are not enteric coated.
- Due to lack of FDA-approval, head-to-head clinical trials comparing the available pancreatic enzymes are limited, and often include small numbers of patients, and are of little clinical significance.
- Pancreatic enzymes have utility in pancreatic exocrine deficiency. Currently there is insufficient evidence to promote one product as more effective than another, and products are generally not considered interchangeable due to differences in enzyme content and release mechanisms. Individuals may require trial with several enzymatic preparations before efficacy is achieved. Enteric coated products may be preferable due to minimizing exposure to the contents resulting in decreased incidence of irritation.

RECOMMENDATION

Pancreatic enzymes are used in patients with pancreatic exocrine deficiency, including chronic pancreatitis, cystic fibrosis, pancreatectomy, pancreatic duct obstruction, pancreatic insufficiency, and steatorrhea, in order to restore natural digestive conditions and decrease the associated diarrhea and malabsorption. Due to the lack of comparative trial data, as well as the lack of recommendations from the FDA, therapeutic equivalence among the products cannot be determined. Therefore, it is recommended that products reflecting a wide range of lipase content be available for use.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION
### Preferred Enzymes

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### References

BACKGROUND

- Although the exact etiology of depressive disorders is unknown, many theories focus on changes in neurotransmitter levels, including abnormal regulation of cholinergic, noradrenergic, dopaminergic, and serotonergic neurotransmission. Serotonin and norepinephrine are also involved in pain modulation in the brain and spinal cord.

- The mechanism of action of the SNRIs is believed to be related to their potentiation of both serotonergic and noradrenergic activity in the CNS, though the exact mechanism is unknown.

- All SNRIs are FDA-approved for the treatment of major depressive disorder (MDD). Duloxetine and extended release venlafaxine are also indicated for generalized anxiety disorder. In addition, duloxetine is approved for the management of diabetic peripheral neuropathic pain (DPNP) and syndrome (FMS). Venlafaxine carries an additional FDA-approved indication for the treatment of social anxiety disorder.

- Adverse events commonly associated with the use of SNRIs include: weight loss, dry mouth, nausea, headache, agitation, insomnia and somnolence.

- There have been spontaneous reports of adverse reactions occurring upon discontinuation of the SNRIs, particularly when abruptly discontinued. These adverse reactions included the following: agitation, anxiety, confusion, dizziness, dysphoric mood, emotional instability, headache, hypomania, insomnia, irritability, lethargy, seizures, sensory disturbances, and tinnitus. Although these reactions are generally self-limiting, some have been reported to be severe. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible.

  o All antidepressants carry the following black box warning: “Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies with major depressive disorder (MDD) and other psychiatric disorders. This risk must be balanced with the clinical need. Monitor patients closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.”

  o Duloxetine is contraindicated in uncontrolled narrow-angle glaucoma due to increased risk of mydriasis.

  o Cautions:
    - All SNRIs are Pregnancy Category C.
    - SNRIs may increase the risk of bleeding events, especially in the presence of aspirin, nonsteroidal anti-inflammatory drugs, warfarin or other anticoagulant therapy. Case reports and epidemiological studies have demonstrated an association between the use of drugs that interfere with serotonin reuptake and the occurrence of bleeding events such as ecchymosis, hematomas, epistaxis, petechiae and life-threatening hemorrhages.
    - Due to risk of hypertension with SNRIs, caution should be used in patients with uncontrolled hypertension.
    - The safety and effectiveness of desvenlafaxine in the pediatric population have not been established.
    - Desvenlafaxine requires a dose adjustment to 50 mg every other day in patients with severe renal impairment or End Stage Renal Disease; however, no dose adjustment is necessary for those with hepatic disease.
Because duloxetine increases the risk of elevation of serum transaminase levels, it is not recommended for use in patients with CrCl <30 ml/min or for patients with any degree of hepatic impairment or for those who use substantial amounts of alcohol.

Dose reductions of venlafaxine may be required in patients with renal or hepatic impairment.

Clinically relevant increases in serum cholesterol were recorded in 5.3% of venlafaxine-treated patients compared to placebo (0%) after 3 months of treatment.

Drug Interactions:

SNRIs are contraindicated with concomitant use of monoamine oxidase inhibitors due to the risk of potentially life-threatening serotonin syndrome.

SNRIs undergo metabolism in the liver via the cytochrome P450 enzyme system and are therefore subject to drug-drug interactions with other drugs metabolized by the same isoenzymes.

Although no head-to-head trials are available, several meta-analyses have been conducted to indirectly compare duloxetine and venlafaxine for the treatment of MDD.

Data obtained from 8 trials and over 1700 patients were evaluated to compare efficacy and safety of duloxetine and venlafaxine XR in the treatment of MDD. There was a trend in favor of venlafaxine XR in regards to efficacy; however, the differences did not reach statistical significance. Reported adverse events were comparable between the drugs.

A review of 39 placebo-controlled, randomized, clinical trials of duloxetine, venlafaxine and the SSRI, fluoxetine, used meta-regression analysis to compare the relative treatment effect of duloxetine with venlafaxine and fluoxetine in patients with MDD. This analysis found no significant difference in treatment effect, as measured by Hamilton Depression Rating Scale, between duloxetine and fluoxetine. It did, however, identify significantly better efficacy of venlafaxine compared to duloxetine with an odds ratio of 2 for the number of responders.

In the absence of head-to-head trial data, results from meta-analyses suggest that venlafaxine is superior to duloxetine for the treatment of major depressive disorder.

There are currently no published head-to-head trials comparing duloxetine to other agents for the management of DPNP or FMS.

SNRIs are claimed to be at least as effective as tricyclic antidepressants (TCAs) in the treatment of depression but with lower toxicity, and more efficacious than selective serotonin reuptake inhibitors (SSRIs).

The current American Psychiatric Association (APA) practice guidelines for the treatment of patients with MDD state “the effectiveness of antidepressant medications is generally comparable between classes” with selection based on adverse events and patient preference; however, these guidelines have not been updated since 2000, prior to the release of duloxetine.

The National Institute for Health and Clinical Excellence (NICE) guidelines for management of depression, updated in April 2007, recommend SSRIs as first line therapy for the treatment of depression, with SNRIs and TCAs as second line therapy. The primary role of SNRIs is as an alternative in patients with MDD who have responded poorly to other agents.
Guidelines for the treatment of anxiety disorders also consider SNRIs to be second line therapy behind the SSRIs.

- The 2007 guidelines from the American Academy of Child and Adolescent Psychiatry recommend SSRIs as first-line agents for the treatment of childhood anxiety disorders. Noradrenergic antidepressants, such as SNRIs and TCAs, may be considered alternatives to SSRIs, although their safety in children has not been as well-established as with the SSRIs.

- The 2004 NICE guidelines for the management of anxiety disorders recommend SSRIs as first line, and if not effective after a 12-week course, then a TCA or other antidepressant (including venlafaxine) may be considered.

Consensus guidelines for the treatment of DPNP from the Journal of Family Practice and the Mayo Clinic place duloxetine as a first-tier agent, along with pregabalin and TCAs. Duloxetine and pregabalin are the only agents FDA-approved for the treatment of DPNP.

Duloxetine is considered as a final step for the treatment of FMS.

- The American Pain Society’s 2004 guidelines for the management of FMS recommend the use of tricyclic antidepressants (particularly 10-30 mg of amitriptyline) or cyclobenzaprine as initial therapy. These guidelines recommend SSRIs alone or in combination with tricyclic antidepressants as second line therapy.

- According to 2004 guidelines for the management of FMS published in JAMA a stepwise approach to the management of FMS should be used. Step 1 is to confirm an appropriate diagnosis, explain the diagnosis to the patient and evaluate and treat comorbid illnesses such as mood disturbances and primary sleep disturbances. Step 2 is a trial with a low dose tricyclic antidepressant or cyclobenzaprine, begin cardiovascular fitness and refer the patient for cognitive behavior therapy. The final step in the treatment of FMS is specialty referral (rheumatologist, physiatrist, pain management); trials with SSRIs, SNRIs or tramadol and consideration should be given for combination medication trials or anticonvulsant therapy.

- According to the 2007 guidelines for the treatment of FMS from the European League Against Rheumatism (EULAR), antidepressants, such as amitriptyline, fluoxetine or duloxetine, are appropriate options for the treatment of FMS because they decrease pain and often improve function. These guidelines also recommend pregabalin for the treatment of FMS.
RECOMMENDATION
The SNRIs are FDA-approved for the treatment of MDD. Duloxetine and extended release venlafaxine are indicated for generalized anxiety disorder as well. Duloxetine is also approved for the management of DPNP and fibromyalgia. Venlafaxine carries an additional FDA-approved indication for the treatment of social anxiety disorder. Current NICE guidelines for the management of depression recommend SSRIs as first line therapy for the treatment of depression, with SNRIs and TCAs as second line therapy. The primary role of SNRIs is as an alternative in patients with MDD who have responded poorly to other agents. For the treatment of anxiety disorders, current guidelines recommend SSRIs as first line therapy, with the SNRIs and TCAs as second line options. Guidelines for the treatment of fibromyalgia recommend TCAs or cyclobenzaprine initially and then they recommend the use of SSRIs, SNRIs or tramadol. Due to the lack of comparative trials and mixed results from meta-analyses, it is unclear whether any significant clinical differences exist between the available SNRIs for the treatment of MDD, anxiety disorders or fibromyalgia. In addition, the guidelines do not distinguish between the available SNRIs for any of these indications. For the treatment of DPNP, current guidelines place duloxetine as a first-tier agent.

Based on this information, the SNRIs can be considered therapeutic alternatives to one another for the treatment of MDD and anxiety disorders. It is recommended at least one SNRI be available with step therapy to restrict its use to patients who have responded poorly to SSRIs. Additionally due to its FDA approved-indications, it is recommended that duloxetine be available for use in the treatment of DPNP and fibromyalgia.

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

REREVIEW: SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

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<tr>
<td>VENLAFAXINE ST, QL (compares to Effexor®)</td>
<td>CYMBALTA® QC, QL (duloxetine)</td>
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<tr>
<td>EFFEXOR XR® ST, QL (venlafaxine)</td>
<td>EFFEXOR® ST, QL (venlafaxine)</td>
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<tr>
<td>PRISTIQ™ ST, QL (DESVENLAFAXINE)</td>
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Quantity Limits
- Cymbalta® 20 & 30 mg: 2/day
- 60 mg: 1/day
- Effexor® 2/day
- Effexor XR® 37.5 & 75 mg: 1/day
- 150 mg: 2/day
- Pristiq 1/day
- Venlafaxine: 2/day

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

Class Step Therapy
SNRIs will only be authorized if the recipient has tried and failed a therapeutic course of SSRI at an appropriate dose (Defined as: 3 weeks at maximum tolerated dose within the recommended therapeutic range). If approved, then venlafaxine or Effexor XR® is the preferred agent.

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION
Clinical Criteria for Cymbalta®:

Cymbalta® will be authorized for the following diagnoses:

- Depression/Major Depressive Disorder/Generalized Anxiety disorder: Approval after trial and failure of:
  - One SSRI and
  - One preferred SNRI
- Diabetic peripheral neuropathic pain: Approved without trial and failure of an SSRI or any preferred agents within the SNRI class.
- Fibromyalgia: Approval will be granted after trial and failure of or intolerance or contraindication to:
  - A tricyclic antidepressant or muscle relaxant AND
  - At least one of the following:
    - SSRI
    - A preferred SNRI
    - Anticonvulsant: pregabalin or gabapentin

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

References

RE-REVIEW: NASAL ANTIHISTAMINES

BACKGROUND

- Rhinitis affects 40 million Americans and is characterized by sneezing, itching of the eyes, nose and palate, rhinorrhea, and nasal obstruction. Rhinitis can be perennial allergic, perennial non-allergic, seasonal allergic or seasonal non-allergic.
- Azelastine and olopatadine exert their physiological effects by blocking histamine (H1) resulting in an inhibitory effect on the release of inflammatory mediators from mast cells. Azelastine also inhibits other mediators of allergic reactions such as leukotrienes and platelet-aggregating factor (PAF), and it reduces chemotaxis and the activation of eosinophils.
- Azelastine is FDA-approved for the symptomatic treatment of seasonal allergic rhinitis in individuals ≥ 5 years old and vasomotor rhinitis in those ≥12 years old. Olopatadine is FDA-approved for relief of symptoms of seasonal allergic rhinitis in adults and children ≥12 years old.
- The most common adverse effects seen with nasal antihistamines include a bitter taste and headache.
  - Azelastine is contraindicated with other CNS depressants as it may cause CNS depression as well. Patients should be cautioned to assess their individual response to azelastine before participating in activities requiring mental alertness, and they should be cautious when coadministering azelastine with other CNS depressants including alcohol.
  - Comparative data for azelastine and olopatadine is not available.
- The American Academy of Allergy, Asthma and Immunology (AAAAI) recommends a stepwise approach to managing allergic rhinitis.

<table>
<thead>
<tr>
<th>Seasonal Allergic Rhinitis</th>
<th>Perennial Allergic Rhinitis</th>
<th>Non-Allergic Rhinitis</th>
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<tbody>
<tr>
<td>Persistent, mild to moderate: Minimally sedating antihistamine (± decongestant) or an inhaled nasal corticosteroid</td>
<td>Persistent, mild to moderate: Minimally sedating antihistamine (± decongestant) and/or an inhaled nasal corticosteroid</td>
<td>Intrasal corticosteroid, oral decongestant, or a combination of both</td>
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<tr>
<td>Severe: Combination therapy including a nasal corticosteroid and a minimally sedating antihistamine (± decongestant)</td>
<td>Severe: Combination therapy including a nasal corticosteroid and a minimally sedating antihistamine (± decongestant)</td>
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<tr>
<td>Alternatives: Minimally sedating antihistamine may be substituted with a nasal antihistamine or nasal cromolyn for children</td>
<td>Alternatives: Minimally sedating antihistamine may be substituted with a nasal antihistamine or nasal cromolyn for children</td>
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RECOMMENDATION:
The nasal antihistamines are effective in the symptomatic treatment of seasonal allergic rhinitis and can be considered an alternative to oral antihistamine therapy. These agents offer advantages over systemic antihistamines with regards to lessened systemic adverse effects such as sedation, and they may be beneficial in those intolerant to, or not well-controlled on, intranasal corticosteroids. Although comparative data are not available, the nasal antihistamines can be considered therapeutic alternatives to one another due to their similar indications and mechanisms of action. Therefore, it is recommended that at least one nasal antihistamine be available for use. However, since azelastine is the only product approved for use in patients less than 12 years of age, it is recommended that azelastine be available for use in this patient population.

COMMITTEE VOTE:

APPROVED     DISAPPROVED     APPROVED with MODIFICATION
## REREVIEW: NASAL ANTIHISTAMINES

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<tr>
<td>ASTELIN® QL (azelastine)</td>
<td>PATANASE® QL (olopatadine)</td>
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### Quantity Limits
- Astelin® Nasal Spray = 3 bottles per month
- Patanase® Nasal Spray = 1 bottle per month

### References
NEW: PERIPHERAL VASODILATORS

BACKGROUND

- There are three distinct agents to be reviewed in this category; ergoloid mesylates, isoxsuprine and papaverine.
- Ergoloid mesylates preparations are approved for the treatment of dementia associated with Alzheimer’s Disease and for the symptomatic treatment of age-related dementia. Isoxsuprine holds FDA-approved indications for dementia as well as circulatory diseases, such as Peripheral Vascular Disease and Raynaud’s syndrome. Oral papaverine is approved for the relief of cerebral and peripheral ischemia associated with arterial spasm and myocardial ischemia complicated by arrhythmias.
- Ergoloid mesylates preparations have most commonly been associated with blurred vision, bradyarrhythmia, flushing, headache, nasal congestion, GI upset and rash. These agents may also rarely cause orthostatic hypotension. Isoxsuprine is most commonly associated with GI upset, dizziness, chest pain, hypotension, rash and tachyarrhythmia. Rarely, isoxsuprine may cause pulmonary edema. The most common adverse effects seen with papaverine are GI upset, headache, hypertension, rash, somnolence, tachyarrhythmias and vertigo. This agent may also rarely cause serious side effects such as acidosis, hepatotoxicity, increased intracranial pressure and priapism.
  - Ergoloid mesylates preparations are contraindicated in patients with acute or chronic psychosis. Isoxsuprine is contraindicated for patients with heart disease, those who are postpartum, and those with recent arterial bleeding. Papaverine should not be administered to patients with complete atrioventricular block.
  - Prescribers should be cautioned against prescribing isoxsuprine to those who have bleeding disorders, chest pain, glaucoma, preterm labor or stroke. There is cautionary labeling associated with papaverine when it is administered to patients with glaucoma, liver disease, parkinsonism, recent myocardial infarction, sickle cell disease, and stroke.
- Place in Therapy:
  - While the effectiveness of ergoloid mesylates for any indication is controversial, a proportion of individuals older than 60 years of age who manifest signs and symptoms of an idiopathic decline in mental capacity such as cognitive and interpersonal skills, mood, self-care or apparent motivation may experience some symptomatic relief with ergoloid mesylates. The prescriber should eliminate the possibility that the patient’s signs and symptoms come from a potentially reversible and treatable condition before prescribing ergoloid mesylates. Additionally, continued clinical evaluations should be performed to determine whether any initial benefit is seen from ergoloid mesylates therapy. The efficacy of ergoloid mesylates was evaluated using the Sandoz Clinical Assessment-Geriatric (SCAG) rating scale. Modest, but statistically significant, changes were seen at the end of 12 weeks in mental alertness, confusion, recent memory, orientation, emotional lability, self-care, depression, anxiety/fears, cooperation, sociability, appetite, dizziness, fatigue, bothersome(ness), and an overall impression of clinical status with ergoloid mesylates treatment.
  - The U.S. Food and Drug Administration has classified isoxsuprine as “possibly effective” in the symptomatic treatment of cerebral vascular insufficiency, and in peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger’s disease) and Raynaud’s disease. Although isoxsuprine was the first beta-adrenergic agent used for inhibiting premature labor; its use has been replaced by other agents such as terbutaline and ritodrine.
Papaverine is occasionally used as a smooth-muscle relaxant for both cerebral and peripheral ischemia, as well as for myocardial ischemia complicated by arrhythmias, despite the lack of objective data demonstrating its efficacy. It may also be useful in some cases of vasospastic disorders (Raynaud's phenomena) where vasoconstriction reduces blood flow to the skin. Papaverine may increase cutaneous blood flow improving vasospastic conditions of skin and extremities occurring as a manifestation of several diseases (collagen disease, occlusive arterial disease, trauma); however, it is of minimal value in advanced cases with an obstructive component. Therapy with papaverine is not effective in treating chronic occlusive peripheral vascular disease. Despite the use of papaverine for years, no good objective evidence is available to support the efficacy of papaverine in the treatment of cerebral vascular disease or organic brain syndrome. It is unlikely that dilation occurs in sclerotic vessels and no objective data exists indicating that papaverine can prevent progression of organic brain disease or arteriosclerotic disease; however, some studies have reported improvement in brain oxygenation in patients with stroke and slight improvement in cerebral blood flow in patients with focal cerebral vascular disease. Due to the drug's non-specific vasodilating effects, papaverine can increase cerebral blood flow to normal as well as to abnormal regions of the brain causing blood to be shunted away from diseased areas which may result in worsened condition. This decrease in blood flow to ischemic areas may occur particularly after an occlusive stroke or subarachnoid hemorrhage.

RECOMMENDATION
It is difficult to compare the safety and efficacy of the peripheral vasodilators due to varying uses and adverse events. However, considering the non-specific vasodilating effects of papaverine and its potential to worsen conditions such as occlusive stroke or subarachnoid hemorrhage, this drug can be considered an inferior agent in the category. Per MICROMEDEX, papaverine has no clinical role in the treatment of ischemia, and use in any ischemic type condition is not recommended. Therefore, it is recommended that papaverine be reserved for patients who have tried and failed alternative therapies for peripheral or cerebral ischemia. Both ergoloid mesylates and isoxsuprine have mixed data with regards to efficacy; however, there are some studies to support the use of ergoloid mesylates in dementia and cerebrovascular disease, and isoxsuprine in peripheral vascular disease, dementia, Raynaud's syndrome, and preterm labor. While these agents are not considered first line agents for these disease states, their low utilization suggests that they are not being overprescribed. Therefore, it is recommended that ergoloid mesylates and isoxsuprine be available for use.

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

NEW: PERIPHERAL VASODILATORS

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<tr>
<td>ERGOLOID MESYLATES</td>
<td>PAPAVERINE</td>
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<tr>
<td>ISOXSUPRINE (Comares to Vasodilan®)</td>
<td>VASODILAN® (isoxsuprine)</td>
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Clinical Criteria for Papaverine

Papaverine will be approved for the treatment of peripheral or cerebral ischemia after trial and failure of at least two of the following:

- Aspirin
- Aspirin/Dipyridamole
- Cilostazol
- Clopidogrel
- Dipyridamole
- Pentoxifylline
- Ticlopidine

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

References


NEW: DECARBOXYLASE INHIBITORS

BACKGROUND

- The only decarboxylase inhibitor currently on the market is carbidopa.
- Carbidopa is always combined with levodopa, because carbidopa prevents the conversion of levodopa to dopamine in the periphery thereby lessening the peripheral adverse effects of dopamine while increasing the cerebral bioavailability of levodopa and subsequently dopamine.
- Carbidopa is used in combination with carbidopa-levodopa or with levodopa for the symptomatic treatment of idiopathic Parkinson's disease, postencephalitic Parkinsonism, and symptomatic Parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and/or manganese intoxication. Carbidopa is used in combination with carbidopa-levodopa for patients who are unable to obtain adequate daily dosage of carbidopa from the combination product. This agent may also be used for patients whose dosage requirement of carbidopa and levodopa necessitates separate titration of each entity. In addition, carbidopa may be used in combination with carbidopa-levodopa to permit lower doses of levodopa resulting in reduced nausea and vomiting, more rapid dosage titration and a smoother response.
- Carbidopa has not been found to have any adverse drug actions at recommended doses. The only observed side effects have been with concomitant use of carbidopa and levodopa or with carbidopa-levodopa combination products. These adverse effects include dyskinesias, other involuntary movements, nausea and psychotic episodes such as delusions, hallucinations, paranoid ideation, depression with or without development of suicidal tendencies, and dementia. Seizures have also occurred; however, a causal relationship has not been established.
- Carbidopa is contraindicated in patients with narrow-angle glaucoma and in patients with suspicious, undiagnosed skin lesions or a history of melanoma. In addition, carbidopa should not be administered concomitantly with non-selective monoamine oxidase inhibitors (MAOIs) due to the potential for severe orthostatic hypotension; however, selective MAOIs, such as selegiline, may be administered with carbidopa cautiously.
Concomitant administration of carbidopa and levodopa may cause involuntary movements and mental disturbances due to increased levels of dopamine in the brain. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. In addition, carbidopa should be administered cautiously to patients with psychosis or history of psychosis. Individuals with chronic wide-angle glaucoma may be treated cautiously with carbidopa provided the intraocular pressure is well controlled and monitored carefully.

- There is no conclusive evidence to prove that carbidopa is beneficial other than to reduce nausea and vomiting resulting in a more rapid dose titration and a smoother response to levodopa. Certain patients who responded poorly to levodopa alone have improved when carbidopa and levodopa were given concurrently, most likely due to decreased peripheral decarboxylation of levodopa. However, it should be noted that, in controlled trials comparing the combination of carbidopa and levodopa with levodopa alone, only about half the patients with nausea or vomiting on levodopa alone improved when treated with combination therapy.

**RECOMMENDATION**

Although carbidopa is always combined with levodopa, it is useful over the combination product for patients who are unable to obtain an adequate daily dosage of carbidopa from the combination product, to permit lower doses of levodopa thereby preventing adverse effects, or for patients whose dosage requirement of carbidopa and levodopa necessitates separate titration of each entity. Therefore, it is recommended that carbidopa be available.

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**NEW: DECARBOXYLASE INHIBITORS**

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<td>LODOSYN* (carbidopa)</td>
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**References**


**NEW: DRUGS TO TREAT HEREDITARY TYROSINEMIA**

**BACKGROUND**

- The only agent within this class is nitisinone. Nitisinone is FDA-approved for the treatment of Type I Tyrosinemia in conjunction with dietary restrictions of tyrosine and phenylalanine.
- The most common adverse effects seen after administration of nitisinone are conjunctivitis, keratitis, leukopenia or thrombocytopenia (3%), liver dysfunction (7-8%), and photophobia (2%).
  - Patients should be instructed to limit their intake of tyrosine and phenylalanine because these agents may increase plasma levels of tyrosine leading to an increased risk of toxicity.
  - Because there are no human studies of pregnancy outcomes after exposure to nitisinone and there are no reports of outcomes after inadvertent exposure during pregnancy, nitisinone is listed as Pregnancy Category C.
Nitisinone is the treatment of choice for hereditary tyrosinemia type 1. Treatment with nitisinone should be initiated early as data suggest that beginning treatment before 2 years of age may reduce the risk of hepatocellular carcinoma. Approximately 10% of children will not respond to nitisinone therapy; therefore, liver transplantation is indicated. In addition, transplantation is indicated for patients with suspected hepatocellular carcinoma.

**RECOMMENDATION**

Nitisinone, along with dietary restrictions of tyrosine and phenylalanine, is FDA-Approved for the treatment of Type I Tyrosinemia. Because nitisinone is the treatment of choice for hereditary tyrosinemia type 1, it is recommended that this agent be available.

**COMMITTEE VOTE:**

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<td>ORFADIN® (nitisinone)</td>
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**References**


**NEW: VAGINAL/CERVICAL CARE AND TREATMENT AGENTS**

**BACKGROUND**

- The only vaginal/cervical care and treatment agent is amino acid cervical cream containing 8.34% urea, 0.5% sodium propionate, 0.83% methionine, 0.35% cystine, 0.83% inositol and 0.000004% chloride. This product is buffered to a pH of 5.5 in order to promote healing of the cervix; however, at this pH, it will not adversely affect the healthy vagina.
- Amino acid cervical cream is indicated for the treatment of mild cervicitis, postpartum cervicitis or cervical tears as a result of conization or surgical procedures.
- The topical application of amino acid cervical cream may be associated with erythema, ischemic skin necrosis, rash or skin irritation.
- This product should be avoided in patients with hypersensitivity to urea or other product ingredients and ruptured membranes, cervical stenosis or uterine fibroids as a result of abortion or miscarriage.
- Amino acid cervical cream is the only topical cream used nightly for 2 to 4 weeks for the treatment of cervicitis or for postpartum or post-surgical cervical tears.

**RECOMMENDATION**

Amino acid cervical cream is a reasonable treatment for mild cervicitis, postpartum cervicitis or cervical tears as a result of postconization or post surgical procedures; therefore, this agent should be available.

**COMMITTEE VOTE:**

**APPROVED**  **DISAPPROVED**  **APPROVED with MODIFICATION**

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<th>NEW: VAGINAL/CERVICAL CARE AND TREATMENT AGENTS</th>
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<tr>
<td>AMINO ACID CERVICAL CREAM (Compares to Amino-Cerv®)</td>
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NEW: VAGINAL SULFONAMIDES

BACKGROUND

• The only prescription vaginal sulfonamide currently available is sulfanilamide.
• Sulfanilamide is indicated for the treatment of vulvovaginitis caused by *Candida albicans*.
• The only adverse effects seen with sulfanilamide are local sensitivity type reactions (0.2%) such as increased discomfort, burning or itching. While systemic absorption is unlikely, prescribers should be cautioned that deaths associated with administration of oral sulfonamides have occurred due to hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. In addition, goiter production, diuresis, and hypoglycemia have occurred rarely in patients receiving oral sulfonamides. Cross-sensitivity may exist with these agents.
• There are many topical alternatives to sulfanilamide for the treatment of vulvovaginitis caused by *Candida albicans* such as miconazole, clotrimazole, tioconazole, and butoconazole. Many of these alternatives may clear the infection with only one to seven days of therapy; however, sulfanilamide must be used for 30 days to adequately clear infection.

RECOMMENDATION

Sulfanilamide is indicated for the treatment of vulvovaginitis caused by *Candida albicans*. This product can be used as an alternative to other topical agents such as miconazole, clotrimazole, tioconazole, and butoconazole; however, sulfanilamide requires 30 days of therapy compared to 1 to 7 days with the other topical agents. Due to its extended length of therapy, sulfanilamide can be considered inferior to the other vaginal antifungals; however, sulfanilamide may have utility in patients who have a failure with or contraindication to other vaginal antifungals. Therefore, it is recommended that sulfanilamide be available after trial and failure of two preferred vaginal antifungals or if there is a contraindication or history of intolerance to other vaginal antifungals.

COMMITTEE VOTE:

APPROVED     DISAPPROVED     APPROVED with MODIFICATION

REVIEW: ANTIFUNGALS VAGINAL

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<tr>
<td>MICONAZOLE-3® VAGINAL SUPPOSITORY</td>
<td>AVC® (sulfanilamide)</td>
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<td>(miconazole nitrate)</td>
<td>MONISTAT® (miconazole nitrate)</td>
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<td>NYSTATIN</td>
<td>TERAZOL® (terconazole)</td>
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<td>TERCONAZOLE (Compares to Terazol®)</td>
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<td>GYNAZOLE-1® (butoconazole)</td>
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<td>ZAZOLE® (terconazole)</td>
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References

NEW: ARTIFICIAL TEARS / OPHTHALMIC LUBRICANTS

BACKGROUND

- Lacrisert®, a hydroxypropyl cellulose insert, is approved for the treatment of moderate to severe dry eyes, including keratoconjunctivitis sicca, especially in patients who remain symptomatic after an adequate trial of artificial tear solutions. FreshKote® is an ophthalmic solution containing 2% polyvinyl pyrrolidone, 0.9% polyvinyl alcohol (87% hydrolyzed), 1.8% polyvinyl alcohol (99% hydrolyzed) and Amisol® clear. FreshKote® is FDA-approved for the treatment of moderate to severe dry eyes.
- The most common adverse effects associated with the hydroxypropyl cellulose insert are blurred vision, eyelash matting or stickiness, eyelid edema, hyperemia, ocular discomfort or irritation or photophobia. Patients should also be warned that corneal abrasion may result if the insert is improperly placed. FreshKote® has been associated with blurred vision or eye pain.
- Both Lacrisert® and FreshKote® are alternatives to over-the-counter ophthalmic lubricants. Available data is unclear as to whether either of these products offer any advantage over OTC artificial tears.

RECOMMENDATION

Both Lacrisert® and FreshKote® are approved for the treatment of moderate to severe dry eyes. These products are considered alternatives to over-the-counter artificial tears; however, the hydroxypropyl cellulose insert is specifically indicated for use in patients who have remained symptomatic after an adequate trial of artificial tears solutions. Due to the difficult administration and potential for corneal abrasion, hydroxypropyl cellulose inserts should be reserved for patients who have failed an adequate trial of artificial tears. Therefore, it is recommended that at least one prescription ophthalmic lubricant be available.

COMMITTEE VOTE:

APPROVED     DISAPPROVED     APPROVED with MODIFICATION

NEW: ARTIFICIAL TEARS / OPHTHALMIC LUBRICANTS

PREFERRED                               NON-PREFERRED
FRESHKOTE® (2% polyvinyl pyrrolidone, 0.9% polyvinyl alcohol (87% hydrolyzed), 1.8% polyvinyl alcohol (99% hydrolyzed) and Amisol® clear) LACRISERT® (hydroxypropyl cellulose insert)

References


NEW: EYE VASOCONSTRICTORS

BACKGROUND

- This review includes the prescription strength ophthalmic vasoconstrictors, naphazoline and phenylephrine.
- Naphazoline is FDA-approved for use as a topical ocular vasoconstrictor, including the temporary relief of redness due to minor eye irritation, protection against further irritation, and temporary relief of burning and irritation due to dryness of the eye. Prescription strength ophthalmic phenylephrine is indicated for use as a vasoconstrictor, decongestant, and mydriatic in a variety of ophthalmic conditions and procedures.
Due to minimal systemic absorption, the most common adverse events associated with the ophthalmic vasoconstrictors are local reactions including: blurred vision, discomfort, increased intraocular pressure, redness, irritation, lacrimation, mydriasis, punctate keratitis, and transient stinging on initial instillation. Phenylephrine 10% ophthalmic solution has been associated with a marked increase in blood pressure in low-weight premature neonates, infants, and adult patients with idiopathic orthostatic hypotension.

Naphazoline is an effective ophthalmic decongestant to relieve redness and irritation associated with allergic and inflammatory ocular conditions caused by dust, smoke, sun glare, contact lenses, colds, allergies, swimming, and reading or other close work. Phenylephrine is the topical drug of choice to produce mydriasis in ophthalmology. It is most commonly used for examination of intraocular structures, to facilitate cataract surgery, and as an adjunct to the treatment of uveitis, postoperative inflammation, and wide angle glaucoma secondary to uveitis.

RECOMMENDATION
Naphazoline is FDA-approved for the temporary relief of redness due to minor eye irritation. It is effective against both allergic and inflammatory ocular conditions. Phenylephrine is indicated for use as a vasoconstrictor, decongestant, and mydriatic in a variety of ophthalmic conditions and procedures and is considered the topical drug of choice to induce mydriasis in ophthalmology. Because the indications for each drug vary significantly, they cannot be considered therapeutic alternatives to one another. It is recommended that both naphazoline and phenylephrine be available for use.

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

### NEW: EYE VASOCONSTRICTORS

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<tr>
<td>AK-CON® (naphazoline)</td>
<td>AK-DILATE 2.5% (phenylephrine 2.5%)</td>
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<td>AK-DILATE® 10% (phenylephrine 10%)</td>
<td>ALBALON® (naphazoline)</td>
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<td>PHENYLEPHRINE 2.5% (compares to AK-DILATE® 2.5%, ALTAFRING®, MYDFRIN®, NEOFRIN®)</td>
<td>ALLERSOL® (naphazoline)</td>
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<tr>
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<td>ALTAFRING® (phenylephrine 2.5%, 10%)</td>
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<td>MYDFRIN® (phenylephrine 2.5%)</td>
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<td>NEOFRIN® (phenylephrine 2.5%, 10%)</td>
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References

### NEW: NASAL VASOCONSTRICTORS

**BACKGROUND**
- The prescription nasal vasoconstrictors are epinephrine and tetrahydrozoline.
- The nasal vasoconstrictors are approved for the treatment of nasal congestion. Tetrahydrozoline is indicated for patients as young as 2 years old.
- The most common adverse effects associated with the nasal vasoconstrictors are topical reactions such as nasal burning, dryness, itching and stinging. Because these agents may be absorbed systemically, prescribers should also watch for tremor or palpitations. Epinephrine has also been associated with asthenia, anxiety and GI upset. Tetrahydrozoline has been associated with insomnia and rebound congestion.
Typically only injectable epinephrine is used for anaphylactic reactions, acute asthma, cardiopulmonary resuscitation, and primary open-angle glaucoma. While epinephrine can be used as a nasal decongestant, oral decongestants are typically utilized first. Tetrahydrozoline is an effective topical decongestant for the symptomatic treatment of acute or chronic rhinitis; however, due to the possibility of rebound congestion, it is not indicated for chronic rhinitis. Oral decongestants are less likely to produce rebound congestion and are indicated before tetrahydrozoline for long-term use in rhinitis.

RECOMMENDATION
Both epinephrine and tetrahydrozoline are approved in children, have a quicker onset of action than oral decongestants, and are effective against allergic rhinitis, non-allergic rhinitis, and rhinitis associated with the common cold. Oral decongestants are less likely than tetrahydrozoline to produce rebound congestion, and they are generally recommended for long term treatment over topical decongestants. Both agents in this class are good topical alternatives for those patients with acute cases of rhinitis who cannot tolerate systemic side effects associated with oral decongestants; therefore, it is recommended that at least one nasal vasoconstrictor be available.

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

NEW: NASAL VASOCONSTRUCTORS

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<tr>
<td>ADRENALIN CHLORIDE™ (epinephrine)</td>
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<td>TYZINE® (tetrahydrozoline)</td>
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References

NEW: AMEBICIDES

BACKGROUND
- Paromomycin is FDA-approved for the treatment of acute and chronic intestinal amebiasis and for the adjunctive treatment of hepatic coma.
  - It is considered the drug of choice for the treatment of Giardia lamblia in the first trimester of pregnancy, in situations where maternal malnutrition and dehydration occur.
  - Paromomycin is also used off-label for treatment of cryptosporidiosis, especially in HIV/AIDS patients.
- Nausea, abdominal cramps, and diarrhea are the most common adverse events associated with the use of paromomycin. These adverse effects are usually only associated with daily doses greater than 3 grams. Prolonged or repeated use may result in bacterial or fungal overgrowth.
- Paromomycin is effective in the treatment of intestinal amebiasis; however, it is ineffective against extra intestinal forms due to lack of absorption. It can be used as an adjunct in the management of hepatic coma, but due to adverse events associated with high dosing, close monitoring is required.

RECOMMENDATION
Paromomycin is FDA-approved for the treatment of acute and chronic intestinal amebiasis as well as for adjunctive treatment of hepatic coma. Due to its lack of systemic absorption, paromomycin is considered the drug of choice for treatment of giardiasis in pregnancy when malnutrition and dehydration occur. For these reasons, it is recommended that paromomycin be available for use.
NEW: AMEBACIDES

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<td>PAROMOMYCIN</td>
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References

NEW: DRUGS TO TREAT GAUCHER’S DISEASE

BACKGROUND
- Miglustat is FDA-approved for the treatment of mild to moderate, chronic, non-neuropathic Gaucher’s disease. Gaucher’s disease is the most common lysosomal storage disease, caused by a deficiency in the enzyme glucocerebrosidase. It results in fatty material collecting in the spleen, liver, kidney, lungs, brain, and bone marrow.
- The FDA has mandated that miglustat only be prescribed by physicians knowledgeable in the management of Gaucher’s disease. Miglustat is distributed from one specialty pharmacy (CuraScript), which requires prescribers to submit a form attesting that they are qualified to diagnose and treat patients with Gaucher’s disease and that they are familiar with the Zavesca® prescribing booklet.
- The most common adverse events associated with miglustat are diarrhea (85%), weight loss (65%) and tremor (17%).
  - Peripheral neuropathy has been reported in patients treated with miglustat; therefore, all patients should undergo neurological examinations at initiation of therapy and every 6 months during treatment.
  - Miglustat is contraindicated in women who are or may become pregnant. (Pregnancy Category X)
- Enzyme replacement therapy is considered the standard of care for non-neuropathic Gaucher’s disease. Miglustat should be considered as an alternative to enzyme replacement therapy with beta-glucocerebrosidase (i.e. alglucerase or imiglucerase) in patients who are unwilling or unable to continue intravenous infusions of enzyme replacement therapy. Miglustat appears to be less effective than enzyme infusions.

RECOMMENDATION
Miglustat is FDA-approved for the treatment of mild to moderate, chronic, non-neuropathic Gaucher’s disease. Although less effective than enzyme replacement therapy, miglustat is considered an alternative therapy in patients who are unwilling or unable to continue intravenous infusions of enzyme replacement therapy. Therefore, miglustat should be available for use by physicians knowledgeable in the management of Gaucher’s disease.

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<tr>
<td>ZAVESCA® (miglustat)</td>
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### References