Proposed Preferred Drug List

with

Clinical Criteria

Proposal for TennCare

November 9, 2010
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.
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)

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

NEW: SMOKING CESSATION AGENTS

BACKGROUND

- Smoking is the cause of multiple cancers, coronary heart disease, stroke, chronic obstructive pulmonary disease (COPD) and pregnancy complications. Although smoking is an avoidable cause of these illnesses, it is estimated over 20% of adults in the United States currently smoke. Smoking cessation reduces the risk of smoking related deaths with the risks of most diseases returning to the equivalent of a non-smoker over time. This review will focus on currently available RX and OTC smoking cessation agents. Currently available agents include bupropion sustained release, various dosage forms of nicotine replacement therapies, and varenicline.

- The nicotine replacement therapies act as a nicotine agonist at nicotine-cholinergic receptors.

- The exact mechanism of action by which bupropion HCl sustained-release works to assist patients with smoking cessation is unknown, but it may be related to its action as a weak inhibitor of norepinephrine and dopamine uptake.

- Varenicline is a partial agonist of the α4β2 neuronal nicotinic acetylcholine receptors; it stimulates receptor-mediated activity and acts to block nicotine from activating the receptors.

- All agents have an FDA indication for smoking cessation assistance; bupropion also has an indication for the treatment of depression related to seasonal affective disorder and major depressive disorder.

- The most common adverse effects associated with bupropion HCL extended release include nausea, dizziness, headache, hypertension, insomnia, and xerostomia. More severe adverse effects include dysrhythmias and seizures.

- The most common adverse effects associated with nicotine replacement products include skin irritation (patch), nasal/airway irritation (inhaler, nasal spray), dizziness, headache, insomnia. More severe effects of nicotine replacement include: hypertension and dysrhythmias.

- The most common adverse effects seen with varenicline include constipation, nausea, abnormal dreams, and insomnia. More severe adverse effects include abnormal psychiatric behavior and suicidal thoughts.

- There are many precautions that must be considered when considering a smoking cessation product:
  - Bupropion carries a black box warning regarding serious neuropsychiatric events (including, but not limited to depression, suicidal ideation, suicidal attempt, and completed suicide reported in patients taking bupropion for smoking cessation.)
  - Varenicline also carries black box warning regarding depression, suicidal ideation, suicidal attempt, and completed suicide reported in patients taking varenicline for smoking cessation. Additionally, patients should be observed for changes in behavior, hostility, agitation, and depressed mood.
  - Bupropion is contraindicated in patients with seizure disorder, bulimia, anorexia, patients taking any other formulations of bupropion, or patients undergoing abrupt withdrawal of alcohol or benzodiazepines due to an increased risk of seizures.
  - Caution should be used in patients with existing cardiovascular disease who are using bupropion or nicotine replacement therapies; both agents have been associated with hypertension, nicotine has also been associated with tachycardia.
  - Caution should be used in patients with existing airway diseases and asthma; nicotine nasal spray & nicotine inhalers have been associated with exacerbations of asthma, bronchospasms or reactive airway disease.
  - Varenicline has been associated with various hypersensitivity reactions (Stevens Johnson syndrome, erythema multiforme, and angioedema) and increased risk of accidental injury due to its neuropsychological effects.
MISCELLANEOUS AGENTS

- The nicotine inhaler, spray and transdermal patches are pregnancy category D; nicotine polacrilex gum & lozenge, varenicline and bupropion sustained release are pregnancy category C.
- There are no known significant drug-drug interactions with these agents.

- Clinical trials for smoking cessation agents in pregnancy are very limited. There are no current trials of varenicline in pregnancy.
- Bupropion is not teratogenic from animal studies conducted by the manufacturer and very limited data available from human studies. One study cited by the manufacturer was a retrospective study reviewing a managed care database for congenital malformations overall and specifically for cardiac malformations (n=7005 infants, 1213 exposed to bupropion in first trimester). Patients had exposure to bupropion in first trimester or had exposure to other antidepressants in first trimester or bupropion in second or third trimester. The study showed no greater risk for congenital malformations or cardiovascular malformations following first trimester exposure to bupropion compared with other antidepressants or bupropion exposure in the second and third trimesters.
- Chan et al published preliminary results from the Mother Risk Program in Toronto, Canada. The program was an observational study of bupropion use in pregnancy, 21% used bupropion for depression and 16% used for smoking cessation. Eighty one pregnancy outcomes were available at the time of publishing. From 56 live births, no major malformations were noted. Additionally, 16 miscarriages and 8 therapeutic abortions occurred. Of the participants, 73% bupropion helped them to smoke less cigarettes per day and of that 73%, 40% quit smoking.
- One double blind prospective trial evaluated the use of nicotine gum versus placebo in pregnant patients who were less than or equal to 26 weeks gestation (N=194). Primary endpoint was biochemically confirmed abstinence rates at six weeks of nicotine gum use and at end of pregnancy. Secondary endpoints were birthweight and measures of smoking reduction. There were no significant differences between the nicotine gum group and the placebo group in abstinence at six weeks of treatment (13.0% vs 9.6%; \( P=0.45 \)) and at 32 to 34 weeks gestation (18.0% vs 14.9%; \( P=0.56 \)). There were no significant differences in cigarettes/day in the nicotine gum group compared to placebo at six weeks after treatment \( (P=0.16) \) and at 32 to 34 weeks gestation \( (P=0.077) \). Birth weight was significantly higher in the nicotine gum treated patients compared to placebo \( (P<0.001) \). Gestational age was also significantly greater in the nicotine gum group compared to placebo \( (P=0.014) \) with significantly more pre-term deliveries in the placebo group \( (P=0.027) \).
- Another study by Wisborg et al compared nicotine transdermal patch with placebo in pregnant smokers. There was no significant difference in the proportion of patients that were continuously abstinent in the nicotine transdermal patch group compared to placebo (21% vs 19%; \( P \) value not reported). Additionally, the mean birth weight difference was 186 g higher in the nicotine group compared to placebo (no \( P \) values reported) and there was no significant difference in the rate of preterm labor.
- The United States Department of Health and Human Service (DHHS): Treating Tobacco Use and Dependence: 2008 Update
  - Combination of counseling and medications are more effective for smoking cessation than either therapy alone.
  - All patients attempting to quit should use effective medications, with the exception of those populations where use is contraindicated or evidence of effectiveness is lacking (pregnant women, smokeless tobacco users, light smokers & adolescents).
  - Bupropion-sustained release, nicotine replacement products (inhaler, nasal spray, polacrilex gum & lozenge, transdermal patch), and varenicline are first line agents.
  - Combinations of first line agents are effective and should be considered in patients willing to quit.
MISCELLANEOUS AGENTS

- All pregnant smokers should be offered psychosocial interventions that exceed minimal advice to quit. However, due to insufficient data, there are no recommendations on the use of medications in pregnancy.

  - Counseling and pharmacotherapy are effective but the combination is more effective than either alone.
  - Pharmacotherapy (defined as bupropion sustained release, nicotine replacement therapy, or varenicline) should be offered to individuals planning to quit.
  - Combinations of pharmacotherapy agents should be offered to patients who have failed monotherapy.
  - Bupropion and varenicline should not be offered to pregnant/breastfeeding women; the risks and benefits of nicotine replacement therapy should be explained to pregnant/breastfeeding women and individuals with unstable cardiac disease.

- The American College of Obstetricians and Gynecologists (ACOG) Committee Opinion on Smoking Cessation during Pregnancy (2005) states use of nicotine replacement agents or other pharmacotherapy options for smoking cessation during pregnancy and lactation have not been sufficiently evaluated to determine efficacy or safety. Pharmacotherapy (nicotine replacement therapy, bupropion) options may be considered when non-pharmacological treatments fail (varenicline was not available at the time this opinion was published). The Opinion states if nicotine replacement agents are utilized, agents with intermittent dosing may reduce fetal nicotine exposure. Fetal exposure to smoking causes intruterine growth restriction, placenta previa, low birth weight, perinatal mortality, and other related complications.

RECOMMENDATION
Currently, coverage for smoking cessation agents is limited to recipients who are pregnant. (or recipients <21 years old who demonstrate medical necessity). All smoking cessation agents can cause significant adverse effects; specifically, bupropion sustained-release and varenicline have been associated with neuropsychiatric symptoms when used for smoking cessation. Guidelines from the US DHHS and NICE recommend bupropion sustained-release, nicotine replacement therapies and varenicline tartrate as first-line agents for smoking cessation and state the agents are more effective when used in combination with counseling. The US DHHS guidelines make no recommendations for use of medications for smoking cessation in pregnancy due to lack of substantial safety and efficacy data. The NICE guidelines state bupropion and varenicline should not be used in pregnant/lactating women; however limited clinical trial data suggest bupropion may not pose additional risk to the fetus. The ACOG Opinion statement recommends non-pharmacological methods should be utilized as first line therapy in pregnant women before pharmacological therapy due to lack of sufficient efficacy and safety information for smoking cessation agents. ACOG recommends if nicotine replacement agents are utilized, agents with intermittent dosing may reduce fetal nicotine exposure. Given this information, it is recommended that at least one intermittent nicotine smoking cessation agent and bupropion be available for use in pregnant women. Additionally, in order to ensure safety and appropriate use for covered populations, it is recommended that the class be subject to clinical criteria.

COMMITTEE VOTE:
APPROVED    DISAPPROVED    APPROVED with MODIFICATION
NEW: SMOKING CESSATION AGENTS

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Clinical Criteria for Smoking Cessation Agents:

For pregnant recipients (regardless of age):

Preferred smoking cessation agents will be approved if patient meets the following criteria:

- The physician has provided the patient with information on available non-pharmacological treatments, including counseling services and the Quit Line
- The recipient must not be on any other concomitant bupropion agent

Note: The PA will be granted for the duration of pregnancy

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

Quantity Limits:

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<tr>
<th>Bupropion SR (Zyban®) 2 per day</th>
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<td>Chantix® 2 per day</td>
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COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

References


BACKGROUND

- The dipeptidyl peptidase-4 (DPP-4) inhibitors represent a novel approach in the management of type 2 diabetes and primarily target postprandial glucose. This class includes the single entity agents of saxagliptin and sitagliptin, as well as the combination product sitagliptin/metformin hydrochloride.

- DPP-4 inhibitors reversibly block DPP-4, which is the enzyme responsible for the rapid degradation of incretin hormones. Incretin hormones are produced by the gastrointestinal tract in response to meals and are involved in the regulation of insulin. The antidiabetic actions of incretin hormones include the enhancement of meal stimulated insulin secretion, decreased glucagon secretion, improvements in β-cell function, and slowing of gastric emptying.

- Saxagliptin and sitagliptin are FDA-approved as adjunct therapy to diet and exercise to improve glycemic control in adult patients with type 2 diabetes as both monotherapy and combination therapy with other antihyperglycemic agents. Sitagliptin/metformin hydrochloride is FDA-approved as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes when therapy with both metformin hydrochloride and sitagliptin is appropriate.

- Therapy with DPP-4 inhibitors is generally well tolerated with the most common reported adverse events being headache, upper respiratory tract infection, and urinary tract infection. The risk of hypoglycemia associated with these agents is relatively low due to the glucose-dependent nature of incretin hormones. There have been postmarketing reports of serious hypersensitivity reactions with sitagliptin, including anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome.

- The combination sitagliptin/metformin product carries a black box warning regarding the risk of lactic acidosis as is found on all products containing metformin.

- The combination product containing sitagliptin and metformin hydrochloride is contraindicated in patients with renal disease or dysfunction, and acute or chronic metabolic acidosis including diabetic ketoacidosis, with or without coma.

- There have been postmarketing reports of serious hypersensitivity reactions with sitagliptin, including anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome.

- A dosage adjustment is recommended for both saxagliptin and sitagliptin in patients with moderate to severe renal insufficiency, as well as, in patients with end-stage renal disease on dialysis.

- When using DPP-4 inhibitors in combination with a sulfonylurea, a decreased dose of the sulfonylurea is recommended to reduce the risk of hypoglycemia. Increases in the concentration of saxagliptin may occur when administered concomitantly with strong CYP3A4/5 inhibitors; therefore, a reduction in the dose of saxagliptin may be necessary. Patients undergoing radiologic studies with iodinated contrast material should temporarily discontinue the combination sitagliptin/metformin product.

- In placebo-controlled, randomized trials saxagliptin and sitagliptin have produced significant reductions in baseline glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), and postprandial glucose (PPG) levels. Multiple studies involving sitagliptin in combination with metformin hydrochloride, as individual agents, have demonstrated an additive effect in glycemic control when compared to monotherapy with either sitagliptin or metformin hydrochloride; however, there are no published trials available to date, that assess the fixed-dose combination product. Additionally, there are no head to head trials comparing the available agents in this class.
A 2007 meta analysis of incretin-based therapies found that DPP-4 inhibitors as a class significantly decreased HbA1c compared with placebo (-0.74%; 95% CI, -0.85% to -0.62%) with similar efficacy as monotherapy or combination. However, DPP-4 inhibitors demonstrated slightly less efficacy in regards to glycemic outcomes when compared to other hypoglycemic agents.

- Guidelines from the American Diabetes Association/European Association for the Study of Diabetes state that lifestyle interventions and metformin are considered first line therapy for the treatment of patients with diabetes. If lifestyle interventions and the maximum tolerated dose of metformin fail to achieve or sustain glycemic goals, insulin or a sulfonylurea should be added. The second tier recommendations state that when hypoglycemia is particularly undesirable, the addition of exenatide or pioglitazone may be considered. The α-glucosidase inhibitors, amylin agonists, DPP-4 inhibitors and glinides are not included in the two tiers of preferred agents in the algorithm due to their lower or equivalent overall glucose-lowering effectiveness compared with the first- and second-tier agents, and/or due to limited clinical data or relative expense. These agents may be appropriate choices in selected patients.

- According to the algorithm for glycemic control released by the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) in 2009, antidiabetic treatment regimens should be based on a patient’s HbA1c. Specifically, patients with a level ≤7.5% may be able to achieve a goal of 6.5% with monotherapy, while patients with a level of > 7.6% should be initiated on combination therapy as they are less likely to achieve glycemic goals with monotherapy. In patients who are candidates for monotherapy, metformin hydrochloride, an α-glucosidase inhibitor, a DPP-4 inhibitor, or a TZD are recommended. Because of the established safety and efficacy of metformin hydrochloride, it is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy according to the AACE/ACE algorithm. When combination therapy is required, either due to HbA1c or failure of monotherapy, metformin is considered the cornerstone of combination therapy for most patients. When contraindicated, a TZD may be used as the foundation for combination therapy options. Due to the mechanism of action of metformin hydrochloride and TZDs, it is recommended that the second agent in combination therapy be an incretin mimetic or DPP-4 inhibitor due to their efficacy and safety in combination with metformin. The algorithm further states the incretin mimetics and DPP-4 inhibitors are associated with less hypoglycemia compared to the secretagogues. None of the currently available guidelines differentiates between agents in this class.

- DPP-4 inhibitors represent a novel approach in the management of type 2 diabetes and appear to have some advantages over other traditional oral antidiabetic agents. DPP-4 inhibitors are associated with a favorable side effect profile and also have a weight neutral effect. Unlike with sulfonylureas, the risk of hypoglycemia associated with the use of these agents is low due to the glucose-dependent nature of incretin hormone activity. Additionally, these agents have not been associated with the same increased risk of cardiovascular disease that has been observed with the thiazolidinediones. As mentioned earlier, DPP-4 inhibitors appear to improve the function of β-cells, and, although thiazolidinediones and metformin hydrochloride treat insulin resistance, they do not address the progressive decline in β-cell function that is observed in patients with type 2 diabetes. However, there is a lack of long-term safety and efficacy data with the DPP-4 inhibitors.
RECOMMENDATION

The DPP-4 inhibitors are FDA-approved as adjunct therapy to diet and exercise to improve glycemic control in adult patients with type 2 diabetes. In clinical trials the DPP-4 inhibitors have produced significant reductions in baseline HbA1c, FPG, and PPG levels both as monotherapy and in combination with other hypoglycemic agents. Clinical guidelines from the AACE/ACE state that metformin is the cornerstone of monotherapy and is considered the most appropriate initial choice for monotherapy for most patients. Other recommendations for patients who are candidates for monotherapy include α-glucosidase inhibitors, DPP-4 inhibitors or TZDs. In patients who require combination therapy, AACE/ACE guidelines recommend the second agent in combination therapy be an incretin mimetic or DPP-4 inhibitor due to their efficacy and safety in combination with metformin. None of the currently available clinical guidelines differentiate between the agents in this class and there are no head to head clinical trials available; therefore, the single-entity agents in this class can be considered therapeutic alternatives. It is recommended at least one single-entity DPP-4 inhibitor be available for use. Additionally, since clinical guidelines do not recommend this class of agents as first line therapy, it is recommended this class be subject to step therapy to ensure appropriate use.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

RE-REVIEW: DPP-4 INHIBITORS

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<td>Janumet® CC, QL</td>
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<tr>
<td>OnglyzaTM CC, QL</td>
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CLINICAL CRITERIA FOR DPP-4 INHIBITORS

Januvia® or Onglyza® will be approved for recipients who meet ALL of the following criteria:
- Diagnosis of type 2 diabetes
- Hemoglobin A1c > 6.5% (for initial approval only)
- Trial and failure of metformin (or sulfonylurea or TZD if recipient has adverse reaction, intolerance or contraindication to metformin)
- Requirement for trial and failure of metformin will be waived if recipient has Hemoglobin A1c > 7.6% AND patient is concomitantly receiving metformin, sulfonylurea or TZD

Janumet® will be approved for recipients who meet ALL of the following criteria:
- Diagnosis of type 2 diabetes
- Hemoglobin A1c > 6.5% (for initial approval only)
- Trial and failure of metformin
- Requirement for trial and failure of metformin will be waived if recipient has Hemoglobin A1c > 7.6%

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

Quantity Limits

<table>
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<tr>
<th>MEDICATION</th>
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<tr>
<td>OnglyzaTM</td>
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COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION
References
BACKGROUND

- The therapeutic class called the “anticonvulsants” encompasses over 20 different chemical entities, and includes hydantoins, succinimides and miscellaneous anticonvulsants.
- All of the agents in this class are FDA approved for the prevention and/or treatment of various seizure disorders either as monotherapy or adjunctive therapy. (Refer to Table 2a Med Metrics Therapeutic Class Review). Additionally, carbamazepine, divalproex sodium, lamotrigine and valproic acid are FDA approved for the treatment of bipolar disorder and divalproex, topiramate and valproic acid are approved for migraine prophylaxis. Pregabalin is FDA-approved for the treatment of fibromyalgia, diabetic neuropathic pain and postherpetic neuralgia in adult patients. Gabapentin also carries an FDA-approval for postherpetic neuralgia in adults and carbamazepine is approved for the treatment of trigeminal neuralgia.
- Anticonvulsants in general are associated with adverse events of GI upset, weight changes, ataxia, asthenia, tremor, somnolence, and dizziness.
  - The most common adverse effects seen with hydantoins are signs and symptoms of CNS depression such as ataxia, dizziness, and slurred speech. Hydantoins may also cause GI upset, gingival hyperplasia and dermatologic disorders such as rash or pruritis. Rarely hydantoins may cause Stevens-Johnson syndrome or disorders of the hematopoietic structure. Phenytoin may also cause nephrotoxicity or osteomalacia.
  - The most common adverse reactions with succinimides include ataxia, dizziness, GI upset, loss of appetite, and somnolence. Rare, but severe, adverse effects associated with the succinimides include disorders of the hematopoietic structure and Stevens-Johnson syndrome. Methsuximide may cause hematuria and proteinuria.
  - In addition to adverse events generally associated with all anticonvulsants, the miscellaneous anticonvulsants are associated with a wide range of adverse events. The following is a listing of agent specific adverse events:
    - Carbamazepine: hyponatremia, rash, thrombocytopenia, anemia, leukopenia
    - Gabapentin: nystagmus
    - Lacosamide: diplopia; atrial fibrillation, PR interval prolongation
    - Lamotrigine: blurred vision, diplopia; blood dyscrasias, life-threatening hypersensitivity reactions
    - Levetiracetam: upper respiratory symptoms, pancytopenia
    - Pregabalin: peripheral edema, blurred vision, angioedema
    - Primidone: megaloblastic anemia (rare), thrombocytopenia
    - Oxcarbazepine: hyponatremia, dermatologic reactions, angioedema
    - Rifaximin: QT interval shortening
    - Tiagabine: seizures in patients without seizure disorder
    - Topiramate: metabolic acidosis, paresthesias, nephrolithiasis, myopia, secondary angle-closure glaucoma, oligohydrosis, hyperthermia
    - Valproic acid/divalproex sodium: thrombocytopenia, bone marrow changes, leukopenia, transient neutropenia, erythroblastopenia, fatal hepatotoxicities, life threatening pancreatitis, hyperammonemia
    - Vigabatrin: anemia, nystagmus, peripheral neuropathy, arthralgia, myalgia, upper respiratory symptoms
    - Zonisamide: life threatening skin rash, hepatic necrosis, agranulocytosis, aplastic anemia, oligohydrosis, hyperthermia, heat stroke
  - The antiepileptic drugs carry the following black box warnings:
    - Carbamazepine may cause aplastic anemia and agranulocytosis
Felbamate use is associated with a marked increase in the risk of incidence of potentially fatal aplastic anemia. Additionally, use of felbamate has been associated with acute hepatic failure which has resulted in both liver transplant and death.

Lamotrigine may cause serious skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Valproate may cause hepatotoxicity, pancreatitis and teratogenicity.

Vigabatrin may cause permanent vision loss. Because of the risk of permanent vision loss, vigabatrin is available only through a special restricted distribution program called SHARE.

- The following is a list of agents and their associated contraindications:
  - Carbamazepine: history of bone marrow depression, or known sensitivity to any tricyclic antidepressant, coadministration with nefazodone
  - Ethotoin: hepatic abnormalities or hematologic disorders
  - Felbamate: history of blood dyscrasias or hepatic dysfunction
  - Primidone: porphyria
  - Rufinamide: familial short QT syndrome
  - Valproate therapy: hepatic disease or known urea cycle disorders

- The antiepileptic drugs may increase the risk of suicidal thoughts or behavior in patients taking these agents for any indication. Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior. Additionally, none of the anticonvulsant agents should be abruptly discontinued due to the possibility of increasing seizure frequency.

- There are numerous clinically significant drug interactions with the anticonvulsants. Refer to Tables 7a-7d in the Med Metrics Therapeutic Class Review for a complete listing of drug-drug interactions.

- Due to the numerous agents, there is a large volume of clinical trial data available in this class. With the exception of Stavzor®, all of the agents in this class have been proven to be safe and effective for their FDA-approved indications. Valproic acid delayed-release capsules (Stavzor®) was FDA approved based on a bioequivalence comparison to Depakote® though Stavzor® is not AB rated to Depakote®. Safety and efficacy studies are not available with Stavzor®.
The chart below outlines the place in therapy for the anticonvulsant agents based on seizure type according to the most recent clinical guidelines.

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<tr>
<th>Seizure Type</th>
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* United States Expert Opinion 2005
† National Institute for Clinical Excellence (NICE) 2004
‡ International League Against Epilepsy (ILAE) 2006
§ American Academy of Neurology (AAN)/American Epilepsy Society 2004

The European Federation of Neurological Societies (EFNS) recently revised their guideline on the drug treatment of migraine. The updated guideline states prophylaxis for migraines should be considered when the quality of life, business duties, or school attendance are severely impaired; frequency of attacks per month is ≥2; migraine attacks do not respond to acute drug treatment; or frequent, very long, or uncomfortable auras occur. According to the EFNS, the drugs of first choice for migraine prophylaxis are metoprolol, propranolol, topiramate and valproic acid.

Anticonvulsant drugs have been used for the management of pain since the 1960s and some have FDA approval for the treatment of diabetic peripheral neuropathy, postherpetic neuralgia, trigeminal neuralgia and fibromyalgia. Guidelines for the treatment of diabetic peripheral neuropathic pain published by the American Society of Pain Educators recommend duloxetine, opioids, pregabalin and tricyclic antidepressants as first-line therapy, based on the number of available placebo-controlled trials with these agents; however, only pregabalin and duloxetine are FDA-approved for this indication. Guidelines from the EFNS on the treatment of neuropathic pain state that treatments with established efficacy for postherpetic neuralgia include gabapentin, opioids, pregabalin and tricyclic antidepressants, with gabapentin, pregabalin or a tricyclic antidepressant considered first-line agents. For the treatment of trigeminal neuralgia, guidelines from the AAN/EFNS state that carbamazepine is considered the treatment of choice. Guidelines from the European League Against Rheumatism state that tramadol is recommended for...
the treatment of pain in fibromyalgia and that analgesics, weak opioids, antidepressants (amitriptyline, duloxetine, fluoxetine) and pregabalin can reduce pain associated with fibromyalgia and should be considered for treatment.

- Current practice parameters from the AAN state that ACTH is probably an effective agent in the short-term treatment of infantile spasms and vigabatrin is possibly effective. Vigabatrin has received FDA-approval for this indication since the publication of these guidelines and is currently the only anticonvulsant FDA-approved for the treatment of infantile spasms. The manufacturers of Acthar® gel have submitted an NDA to the FDA, and on May 11, 2010, members of the US FDA Peripheral and Central Nervous System Drugs Advisory Committee endorsed the NDA for the treatment of infantile spasms.

**RECOMMENDATION**

All of the agents in this class are FDA approved for the prevention and/or treatment of various seizure disorders either as monotherapy or adjunctive therapy. International and national consensus guidelines consider carbamazepine, divalproex, ethosuximide, gabapentin, lamotrigine, oxcarbazepine, phenytoin, topiramate and valproic acid as first-line agents for the treatment of seizures; though the agents of choice vary by seizure type. Patient responses may vary from agent to agent; therefore, it is necessary to have multiple agents for each seizure type. For this reason, it is recommended that the above listed chemical entities recommended as first line therapy for seizures should all be available for use.

Due to the significant safety concerns (aplastic anemia, hepatotoxicity) and lack of endorsement by current treatment guidelines, felbamate can be considered an inferior agent in this class. It is recommended felbamate be reserved for patients with refractory seizures in which the benefits of therapy outweigh the risks.

Vigabatrin is the only anticonvulsant currently FDA-approved for the treatment of infantile spasms but its use is associated with the potential for permanent vision loss; therefore, it is recommended vigabatrin be subject to step therapy criteria.

In addition to its indication as adjunct therapy for the treatment of partial seizures, pregabalin is FDA-approved for the treatment of fibromyalgia, diabetic neuropathic pain and postherpetic neuralgia in adult patients. Current clinical guidelines recommend pregabalin as first line therapy for the treatment of diabetic peripheral neuropathy along with duloxetine, opioids, and tricyclic antidepressants. Pregabalin is also recommended as first line therapy for postherpetic neuralgia along with gabapentin and tricyclic antidepressants. Guidelines for the treatment of fibromyalgia recommend tramadol for pain and state that analgesics, weak opioids, antidepressants and pregabalin can reduce pain associated with fibromyalgia and should be considered for treatment. Given the differing place in therapy for pregabalin dependent on indication, it is recommended that pregabalin be subject to clinical criteria.

**COMMITTEE VOTE:**

APPROVED    DISAPPROVED    APPROVED with MODIFICATION
### CNS AGENTS

#### RE-REVIEW: ANTICONVULSANTS

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*Agents moving to NP status will be grandfathered via 60 day look-back

#### Clinical Criteria for topiramate/Topamax®

- Unrestricted in patient ≤ 20 years old for all indications.
- For those > 20 years old, unrestricted in the treatment of seizures

*For migraine prophylaxis must meet ALL of the following criteria:

- Diagnosis of frequent migraines (defined as 4 or more migraines per month) that fail typical abortive therapy or are so severe that having one leads to debility (hemiplegic migraine, seizure, etc.): **AND**

- Has tried and failed migraine prophylaxis with a beta-blocker AND amitriptyline

  **Approval may also be given if the prescriber has a reason not to try both classes of medications, including:**

  1. Intolerance to one or more medications.
  2. Failure of a similar medication within the class.
  3. History of seizure and would like to combine therapy.
  4. Concerns in pregnant women

*For Bipolar Disorder must meet the following criteria:

- Has tried and failed treatment with lithium, **AND** lamotrigine OR valproate

  **(NOTE:** Failure on valproate due to weight gain would be indicated by an increase in baseline weight by ≥ 10 pounds or ≥ 7%.)

- Use must be in combination with an atypical antipsychotic, unless the recipient has a history of intolerance or contraindication to atypical antipsychotics.

SXC recommends removing the above clinical criteria.
CNS AGENTS

COMMITTEE VOTE:

APPROVED          DISAPPROVED  APPROVED with MODIFICATION

Clinical Criteria for Lamictal® ODT

Lamictal® ODT will be approved if ONE of the following criteria has been met:
  o Patient is unable to swallow OR
  o Patient is unable to absorb medications through the GI tract

This criteria is listed only for informational purposes as it was approved by PAC at the Aug 2010 meeting.

Clinical Criteria for Lyrica®

Lyrica® will be approved if ONE of the following criteria has been met:
  • Diagnosis of seizure disorder AND recipient has tried and failed at least TWO preferred anticonvulsants
  • Diagnosis of diabetic peripheral neuropathy
  • Diagnosis of fibromyalgia
    o Recipient MUST have tried and failed, or have contraindication, or intolerance to:
      ▪ A tricyclic antidepressant or muscle relaxant, AND
      ▪ At least ONE of the following: SSRI, preferred SNRI, duloxetine, or gabapentin
  • Diagnosis of postherpetic neuralgia or other non-diabetic peripheral neuropathy
    o Recipient MUST have tried and failed, or have contraindication, or intolerance to:
      ▪ A tricyclic antidepressant AND
      ▪ Gabapentin

COMMITTEE VOTE:

APPROVED          DISAPPROVED  APPROVED with MODIFICATION

Step Therapy for Felbatol®

Felbatol® will be approved if ONE of the following criteria has been met:
  1. Used as adjunctive therapy in Lennox-Gastaut Syndrome AND there has been a contraindication to, or trial and failure of, two of the following medications:
    • Valproic acid/Divalproex sodium
    • Lamotrigine
    • Topiramate
  2. Used for the treatment of partial seizures AND there has been a contraindication to, or trial and failure of, three of the following medications:
    • Carbamazepine
    • Gabapentin
    • Lamotrigine
    • Oxcarbazepine
    • Phenytoin
    • Topiramate
    • Valproic acid/Divalproex sodium

Of note, Felbatol® will not be approved for patients with a history of blood dyscrasia or liver disease unless the prescriber can make a compelling clinical case demonstrating that the benefits of the drug outweigh the risks.

COMMITTEE VOTE:

APPROVED          DISAPPROVED  APPROVED with MODIFICATION
### Clinical Criteria for Sabril®

Sabril® will be approved if ONE of the following criteria has been met:
- Diagnosis of seizure disorder AND recipient has tried and failed at least TWO preferred anticonvulsants
- Diagnosis of infantile spasms:
  - Recipient MUST have tried and failed, or have contraindication, or intolerance to adrenocorticotropic hormone (ACTH)

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### Clinical Criteria for Dilantin Infatab®

Dilantin Infatab® will be approved for recipients who meet ALL of the following criteria:
- Inability to swallow solid oral dosage forms, AND
- Recipient, or caregiver, has physical limitation such that measuring of suspension may result in dosing errors

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### Clinical Criteria for Neurontin® solution

Neurontin® solution will be approved for recipients who meet ALL of the following criteria:
- Inability to swallow solid oral dosage forms, AND
- Inability to open capsule and empty contents in food or drink

### COMMITTEE VOTE:

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### References


BACKGROUND

- The immunosuppressants are an important category of drugs for the increase in survival after organ transplant. Additionally, selected agents are also used in the treatment of autoimmune disorders. The agents can be grouped into main three categories: antimetabolites (azathioprine, mycophenolate mofetil and mycophenolate sodium), calcineurin inhibitors (cyclosporine, cyclosporine microemulsion and tacrolimus) and mammalian target of rapamycin inhibitors (everolimus and sirolimus).
- The antimetabolites act to reduce the synthesis of purines which are required for T-and B-cells for proliferation.
- The calcineurin inhibitors act to inhibit the phosphatase activity of calcineurin which leads to a reduced transcription of cytokines involved in T-cell activation.
- The mammalian target of rapamycin inhibitors acts to inhibit the activation of the mammalian target of rapamycin which reduces the proliferation of T- and B-cells.
- FDA-Approved Indications:

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RA=Rheumatoid arthritis, MTX=methotrexate, CI=contraindication

- All of the immunosuppressant agents are associated with numerous common & severe adverse effects. The more common adverse effects are listed below.
  - Azathioprine: gastritis, nausea & vomiting
  - Cyclosporine (& microemulsion): hypertension, hirsuitism, gingival hyperplasia, nausea, vomiting, diarrhea
  - Everolimus: hypertension, constipation, gastrointestinal (GI) upset
  - Mycophenolate (both salts): hypertension, nausea, vomiting, diarrhea, asthenia, tremor, hyperlipidemia
  - Sirolimus: hypertension, constipation, nausea, vomiting, rash
  - Tacrolimus: alopecia, constipation, nausea, vomiting, anemia, headache
- All immunosuppressant agents carry black boxed warnings; summaries listed below:
  - Azathioprine: increased risk of neoplasms; physicians should be well trained in potential mutagenic and hematological toxicities.
  - Cyclosporine: physician should be trained in use of immunosuppressive therapy and have adequate resources available; administer with corticosteroids; therapy may cause increased risk of infection and lymphomas.
  - Cyclosporine microemulsion: physician should be trained in use of immunosuppressive therapy and have adequate resources available; therapy may cause increased risk of infection, neoplasms, hypertension & nephrotoxicity; warning about differences in bioavailability between cyclosporine & cyclosporine microemulsion.
IMMUNOLOGIC AGENTS

- Everolimus: physician should be trained in use of immunosuppressive therapy and have adequate resources available; therapy may cause increased risk of infection, malignancies, and kidney arterial & venous thrombosis.
- Mycophenolate (both salts): physician should be trained in use of immunosuppressive therapy and have adequate resources available; therapy may cause increased risk of infection and malignancies; use during pregnancy is associated with pregnancy loss and congenital malformations.
- Sirolimus: physician should be trained in use of immunosuppressive therapy and have adequate resources available; therapy may cause increased risk of infection and malignancies; safety & efficacy in liver and lung transplants has not been established fully.
- Tacrolimus: physician should be trained in use of immunosuppressive therapy and have adequate resources available; therapy may cause increased risk of infection and malignancies.

- Azathioprine increases the risk of severe bone marrow suppression including leukopenia, thrombocytopenia, macrocytic anemia and pancytopenia.
- Cyclosporine & cyclosporine microemulsion can cause nephrotoxicity and hepatotoxicity and hypertension may develop in patients taking either agent. Additionally, cyclosporine microemulsion is contraindicated in rheumatoid arthritis and psoriasis patients with abnormal renal function, uncontrolled hypertension or malignancies.
- Patients with malabsorption issues may have difficulty achieving adequate cyclosporine levels.
- Everolimus has been associated with angioedema, delays in wound healing, fluid accumulation, hyperlipidemia, proteinuria, new onset diabetes mellitus after transplant and infertility.
- Mycophenolate mofetil and mycophenolate sodium have been associated with severe neutropenia and pure red cell aplasia. Severe gastrointestinal bleeding has been observed in some patients.
- Sirolimus has been associated with angioedema, delays in wound healing, fluid accumulation, hyperlipidemia, proteinuria and interstitial lung disease.
- Tacrolimus has been associated with new onset diabetes mellitus after transplant, hyperkalemia, hypertension and myocardial hypertrophy. Tacrolimus can also cause nephrotoxicity and neurotoxicity, especially at high doses.
- There are numerous drug-drug interactions with all of the immunosuppressant agents. Each agent should be individually evaluated in a therapeutic regimen. (Please refer to Table 7 in the MedMetrics full class review for a listing of drug-drug interactions.)
- Clinical trials have consistently demonstrated efficacy of all immunosuppressive agents, head to head comparisons & expert consensus from clinical guidelines have identified first line agents in the antimetabolite and calcineurin inhibitor categories.

Kidney Transplant

- Knight et al conducted a meta analysis reviewing kidney transplant recipients receiving either mycophenolate mofetil or azathioprine (N=3143). Primary endpoint was identified as acute rejection, patient & graft survival, and side effects. Mycophenolate mofetil significantly reduced the risk of acute rejection compared to azathioprine (P<0.0001). There was no significant difference in death between the mycophenolate mofetil and azathioprine groups (HR, 1.02; 95% CI, 0.68 to 1.53; P=0.92). There was a significant reduction in the hazard of graft loss including death in the mycophenolate mofetil group (HR, 0.76; P=0.037). There was no significant difference between groups in graft function as measured by serum creatinine (P=0.86). There was also significant difference between groups in graft function as measured by glomerular filtration rate (P=0.21). There was a significantly higher risk of diarrhea in the mycophenolate mofetil group (P<0.0001). There were no significant differences in total infection (P=0.75), cytomegalovirus infection (P=0.53), anemia (P=88), leukopenia.

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(P=0.52) or malignancy (P=0.48) between the mycophenolate mofetil and azathioprine groups.

- Through a Cochrane review, Webster et al evaluated kidney transplant patients receiving either cyclosporine or cyclosporine microemulsion versus tacrolimus (N=4102). Primary endpoints were graft loss (censored for death), acute rejection, & steroid resistant rejection. Secondary endpoints included death, graft loss including death with functioning allograft, graft function, malignancy, infectious complications, chronic allograft nephropathy, and incidence of diabetes and side effects of treatment. There was a significant reduction in the tacrolimus group for graft loss censored for death at two time points, six months (P=0.008) and three years (P=0.03). Acute rejection was significantly less in the tacrolimus group at six months (P<0.00001), one year (P<0.00001) and two years (P<0.00001). At six months, there was 55% reduction in steroid resistant patients for tacrolimus treated patients (P<0.00001). There were no significant differences in death, graft loss including death with functioning allograft, malignancy, and infectious complications. At six months, tacrolimus treated patients had a significantly lower creatinine (P value not reported). The risk of new onset diabetes mellitus was significantly increased in the tacrolimus treated patients at six months (P=0.003), one year (P=0.02) and three years (P<0.0001).

- Additionally, different formulations of immunosuppressant agents have demonstrated varying pharmacokinetic profiles when compared to one another.
  - A study comparing the different formulations of cyclosporine was conducted to evaluate the effect on clinical outcomes. In cyclosporine microemulsion treated patients there was less acute rejection compared to the cyclosporine group at one year (34.35 vs 46.9%; P=0.037). The time to reach therapeutic blood concentrations was shorter in the cyclosporine microemulsion group (2 days versus 4 days; P=0.0017). Survival was similar between the groups at one year.
  - A study compared a 1 to 1 mg conversion from Neoral® (cyclosporine microemulsion) to the generic, Gengraf® (cyclosporine microemulsion). There was a significant difference in trough concentrations from baseline to two weeks (P=0.005) and over 17% of patients switched to the generic formulation required dose adjustments. After dose adjustments there was no significant difference in trough concentrations at four weeks in any group.

  - A combination of immunosuppressive medications including a calcineurin inhibitor (cyclosporine, cyclosporine microemulsion or tacrolimus) and antimetabolite agent (azathioprine or mycophenolate) with or without corticosteroids is recommended for maintenance immunosuppression.
    - Tacrolimus is suggested as the first line calcineurin inhibitor.
    - Mycophenolates are suggested as the first-line antimetabolite agents.
    - If mammalian target of rapamycin inhibitors are used, it is recommended that they should not be started until graft function is established and surgical wounds are healed.

  - The choice of calcineurin inhibitor should be based on individual patient profiles and the relative importance of side effects.
  - Mycophenolate mofetil is recommended as part of an immunosuppressive regimen when:
    - Intolerance to calcineurin inhibitor, especially nephrotoxicity leading to risk of chronic graft dysfunction.
    - Very high risk of nephrotoxicity requiring reducing or withdrawing calcineurin inhibitor.
Sirolimus is recommended as an option as part of immunosuppressive regimen when there is intolerance to calcineurin inhibitor requiring complete withdrawal of the agent. Of note, everolimus was not available when at the time of publication of this guideline.

- International Society for Heart and Lung Transplantation clinical guidelines (ISHLT) do not provide specific recommendations for first line agents: however, the guidelines discuss utilization and monitoring of cyclosporine, tacrolimus, mycophenolate, and mammalian target of rapamycin inhibitors.
- Additionally, clinical guidelines from American College of Gastroenterology Management of Crohn’s Disease and Ulcerative Colitis practice guidelines and the American Academy of Dermatology’s Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis all include azathioprine as a treatment alternative in more severe disease.

**RECOMMENDATION**

Immunosuppressants are a primary part of the pharmacologic regimens used to prevent organ rejection post-transplant. Selected immunosuppressants are also utilized in the treatment of autoimmune diseases. The immunosuppressants are identified by three main categories: antimetabolites, calcineurin inhibitors, and mammalian target of rapamycin inhibitors. Clinical trials have consistently demonstrated efficacy of all immunosuppressive agents and documented significant adverse effects with all agents. All agents carry black box warnings primarily regarding risk of infection, malignancies and other serious adverse effects. Specifically for the prevention of kidney transplant rejection, head to head comparisons & expert consensus from Kidney Disease Improving Global Outcomes Transplant Workgroup clinical guidelines have identified first line agents in the antimetabolite and calcineurin inhibitor categories. The NICE kidney transplant guidelines and ISHLT heart & lung transplant guidelines do not recommend one agent as first line therapy over another, however the NICE guidelines do recommend mammalian target of rapamycin inhibitors be used when therapy with calcineurin inhibitors fail. Different formulations of immunosuppressant agents have demonstrated varying pharmacokinetic profiles when compared to one another. Additionally, clinical guidelines from the American College of Gastroenterology for Crohn’s disease and Ulcerative Colitis and the ADA’s guidelines for Psoriasis and Psoriatic Arthritis include azathioprine as alternative treatment for severe disease. Therefore, it is recommended that at least azathioprine, cyclosporine and cyclosporine microemulsion, mycophenolate mofetil, and tacrolimus be available for use. Due to the complex management of prevention of transplant rejection, it is also recommended that the prior authorization process can be bypassed via submission of ICD-9 transplant diagnosis code.

**COMMITTEE VOTE:**

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**REVIEW: IMMUNOSUPPRESSANTS**

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<tr>
<td>Zortress® CC (everolimus)</td>
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**Immunosuppressants Clinical Criteria:**

Non-Preferred agents will be approved if the following criteria is met:

- All transplant recipients will be allowed a prior authorization for any drug. (Note: The PA requirement may be overridden at POS via an ICD-9 code override)
- New recipients requiring immunosuppressants for autoimmune diseases (i.e. rheumatoid arthritis, plaque psoriasis) will be required to have tried and failed or have a contraindication to one of the preferred agents.
- Cellcept may be approved without requirement of a failure to one of the preferred agents (cyclosporine (CYA) product or azathioprine) if the diagnosis is Myasthenia Gravis (MG) or pemphigus vulgaris.

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**Current Approvable Transplant ICD-9 Codes:**

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<td>Specified transplanted organ, other</td>
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</table>

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**References**

7. Knight SR, Russell NK, Barcena L, Morris PJ. Mycophenolate mofetil decreases acute rejection and may improve graft survival in renal transplant recipients when compared...
IMMUNOLOGIC AGENTS


RE-REVIEW: TOPICAL IMMUNOMODULATORS

BACKGROUND

- Atopic dermatitis, also referred to as atopic eczema, is a chronic, highly pruritic, and relapsing inflammatory skin condition. The pathogenesis of atopic dermatitis is due to impaired epidermal barrier function related to structural and functional abnormalities in the skin as well as cutaneous inflammatory response to environmental factors. Pruritus is one of the most common symptoms of atopic dermatitis and causes an “itch-scratch” cycle that compromises the epidermal barrier which results in water loss, xerosis, microbial colonization and secondary infection. The topical immunomodulators are a second line therapy in the treatment of atopic dermatitis; currently available agents include pimecrolimus and tacrolimus.
- The mechanism of action of both agents is not completely understood, however, it has been demonstrated that both agents inhibit the phosphatase activity of calcineurin. Inhibition of calcineurin inhibits the transcription of cytokines involved in T-cell activation. Both agents have been shown to prevent the release of inflammatory cytokines and mediators from mast cells stimulated by antigen/immunoglobulin E.
- FDA-Approved Indications:
  - Pimecrolimus is indicated as second-line therapy for short-term and noncontinuous chronic treatment of mild to moderate atopic dermatitis in nonimmunocompromised patients 2 years of age and older who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.
  - Tacrolimus is indicated as second-line therapy for the short-term and noncontinuous chronic treatment of moderate to severe atopic dermatitis in nonimmunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when
those treatments are not advisable. (Both 0.03% and 0.1% ointment are indicated for adults, and only the 0.03% ointment is indicated for children 2 to 15 years of age)

- The most common adverse effects for pimecrolimus include sensation of skin burning, headache, fever and pruritis. More severe adverse effects include basal and squamous cell carcinoma, malignant melanoma and septic arthritis.
- The most common adverse effects for tacrolimus include erythema, pruritis, headache, and flu like symptoms. More severe adverse effects include bullous impetigo, headache, and malignant lymphoma.
  - Both agents carry the same black boxed warning: long term safety of topical calcineurin inhibitors has not been established; rare cases of malignancy (skin cancer and lymphoma) have been reported with use; continuous long term use should be avoided and agents should not be used in patients less than 2 years old.
  - Pimecrolimus and tacrolimus use should be avoided in patients with malignant and pre-malignant skin conditions.
  - Pimecrolimus and tacrolimus should not be used in patients with Netherton’s syndrome or other skin diseases where there is potential for increased systemic absorption.
  - There is a lack of safety and efficacy data for the use of pimecrolimus and tacrolimus in immunocompromised patients and should be avoided.
  - A definitive causal link between the topical immunosuppressants and the incidence of malignancy is not yet fully established. Caution should be used to avoid long term continuous therapy.

- Due to limited systemic absorption with immunomodulators applied topically, drug interactions with other systemically absorbed drugs are unlikely to occur and none are documented with these agents.
- Several smaller head to head clinical trials have been conducted comparing the two available agents.
  - Fleisher et al evaluated tacrolimus versus pimecrolimus in the treatment of adults with moderate to severe atopic dermatitis (N=281). The primary endpoint was the percent change in Eczema Area Severity Index (EASI) score from baseline to week six or end of study. The tacrolimus group had significantly greater improvement in EASI score than the pimecrolimus group (a reduction of 57% vs 39% at study end; \(P=0.0002\)). Adverse events reported were comparable for both treatment groups, and they occurred at a similar frequency (\(P=0.823\)). The most commonly reported adverse events were application-site burning and application-site pruritus. Two tacrolimus-treated patients and four pimecrolimus-treated patients discontinued study due to adverse effects (\(P=0.447\)).
  - Abramovits et al also compared tacrolimus versus pimecrolimus in adult patients with mild to severe atopic dermatitis (N=188). Primary endpoint was percent change in EASI score from baseline to end of study. Tacrolimus-treated patients had significantly greater improvement in EASI score compared with pimecrolimus-treated patients at the end of study (59% vs 43% reduction; \(P=0.01\)). The percent improvement from baseline in EASI score was also significantly greater for the tacrolimus group than the pimecrolimus group at weeks 1 and 3 (\(P=0.05\) and \(P=0.03\) respectively). Patient's assessment of itch decreased by half in the tacrolimus ointment group from a baseline value of 6 cm to 3 cm and a similar decrease was also observed with pimecrolimus cream (\(P\) value not reported and data not shown). Overall, there were no significant differences in adverse events between the groups (\(P=0.19\)). The most common adverse events were application-site burning and application-site itching for both treatment groups (\(P=0.33\) and \(P=0.41\)).
Paller et al conducted a meta analysis comparing the two agents in patients greater than 2 years old with mild to severe atopic dermatitis (N=1065). Primary endpoint was defined as change from baseline in EASI score at week six. The change in baseline in EASI score at week 6 was significantly greater in the tacrolimus groups compared to the pimecrolimus groups in adults (54.1% and 34.9%, respectively; \(P<0.0001\)), children with moderate to severe disease (67.2% and 56.4%, respectively; \(P=0.04\)), and in the combined analysis (52.8% and 39.1%, respectively; \(P<0.0001\)). The most common adverse effects in all studies were local application site reactions including burning and stinging. In both pediatric studies, there were no significant differences observed in adverse effects between the tacrolimus and pimecrolimus groups (\(P\) values not reported). In the adult study, application site burning occurred more frequently in the tacrolimus group compared to the pimecrolimus group (\(P=0.02\)) early in treatment, but by week one there were no significant differences observed between the groups (\(P\) value not reported).

Kemmers et al compared pimecrolimus to tacrolimus 0.03% in patients 2-17 years of age (N=141, 6 weeks). Primary endpoint was incidence of local site reactions. Application site reactions were experienced by 24% of patients in the pimecrolimus group and 26% in the tacrolimus group (\(P\) value not reported). The authors found no difference in the incidence of application site reactions between the two topical immunomodulators. However, itching was reported at a significantly higher rate in the tacrolimus group than the pimecrolimus group (20% versus 8%; \(P=0.073\)).

- The American Academy of Dermatology, Clinical Guidelines Task Force: Guidelines of Care for Atopic Dermatitis state topical corticosteroids are the standard of care to which other treatments are compared. Additionally, the guidelines state calcineurin inhibitors (pimecrolimus and tacrolimus) have demonstrated efficacy in reducing the severity, extent and symptoms of atopic dermatitis in adults and children. The long-term safety of these agents is unknown, including the potential for malignancy and immunosuppression.

- The Joint Task Force on Practice Parameters in Collaboration with the American College of Allergy, Asthma and Immunology (ACAAI), the American Academy of Allergy, Asthma, and Immunology (AAAAI), and the Joint Council of Allergy, Asthma and Immunology (JCAAI) also recommends topical steroids as an effective treatment for atopic dermatitis. Additionally the Joint Task force state tacrolimus is effective for mild to moderately severe atopic dermatitis and pimecrolimus can decreases the number of flares of atopic dermatitis, reduce the need for corticosteroids, and control pruritus.

- Lastly, the British Association of Dermatology recommends topical corticosteroids as first line therapy and recommends topical immunomodulators when patient has been intolerant to or has a contraindication to topical corticosteroids.

**RECOMMENDATION**

The topical immunomodulators are indicated as second line therapy for mild to moderate atopic dermatitis and moderate to severe atopic dermatitis. Clinical trials have consistently demonstrated efficacy of the agents. National and international consensus guidelines recommend topical corticosteroids as first line therapy for atopic dermatitis. Currently, there is concern that continuous utilization of topical immunomodulators may be associated with more severe & long term adverse effects such as malignancies. Further studies are needed to fully evaluate the long-term safety of these agents. Therefore it is recommended that at least one topical immunomodulator be available for use, with the class subject to step therapy criteria to ensure safety and appropriate use.

**COMMITTEE VOTE:**

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IMMUNOLOGIC AGENTS

RE-REVIEW: TOPICAL IMMUNOMODULATORS

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Step Therapy for Topical Immunomodulators:

Step Therapy for Elidel®:
- Patient must have diagnosis of mild to moderate atopic dermatitis.
- Patient must have history of a therapeutic failure on a corticosteroid, but requirement is waived if treatment is for face or groin.

Step Therapy for Protopic®:
- Patient must have a diagnosis of moderate to severe atopic dermatitis.
- Patient must have history of a therapeutic failure on a corticosteroid, but requirement is waived if treatment is for face or groin.
- For Protopic® 0.1% the patient must be greater than or equal to 16 years of age.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

References

12. Primary Care Dermatology Society and British Association of Dermatologists. Guidelines for the management of atopic eczema. Available at: http://www.allergyparameters.org/file_depot/0-10000000/30000-
BACKGROUND

- Glaucoma is an optic neuropathy which causes gradual degeneration of the cells making up the optic nerve. Glaucoma initially manifests as visual field loss and may progress to blindness. It is the leading cause of irreversible blindness and second leading cause of vision loss. Treatment of glaucoma currently focuses on decreasing intra-ocular pressure (IOP) by laser therapy, surgery or medical intervention. Ophthalmic beta blockers are a primary treatment option for the management of glaucoma. Currently available agents include: betaxolol, carteolol, levobunolol, metipranolol, timolol, and timolol maleate.
- Ophthalmic beta blockers act to decrease aqueous humor production.
- FDA Approved Indications:
  - Betaxolol: treatment of chronic open angle glaucoma or ocular hypertension
  - Carteolol: treatment of chronic open angle glaucoma or ocular hypertension either alone or in combination with other IOP lowering therapies
  - Levobunolol: treatment of chronic open angle glaucoma or ocular hypertension
  - Metipranolol: for the reduction of IOP in patients with open angle glaucoma or ocular hypertension
  - Timolol: treatment of elevated IOP in patients with open angle glaucoma or ocular hypertension
- The most common adverse effects seen with ophthalmic beta blockers are primarily ocular in nature and are similar between the agents; adverse effects include blurred vision, transient ocular discomfort, burning sensation, and tearing.
  - Due to timolol's potential cardiac and pulmonary effects, timolol is contraindicated in patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock.
  - Asthmatic attacks and pulmonary distress have been reported with the use of some beta-blocking agents. Caution should be exercised in the treatment of glaucoma in patients with excessive restriction of pulmonary function.
  - Due to limited systemic absorption ophthalmic beta blockers should not be used in combination with each other or with oral beta-blockers.
  - Ophthalmic beta blockers have low incidence of systemic absorption and no significant drug-drug interactions have been identified.
- Head-to-head trials in the ophthalmic beta-blockers class involving patients with open-angle glaucoma or ocular hypertension show that all treatments are efficacious in decreasing IOP from baseline; however, various results were seen when groups were compared to each other.
  - Evans et al compared betaxolol to timolol in patients with primary open angle glaucoma (n=26). The study was conducted over a 16 week period with alternating 4 week treatment periods & 4 week washout periods. The primary endpoint was change in IOP from baseline/washout period. The timolol group had a significant reduction in IOP when compared to baseline (22.2 mmHg vs 17.7 mmHg; \( P=0.007 \)). However, the betaxolol group did not show a significant change in IOP (21.7 mmHg vs 20.0 mmHg; \( P=0.09 \)). Neither drug produced significant changes with regards to heart rate, blood pressure, and visual field sensitivity.
  - Berry et al also compared betaxolol versus timolol in patients with IOP with or without glaucoma (N=46). Primary endpoint was change in IOP from baseline and patients in need of adjunctive therapy with pilocarpine or epinephrine. The decrease in IOP from baseline was statistically significant for both drugs (\( P<0.05 \)), and there was no statistically significant difference seen between the two groups (\( P \) value not reported). IOP was controlled without adjunctive therapy in 35% of the betaxolol group and 46% of the timolol group, this difference was not found to be significant (\( P>0.05 \)).
OPHTHALMIC AGENTS

- Krieglstein et al compared levobunolol versus metipranolol in patients with open angle glaucoma or ocular hypertension (N=46). Primary endpoint was change in mean IOP from baseline. At each visit both groups had significant decreases from baseline in mean IOP, however no significant between group differences were seen at any visit or for overall mean change (P values not reported).

- Watson et al compared betaxolol versus carteolol versus timolol in patients with primary open angle glaucoma (N=153). The primary endpoint was change in IOP. The initial IOP fell from an average of 27.8 mmHg to an average of 20.6 mmHg after the fourth visit (month 12). Carteolol and timolol achieved greater reductions in IOP than betaxolol initially and maintained this difference through the follow up period (P value not reported). Eventually betaxolol achieved the same level of IOP after 12 months.

- Shedden et al compared timolol gel forming solution (GFS) versus timolol solution in patients with open angle glaucoma or ocular hypertension (N=286). The primary endpoint was change in IOP from baseline. Secondary endpoints were adverse events, change in heart rate and blood pressure. No statistically significant differences between the two treatment groups were seen with regard to decreases in IOP. There were significantly more reports of blurred vision in the timolol GFS group than the timolol group (29% vs 18%; P=0.04) as well as the incidence of tearing (7% vs 1%; P=0.04). Burning and/or stinging was reported at a significantly higher rate in the timolol group when compared to the timolol GFS group (22% vs 12%; P=0.04). At week 12, the decrease in mean heart rate was significantly less in the timolol GFS group when compared to the timolol group (-1.1 vs -4.2 beats per minute; P=0.024). At week 24 the decrease in mean heart rate was less for the timolol GFS group, however this was not found to be significant (-1.1 vs -3.6 beats per minute; P=0.051). The mean change in blood pressure in both groups ranged from -4.1 mmHg to 0.8 mmHg and was not found to be statistically significant between the two groups (P>0.05).

The American Academy of Ophthalmology Preferred Practice Patterns for Primary Open Angle Glaucoma state that prostaglandin analogs and beta blockers are the most commonly used agents for the treatment of open angle glaucoma. AAO guidelines state prostaglandins are the most effective agents for lowering IOP and should be considered first line therapy unless contraindicated. The National Institute for Clinical Excellence (NICE) Glaucoma and Ocular hypertension guidelines also state that first line therapy should consist of ophthalmic beta blockers and ophthalmic prostaglandin analogues. Both guidelines state if initial therapy is unsuccessful at lowering IOP then pharmacological agents should be switched or combination therapy should be utilized.

RECOMMENDATION
Ophthalmic beta blockers are a primary treatment option for the management of glaucoma. Head-to-head trials in the ophthalmic beta-blockers class involving patients with open-angle glaucoma or ocular hypertension show that all treatments are efficacious in decreasing IOP from baseline; however, various results were seen when groups were compared to each other. Current clinical guidelines from the AAO and NICE, recommend ophthalmic beta blockers and prostaglandin analogues should be used as first-line therapies for the treatment of open angle glaucoma and ocular hypertension. Combination or monotherapy with agents from another class is recommended in patients that experience intolerable side effects or do not achieve IOP reductions with first-line agents. None of the currently available clinical guidelines differentiate between agents. It is recommended that at least two ophthalmic beta blockers be available for use.

COMMITTEE VOTE:
- APPROVED
- DISAPPROVED
- APPROVED with MODIFICATION

November 9, 2010 Tennessee PAC
OPHTHALMIC AGENTS

RE-REVIEW: OPHTHALMIC BETA BLOCKERS

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References

RE-REVIEW: GLAUCOMA COMBINATION AGENTS

BACKGROUND

- Glaucoma is an optic neuropathy which causes gradual degeneration of the cells making up the optic nerve. Glaucoma initially manifests as visual field loss and may progress to blindness. It is the leading cause of irreversible blindness and second leading cause of vision loss. There are four distinct types of glaucoma: primary open-angle, acute angle-closure, secondary, and congenital. The most common of which is open-angle glaucoma. Treatment of glaucoma currently focuses on decreasing intra-ocular pressure (IOP) by laser therapy, surgery or medical intervention. Combination or monotherapy with agents from additional classes is recommended in patients that experience intolerable side effects or do not achieve goal IOP reductions with first-line agents.
The only available combination agent available for glaucoma at this time is the combination of brimonidine/timolol maleate.

Brimonidine is an ophthalmic alpha agonist and acts to decrease the amount of aqueous humor formed and increase its outflow; timolol maleate is an ophthalmic beta blocker and acts to decrease aqueous humor production.

Brimonidine/timolol is FDA indicated to reduce elevated intraocular pressure in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP.

The most common adverse reactions seen with brimonidine include conjunctival hyperemia, ocular irritation, blurred vision, foreign body sensation, and ocular pruritis. The most common adverse effects seen with timolol include blurred vision, transient ocular discomfort, burning sensation, and tearing.

- Brimonidine is contraindicated in patients being concomitantly treated with monoamine oxidase inhibitors (MAOIs).
- Due to timolol’s potential cardiac and pulmonary effects, timolol is contraindicated in patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock.
- Caution should be used with brimonidine and timolol in treating patients with significant cardiovascular disease due to their potential effect on blood pressure.
- Asthmatic attacks and pulmonary distress have been reported with the use of some beta-blocking agents. Caution should be exercised in the treatment of glaucoma in patients with excessive restriction of pulmonary function.
- No specific drug-drug interactions with the ophthalmic glaucoma drugs have been identified.

There are no clinical trials comparing combination therapy to therapy with both individual agents. Clinical trials have consistently demonstrated that that each individual agent is effective in lowering IOP.

One trial compared the combination of brimonidine/timolol to individual therapy with brimonidine or timolol monotherapy. The primary endpoint was mean change in IOP. The combination brimonidine/timolol provided a significantly lower mean change in IOP than either monotherapy with brimonidine or timolol.

The American Academy of Ophthalmology Preferred Practice Patterns for Primary Open Angle Glaucoma state that prostaglandin analogs and beta blockers are the most commonly used agents for the treatment of open angle glaucoma. AAO guidelines state prostaglandins are the most effective agents for lowering IOP and should be considered first line therapy unless contraindicated. The National Institute for Clinical Excellence (NICE) Glaucoma and Ocular hypertension guidelines also state that first line therapy should consist of ophthalmic beta blockers and ophthalmic prostaglandin analogues. Both guidelines state if initial therapy is unsuccessful at lowering IOP then pharmacological agents should be switched or combination therapy should be utilized.

**RECOMMENDATION**

The glaucoma combination of brimonidine/timolol is indicated to reduce elevated intraocular pressure in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP. Consensus guidelines recommend beta blockers and prostaglandin analogues as first-line therapy for open angle glaucoma. Combination or monotherapy with agents from another class is recommended in patients that experience intolerable side effects or do not achieve goal IOP reductions with first-line agents. Currently, there are no clinical trials comparing combination therapy to therapy with both individual agents. While it is recommended that combination therapy be available for patients who have not achieved adequate IOP lowering with monotherapy, there is no data to suggest superior efficacy with the combination product(s). Given the significantly higher relative costs of the combination product(s) compared to the individual components, it is recommended that this class be subject to clinical criteria to reserve it for patients who have tried the individual agents and demonstrated non-compliance.
OPHTHALMIC AGENTS

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

RE-REVIEW: GLAUCOMA COMBINATION AGENTS

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Clinical Criteria for Combigan®:
Combigan® will be approved if the following criteria is met:
- Patient is on simultaneous therapy with brimonidine and timolol for at least 60 days
- Patient demonstrates non-compliance with 2 products individually.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

References


RE-REVIEW: OPHTHALMIC: ALPHA AGONISTS

BACKGROUND

- Glaucoma is an optic neuropathy which causes gradual degeneration of the cells making up the optic nerve. Glaucoma initially manifests as visual field loss and may progress to blindness. It is the leading cause of irreversible blindness and second leading cause of vision loss. There are four distinct types of glaucoma: primary open-angle, acute angle-closure, secondary, and congenital. The most common of which is open-angle glaucoma. Treatment of glaucoma currently focuses on decreasing intra-ocular pressure (IOP) by laser therapy, surgery or medical intervention. Ophthalmic alpha agonists are one class of medications used to treat glaucoma. Currently available agents include apraclonidine and brimonidine.
- Both agents are relatively selective alpha agonists and exert their pharmacological effect by both decreasing the amount of aqueous humor formed and increasing its outflow.
- Apraclonidine is FDA approved to control or to prevent postsurgical elevations in intraocular pressure that occur in patients after argon laser trabeculoplasty, argon laser iridotomy or neodymium: yttrium-aluminum-garnet posterior capsulotomy & indicated for
OPHTHALMIC AGENTS

the short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional intraocular pressure reduction.

- Brimonidine is FDA approved for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.
- The most common adverse reactions seen with ophthalmic alpha agonists include conjunctival hyperemia, ocular irritation, blurred vision, foreign body sensation, and ocular pruritis. More severe adverse effects include dizziness, hypertension and xerostomia.
  - Both agents are contraindicated in patients being concomitantly treated with monoamine oxidase inhibitors (MAOIs).
  - Caution should be used with alpha agonists in treating patients with significant cardiovascular disease due to their potential effect on blood pressure.
  - Use of ophthalmic apraclonidine can lead to an allergic-like reaction characterized by hyperemia, pruritus, discomfort, tearing, foreign body sensation, edema of the lids and conjunctiva.
  - Ophthalmic brimonidine used to be available as two different branded products (Alphagan and Alphagan P) the products were distinguishable by the preservative used in each formulation. The Alphagan® formulation used benzalkonium chloride as its preservative, while Alphagan P® uses purite. Only the Alphagan P® formulation is still being produced; however, generic formulations of ophthalmic brimonidine which contain benzalkonium chloride are available. The effectiveness of the two formulations is similar.
  - No specific drug-drug interactions with the ophthalmic glaucoma drugs have been identified.

- Clinical trials have demonstrated alpha-agonists are effective for reducing IOP when the ophthalmic α-agonists are used for the management of postoperative elevations in IOP; both brimonidine and apraclonidine are effective treatment options with similar efficacy.
- Yuksel et al compared brimonidine 0.2% to apraclonidine 0.5% and placebo in patients with newly diagnosed ocular hypertension. The primary endpoints were defined as measure of IOP, systolic blood pressure (SBP) and heart rate. Brimonidine and apraclonidine significantly reduced IOP from baseline at all observation times (P values not reported). No significant difference was observed between the treatment groups. Heart rate and BP decreased significantly in the brimonidine group compared with placebo (P values not reported). Apraclonidine did not affect BP or heart rate any differently than placebo. There were no significant differences in the overall incidence of foreign body sensation, burning and stinging and dry mouth in the treatment groups.
- Barnes et al compared brimonidine to apraclonidine in patients with open-angle glaucoma, pigmentary glaucoma, pseudoexfoliation syndrome or ocular hypertension undergoing Argon laser therapy (ALT). The primary endpoint was the mean maximum IOP change from baseline (prior to surgery, and one, two, and four hours post-operatively). Neither group experienced an IOP elevation of ≥5 mmHg. The mean of the maximum IOP change (least decrease or maximum increase) from baseline was -2.6 mmHg for brimonidine and -2.3 mmHg for apraclonidine. This difference was not found to be statistically significant (P=0.8).
- Chen et al also reviewed brimonidine versus apraclonidine for the post-surgical treatment of IOP in patients needing ALT or other types of laser procedures. The primary endpoints were change in IOP, heart rate and blood pressure. Between the brimonidine and apraclonidine groups, baseline and all subsequent IOPs measured at each follow-up time were not statistically different. Including all time points after laser treatment, peak postoperative IOP elevations of ≥10 mmHg occurred in 9.1% (3/33) in both the brimonidine and apraclonidine groups (P=0.95). There were also no significant differences in all time points in which postoperative IOP elevations of ≥5 mmHg between groups (24.2% vs 27.3%; P=0.80). Changes in both SBP and DBP were also not significantly different in either group at any time, except for there being a greater decrease in DBP in the brimonidine group at only the one hour time.
The American Academy of Ophthalmology Preferred Practice Patterns for Primary Open Angle Glaucoma state that prostaglandin analogs and beta blockers are the most commonly used agents for the treatment of open angle glaucoma. AAO guidelines state prostaglandins are the most effective agents for lowering IOP and should be considered first line therapy unless contraindicated. AAO designates alpha agonists as a second line therapy option. The National Institute for Clinical Excellence (NICE) Glaucoma and Ocular hypertension guidelines also state that first line therapy should consist of ophthalmic beta blockers and ophthalmic prostaglandin analogues. Both guidelines state if initial therapy is unsuccessful at lowering IOP then pharmacological agents should be switched or combination therapy should be utilized.

RECOMMENDATION
Brimonidine and apraclonidine are ophthalmic alpha agonists indicated for the management of elevated IOP from glaucoma, ocular hypertension and after surgical treatments. Current clinical guidelines from the AAO and NICE, recommend ophthalmic β-antagonists and prostaglandin analogues are used as first-line therapies; ophthalmic alpha agonists are considered alternative therapy. Combination or monotherapy with agents from another class is recommended in patients that experience intolerable side effects or do not achieve IOP reductions with first-line agents. None of the currently available clinical guidelines differentiate between agents in this class and head to head comparisons demonstrate the alpha agonists are comparable in efficacy. Therefore it is recommended that at least one alpha agonist be available for use.

COMMITTEE VOTE:
APPROVED   DISAPPROVED  APPROVED with MODIFICATION

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<td>apraclonidine 0.5% (compares to Iopidine®) brimonidine 0.15% lopidine® (apraclonidine)</td>
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References
9. Barnes SD, Compagna JA, Dirks MS, Doe EA. Control of intraocular pressure.
OPHTHALMIC AGENTS

Elevations after argon laser trabeculoplasty: comparison of brimonidine 0.2% to apraclonidine 1.0%. Ophthalmology. 1999;106:2033-7.

RE-REVIEW: GLAUCOMA DIRECT-ACTING MIOTICS

BACKGROUND

- Glaucoma is an optic neuropathy which causes gradual degeneration of the cells making up the optic nerve. Glaucoma initially manifests as visual field loss and may progress to blindness. It is the leading cause of irreversible blindness and second leading cause of vision loss in the world. Treatment of glaucoma currently focuses on decreasing intraocular pressure (IOP) by one of three methods: laser therapy, surgery or medical intervention. Medical intervention includes five ophthalmic classes of drugs used for the long-term management of glaucoma: α-agonists, β-antagonists, carbonic anhydrase inhibitors, parasympathomimetics, and prostaglandin analogues. The parasympathomimetics are also referred to as direct-acting miotics, which include ophthalmic pilocarpine and carbachol.
- Agents in this class directly stimulate cholinergic receptors. Effects of these agents include contraction of the iris sphincter muscle, resulting in pupillary constriction (miosis); constriction of the ciliary muscle, resulting in increased accommodation; and reduction in IOP, associated with an increase in the outflow and a decrease in the inflow of aqueous humor.
- Carbachol and pilocarpine are FDA approved for the induction of miosis. Ophthalmic pilocarpine has several additional FDA approved indications including control of IOP, management of acute angle-closure glaucoma, prevention of postoperative elevated IOP associated with laser surgery and reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension.
- Due to the topical nature of administration of these agents, adverse events are usually limited to ophthalmic effects including blurred vision, burning sensation, eye irritation and night blindness. Rare cases of retinal detachment have been reported with use of these agents.
  - Ophthalmic pilocarpine gel is contraindicated where constriction is undesirable, such as in acute iritis.
  - The miosis caused by the ophthalmic miotics usually causes difficulty in dark adaptation; therefore, patients should be advised to exercise caution in night driving and other hazardous occupations in poor illumination.
  - There are no documented drug-drug interactions with these agents.
- The clinical trial data regarding the safety and efficacy of the ophthalmic miotics is limited. These agents have been available for several years and as such are recognized as an established treatment option.
  - For the treatment of glaucoma, ophthalmic pilocarpine has demonstrated comparable efficacy (ability to reduce IOP) to ophthalmic carbonic anhydrase inhibitors, β-antagonists and prostaglandin analogues.
  - There is currently no head to head trial data available comparing the available agents in this class.
- In their recently updated preferred practice patterns for primary open-angle glaucoma, the American Academy of Ophthalmologists (AAO) states that prostaglandin analogs are the most effective drugs at lowering IOP and should be considered initial medical therapy for most patients. If target IOP is not achieved by one medication, then adding, combining or switching medications may be considered to reach the target IOP. Guidelines from the National Institute for Clinical Excellence (NICE) state that first-line medication therapy for the treatment of open angle glaucoma should consist of ophthalmic β blockers or ophthalmic prostaglandin analogues. Ophthalmic carbonic anhydrase inhibitors and ophthalmic sympathomimetics should be considered second line medication therapy.
RECOMMENDATION

Carbachol and pilocarpine are ophthalmic miotic agents Food and Drug Administration (FDA) approved for the management of several ophthalmic conditions. Specifically, both agents are FDA approved for the induction of miosis. Ophthalmic pilocarpine is indicated for additional ophthalmic conditions including control of IOP, management of acute angle-closure glaucoma, prevention of postoperative elevated IOP associated with laser surgery and reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. According to current clinical guidelines, the β- antagonists and prostaglandin analogues are used as first-line therapies. Combination or monotherapy with agents from another class is recommended in patients that experience intolerable side effects or do not achieve goal IOP reductions with first-line agents. None of the currently available clinical guidelines differentiate between agents in this class and there are no head to head clinical trials available comparing the agents in this class. Given the additional FDA-approved indications, it is recommended that at least pilocarpine solution should be available for use.

COMMITTEE VOTE:

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RE-REVIEW: OPHTHALMIC MYDRIATICS & MYDRIATIC COMBOS

BACKGROUND

- Medications that dilate the pupil and paralyze accommodation are known as ophthalmic mydriatics and cycloplegics. These agents are most commonly used topically in the examination of the eye and during ophthalmic procedures. They also may be used in the management of inflammatory conditions of the eye to treat or prevent the formation of adhesions between the lens and the iris (e.g., uveitis) and in strabismus.
- Atropine, cyclopentolate, homatropine, scopolamine and tropicamaide are ophthalmic anticholinergics which produce mydriasis via paralysis of the pupillary constrictor muscles and cycloplegia via paralysis of the ciliary muscles. Ophthalmic cyclopentolate and scopolamine are also available in combination with phenylephrine, a sympathomimetic which enhances mydriasis via stimulation of the dilator muscles.
• Ophthalmic anticholinergics FDA approved for the induction of mydriasis and cycloplegia include atropine sulfate, cyclopentolate, homatropine, scopolamine and tropicamide. Ophthalmic homatropine is also FDA approved for the management of uveitis and ophthalmic scopolamine is also FDA approved for the treatment of iridocyclitis, a type of uveitis. The combination cyclopentolate/phenylephrine product is approved for producing mydriasis while the combination scopolamine/phenylephrine product is approved for producing cycloplegia and mydriasis as well as uveitis.

• Adverse events commonly associated with the ophthalmic mydriatics are blurred vision, burning sensation, eye irritation and light intolerance. Additionally, use of these agents can be associated with a transient increase in intraocular pressure.
  - All of the agents in this class are contraindicated in narrow-angle glaucoma.
  - Atropine is also contraindicated in patients with adhesions between the iris and lens. Ophthalmic homatropine and the combination scopolamine/phenylephrine product are also contraindicated in patients with acute hemorrhage, paralytic ileus, tachycardia secondary to cardiac insufficiency, or myasthenia gravis. Both of the combination products are contraindicated in patients with hypertension and ventricular arrhythmia due to their phenylephrine component.
  - Use of cyclopentolate-containing products may cause central nervous system disturbances, which is of greater concern in pediatric patients, but may occur at any age, especially with higher strength solutions.
  - Ophthalmic scopolamine preparations may contain benzalkonium chloride which may be absorbed by contact lenses; therefore, contacts should be removed prior to administration and reinserted 15 minutes after application.
  - There are no clinically significant and/or reported drug interactions associated with the majority of the ophthalmic mydriatics.

• There is limited clinical trial data regarding the efficacy and safety of the ophthalmic mydriatics; however, these agents have been available for several years and are established treatment options.
  - Hofmeister, et al compared tropicamide to cyclopentolate in 30 myopic adult patients undergoing refractive surgery. No statistically significant difference was found between the two treatments’ cycloplegic refractions (tropicamide; $P=0.10$ and cyclopentolate; $P=0.14$).

• The ophthalmic mydriatics vary in onset and duration of action; with cyclopentolate, homatropine and tropicamide being preferred for ophthalmic procedures due to a more rapid onset of action and a shorter duration of action compared to atropine sulfate and scopolamine. The combination mydriatic agents are typically used to enhance mydriasis, especially in patients who might respond poorly to anticholinergics alone, such as those with dark irides or diabetes, or those who are receiving prolonged miotic therapy. There are no pertinent clinical guidelines associated with these agents.

**RECOMMENDATION**

Atropine sulfate, cyclopentolate, homatropine, scopolamine and tropicamide are ophthalmic mydriatics FDA approved for the induction of cycloplegia and mydriasis. These agents are most commonly used topically in the examination of the eye and during ophthalmic procedures. They also may be used in the management of inflammatory conditions of the eye to treat uveitis and in strabismus. There is limited clinical trial data regarding the efficacy and safety of the ophthalmic mydriatics; however, these agents are established treatment options. There are no pertinent clinical guidelines associated with these agents; however, the combination mydriatic agents are typically reserved to enhance mydriasis in patients who respond poorly to single entity agents. Therefore, it is recommended at least two ophthalmic mydriatics should be available for use.

**COMMITTEE VOTE:**

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

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November 9, 2010 Tennessee PAC
## RE-REVIEW: OPHTHALMIC MYDRIATICS & MYDRIATIC COMBOS

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### References