Drug Class Review

Ophthalmic Cholinergic Agonists

52:40.20 Miotics

Acetylcholine (Miochol-E)
Carbachol (Isopto Carbachol; Miostat)
Pilocarpine (Isopto Carpine; Pilopine HS)

Final Report
November 2015

Review prepared by:
Melissa Archer, PharmD, Clinical Pharmacist
Carin Steinvoort, PharmD, Clinical Pharmacist
Gary Oderda, PharmD, MPH, Professor

University of Utah College of Pharmacy

Table of Contents

Executive Summary

Introduction: Three ophthalmic cholinergic agonist agents are currently available for use in the United States: acetylcholine (Miochol-E), carbachol (Isopto Carbachol; Miostat), pilocarpine (Isopto Carpine; Pilopine HS). Echothiophate Iodide (Phospholine Iodide) is a miotic agent that is sometimes considered an agent in this class. Carbachol, echothiophate iodide and pilocarpine are labeled for use in the treatment of glaucoma. Acetylcholine and carbachol are labeled for use to induce miosis in cataract surgery and other ophthalmic surgeries where rapid miosis is required. Echothiophate iodide is also labeled for use in the treatment of accommodative esotropia.

Glaucoma is a leading cause of blindness worldwide. Reducing intraocular pressure (IOP) is directly associated with slowing glaucoma progression and protecting the optic nerve, and is the main measurable goal of open-angle glaucoma treatment. Options for lowering IOP include medications, surgery and laser procedures. Current treatment guidelines from the American Academy of Ophthalmology do not specify a preferred procedure or medication for treating glaucoma. The cholinergic agonists are not listed in the guidelines as a preferred drug class in the treatment of glaucoma. Topical prostaglandins and beta-adrenergic blockers are the most commonly used medications for open-angle glaucoma. The cholinergic agonists may be used to induce pupil miosis in ophthalmic procedures and laser surgeries to facilitate the procedure and/or improve patient outcomes. In addition, echothiophate iodide may be used as a second-line or add-on therapy in the treatment of accommodative esotropia.

Clinical Efficacy: Clinical evidence evaluating the efficacy of the ophthalmic cholinergic agonists is limited. Several placebo-controlled trials evaluating the agents in the treatment of ocular hypertension and for use during/after ocular procedures are available. According to the limited evidence, the cholinergic agonists demonstrate efficacy in reducing IOP and constricting pupil size in patients with ocular hypertension and in those undergoing ophthalmic procedures and surgeries.

Adverse Drug Reactions: The ophthalmic cholinergic agents are generally well-tolerated and the most common ocular adverse events reported with agents include myopia, eye pain, accommodative spasm and eye irritation. Benzalkonium chloride is a preservative used in a number of the ophthalmic agents and is also associated with allergic reactions, corneal opacity and keratitis. Systemic adverse events reported with the agents are rare and may include nausea, vomiting, bradycardia, diarrhea, salivation and perspiration.

Summary: The ophthalmic cholinergic agonists have demonstrated efficacy in reducing IOP and constricting pupil size in patients with ocular hypertension and in those undergoing ophthalmic procedures. Ocular and systemic adverse effects reported with the agents tend to be rare and mild. Currently, the ophthalmic cholinergic agonists are not recommended as first-line treatment options in the treatment of glaucoma and are occasionally used in ophthalmic procedures requiring miosis.

Introduction

Several classes of topical ophthalmic medications are available for treating glaucoma in the United States: beta-adrenergic blockers, carbonic anhydrase inhibitors, ophthalmic cholinergic agonists, prostaglandins and sympathomimetics.[1,2] Table 1 compares these medication classes. This review focuses on the ophthalmic cholinergic agonists. Three ophthalmic cholinergic agents are currently available for this use in the United States: acetylcholine (Miochol-E), carbachol (Isopto Carbachol; Miostat), pilocarpine (Isopto Carpine; Pilopine HS). Echothiophate Iodide (Phospholine Iodide) is a miotic agent that is sometimes considered an agent in this class. Table 2 provides a summary of the available ophthalmic cholinergic agonist agents.

Table 1. Glaucoma Therapies[1,3]

Characteristic	Prostaglandins	Beta-Adrenergic Blockers	Carbonic Anhydrase Inhibitors	Sympathomimetics	Cholinergic Agonists
Agents in Class	Bimatoprost Latanoprost Tafluprost Travoprost	Betaxolol Carteolol Levobetaxolol [DSC] Levobunolol Metipranolol Timolol	Brinzolamide Dorzolamide	Apraclonidine Brimonidine Dipivefrin	Acetylcholine Carbachol Echothiophate Iodide Pilocarpine
Generics Available in Class	Yes	Yes	None	Yes	Yes
Combination Products	Latanoprost/Timolol [NA] Travoprost/Timolol [NA]	Brimonidine/Timolol Brinzolamide/Timolol [NA] Dorzolamide/Timolol Latanoprost/Timolol [NA] Travoprost/Timolol [NA]	Brinzolamide/Brimonidine Brinzolamide/Timolol [NA] Dorzolamide/Timolol	Brinzolamide/Brimonidine Brimonidine/Timolol	None
Duration of Action	24 hrs	12 – 24 hrs	8 – 12 hrs	7 – 12 hrs	Eyedrops: 4 – 8 hrs Echothiophate: 1–4 weeks Pilocarpine gel: 18–24 hrs Pilocarpine insert: 1 week
Pharmacologic Effects					
Decrease aqueous production	Not reported	Significant effect	Significant effect	Apraclonidine, Brimonidine: Moderate to significant effect Dipivefrin, Epinephrine: Some effect	Not reported
Increase aqueous outflow	Significant effect	No effect to Some effect	Not reported	Moderate effect	Significant effect
Effect on pupil	Not reported	Not reported	Not reported	Mydriasis	Miosis
Effect on ciliary muscle	Not reported	Not reported	Not reported	Not reported	Accommodation
Magnitude of IOP Lowering	25 – 35%	20 – 30%	15 – 26%	2 – 5 hrs: 18 – 27% 8 – 12 hrs: 10%	20 – 30%
Key adverse effects					
Ocular	Redness, increased iris pigmentation, eyelash changes	Stinging, burning	Allergic sensitivity, burning, stinging	Hyperemia, lid edema, itching, foreign-object sensation	Stinging, irritation, miosis
Systemic	Upper respiratory tract infections	Bradycardia, bronchial constriction, blood pressure reduction	Altered taste	Dizziness, dry mouth, fatigue	Headache

Key: DSC - discontinued, NA - not available in the US

Table 2. Summary of Agents*[1,3-5]

Characteristic	Acetylcholine (Miochol-E)	Carbachol (Isopto Carbachol; Miostat)	Echothiophate Iodide (Phospholine Iodide)	Pilocarpine (Isopto Carpine; Pilopine HS)
Concentrations	Intraocular reconstituted solution: 1%	Intraocular solution (Miostat): 0.01% Ophthalmic solution (Isopto Carbachol): 1.5%, 3%	Ophthalmic reconstituted solution: 1.5 mg (0.03%), 3 mg (0.06%), 6.25 mg (0.125%), or 12.5 mg (0.25%)	Ophthalmic Gel (Pilopine HS): 4% Ophthalmic Solution: 1%, 2%, 4%
Package Sizes Available	Blister pack containing one vial (20 mg acetylcholine and 56 mg mannitol) and one ampule (2mL diluent)	Miostat: 1.5 mL Isopto Carbachol: 15 mL each	Each package contains materials for dispensing 5 mL of eyedrops: (1) bottle containing sterile echothiophate iodide for ophthalmic solution in one of four potencies, with 40 mg potassium acetate in each case. (2) a 5 mL bottle of sterile diluent containing chlorobutanol (chloral derivative), 0.55%; mannitol, 1.2%; boric acid, 0.06%; and sodium phosphate, 0.026%. (3) sterilized dropper	Ophthalmic Gel (Pilopine HS): 4 g Ophthalmic Solution: 1% (15 mL); 2% (15 mL); 4% (15 mL)
Generic Available?	No	No	No	Ophthalmic Gel (Pilopine HS): No Ophthalmic Solution: Yes
Labeled Use	To induce miosis in cataract surgery, keratoplasty, iridectomy, and other anterior segment surgery where rapid miosis is required	Ophthalmic solution: To lower intraocular pressure in the treatment of glaucoma Intraocular solution: To induce miosis during surgery	Accommodative esotropia: Concomitant esotropias with a significant accommodative component Glaucoma: Treatment of chronic open-angle glaucoma; subacute or chronic angle-closure glaucoma (postiridectomy or where surgery is refused or contraindicated); certain nonuveitic secondary types of glaucoma, especially glaucoma following cataract surgery	Management of chronic simple glaucoma, chronic and acute angle-closure glaucoma Off-Label: Counter effects of cycloplegics
pH	5.0-8.2	Ophthalmic: 5-7 Intraocular: 5.5-7	~4-6	~3.5-5.5
Osmolality	275-330 mOsmol/kg	~300 mOsmol/kg	~283 mOsm	290 to 350 mOsm/kg (1% and 2% products) 550 to 600 mOsm/kg (4% product)
Onset	Rapid	Ophthalmic: 4 hours Intraocular: 2-5 minutes	Miosis: < 60 minutes IOP: 24 hours	Miosis: 10-30 minutes IOP: 1 hour

Characteristic	Acetylcholine (Miochol-E)	Carbachol (Isopto Carbachol; Miostat)	Echothiophate Iodide (Phospholine Iodide)	Pilocarpine (Isopto Carpine; Pilopine HS)
Labeled Dosage Range, Adults	0.5-2 mL of 1% injection (5-20 mg) instilled into anterior chamber before or after securing one or more sutures Not indicated in the pediatric population	Glaucoma: Ophthalmic: Instill 1-2 drops up to 3 times/day Ophthalmic surgery (miosis): Intraocular: 0.5 mL instilled into anterior chamber before or after securing sutures Not indicated in the pediatric population	Glaucoma: 1 drop (0.03%) twice daily into eyes with 1 dose just prior to bedtime Pediatric: Accommodative esotropia: Diagnosis: Instill 1 drop (0.125%) once daily into both eyes at bedtime for 2 to 3 weeks Treatment: 1 drop of 0.06% once daily or 0.125% every other day (maximum: 1 drop of 0.125% in both eyes/day)	Glaucoma: Solution: 1-2 drops up to 6 times/day; adjust the concentration and frequency as required to control elevated intraocular pressure. Gel: 0.5” ribbon into lower conjunctival sac once daily at bedtime. Not indicated in the pediatric population
Preservative in Product	None	Intraocular solution (Miostat): None Ophthalmic solution (Isopto Carbachol): benzalkonium chloride 0.005%	Chlorobutanol	Ophthalmic Gel (Pilopine HS): benzalkonium chloride Ophthalmic solution: benzalkonium chloride 0.01%
Contraindications	Hypersensitivity	Hypersensitivity; acute iritis, acute inflammatory disease of the anterior chamber	Hypersensitivity; most cases of angle-closure glaucoma; active uveal inflammation	Hypersensitivity; acute inflammatory disease of the anterior chamber of the eye
Storage	Store unopened vial at 4°C to 25°C (39°F to 77°F); prevent from freezing. Prepare solution immediately before use and discard unused portion. Acetylcholine solutions are unstable. Only use if solution is clear and colorless.	Store at controlled room temperature 15° - 30°C (59° - 86°F)	Store undiluted vials at 2°C to 8°C (36°F to 46°F). Store reconstituted solutions at ~25°C (~77°F); do not refrigerate; discard unused solution after 4 weeks.	Gel: Store at room temperature of 2°C to 27°C (36°F to 80°F); do not freeze. Avoid excessive heat. Solution: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F).
Latest Patent/ Exclusivity Expiration Date	04/2019	may be expired, no generic available	may be expired, no generic available	may be expired, no generic available

Disease Overview

Glaucoma is one of the leading causes of blindness in the United States and abroad. All forms of glaucoma are characterized by optic neuropathy resulting in a loss of visual sensitivity and visual field.[6,7] The two major forms are open-angle glaucoma and angle-closure glaucoma. Optic neuropathy associated with angle-closure glaucoma results from reduced access of aqueous fluid to the drainage system. Open-angle glaucoma is characterized by a chronic, persistent worsening of optic neuropathy, with associated optic disk and visual field decline as a result of abnormalities within the drainage system.[8] Open-angle glaucoma is usually a bilateral disease but disease severity is generally greater in one eye than the other. Primary OAG accounts for the majority of glaucoma cases. Less common forms of OAG include congenital glaucomas and secondary glaucomas caused by medication, disease or injury. [6,9]

In OAG, the trabecular meshwork of the eye is compromised, impairing outflow of aqueous humor from the anterior chamber of the eye. Build-up of aqueous humor results in elevated intraocular pressure (IOP, > 21 mm Hg).[7,8] Although elevated IOP is the primary known contributor to glaucoma-associated optic neuropathy, 16-50% of patients with OAG do not have consistently elevated IOP and glaucoma can progress even when IOP is normal. Other factors associated with disease progression are unclear.[8] The loss of vision associated with OAG is thought to result from loss of retinal ganglion cells resulting in defects in field of vision. The reasons for ganglion cell loss are unclear but may be tied to a combination of hypoxia linked to reduction of retinal circulation in addition to chronic increased IOP.[10] Regardless of whether IOP is elevated or normal, IOP reduction is directly related to slowing glaucoma progression and protecting the optic nerve. The primary measurable short-term goal in OAG treatment is IOP reduction.[6,9] Because patients with OAG present with IOP measurements ranging from normal to extremely elevated, there is no commonly established target IOP goal. Target IOPs are specific to each patient depending on the presence of other risk factors and disease severity. In general, an initial IOP reduction of at least 25% is sought, even in patients with normal baseline IOP. Patients with disease progression at the established target IOP reduction require adjustment to a lower target.[6] Intraocular hypertension (IOH) is defined as IOP > 21 mm Hg with no visual field or optic disk involvement in patients with open angles.[8] Only a small percentage of patients with IOH develop OAG but patients with IOH are 16 times more likely to develop OAG than those with IOP < 16 mm Hg. The 5-year risk of visual field impairment is 6.7% for patients with IOP > 21 mm Hg, compared to 1.5% in those with IOP < 20 mm Hg.

The US guidelines for diagnosing and treating primary OAG developed by the American Academy of Ophthalmology (2005, 2010) are considered the standard of care.[6] Guidelines do not specify a preferred ophthalmic medication for treating of OAG. Treatment selection is tailored to the needs of the individual. Prostaglandins and beta-adrenergic blockers are the most commonly used medications for OAG. Prostaglandins are often preferred because they can be dosed once daily and are well tolerated. Beta-adrenergic blockers are also commonly used because they are well tolerated and generic formulations are available.[6,8] The cholinergic agonists are not currently listed as a

recommended glaucoma medication Patients with an inadequate IOP response to a single medication are either treated with combination therapy or switched to a different medication class. Concurrent use of multiple ophthalmic medications should be avoided, as increased regimen complexity is associated with decreased compliance, and noncompliance is a major source of treatment failure in OAG.[11] Surgical or laser treatment for OAG can also be considered initially or after inadequate response to ophthalmic medications. However, many patients still require treatment with an ophthalmic medication for additive IOP lowering effects after these procedures. Five to ten year failure rates after common OAG surgeries or laser treatments range from 20-50%, and failure rates increase dramatically after subsequent procedures.[6]

Table 3. Summary of Current Glaucoma Clinical Practice Guidelines[12]

Guideline	Recommendations
American Academy of Ophthalmology (AAO, 2010)[6]	Definition of OAG: Evidence of either or both: (a) optic disc or RNFL defects; (b) VF defect; Adult-onset; Open angles; Absence of other causes Goals of Treatment: Stable optic nerve/RNFL status; Controlled IOP; Stable visual fields Target IOP: Initial target IOP should be 20% lower than pretreatment IOP; the more advanced damage, the lower the IOP target; continued lowering of target IOP with disease progression
American Optometric Association (AOA, 2010)[9]	Definition of OAG: chronic, progressive disease with characteristic optic nerve (ON) damage, retinal nerve fiber layer (NFL) defects, and subsequent visual field (VF) loss. Goals of Treatment: Reducing or preventing further ON damage Target IOP: 30-50% lower than the pretreatment level
European Glaucoma Society (EGS, 2008)[12]	Definition of OAG: Acquired characteristic optic disc or RNFL defects; Glaucomatous VF defects; Age $\geq$ 35 years; Open angles; Untreated IOP > 21 mm Hg Goals of Treatment: Maintain the patient's quality of life at a sustainable cost Target IOP: Aim for at least a 20% reduction from initial IOP; target IOP varies according to pretreatment IOP, overall risk of IOP-related damage, stage of glaucoma, rate of progression, age, life expectancy, and risk factors
South East Asia Glaucoma Interest Group (SEAGIG, 2008)[12]	Definition of OAG: Chronic progressive optic neuropathy with characteristic changes in the optic nerve or VF; Absence of other causes Goals of Treatment: Tailor treatment to severity of glaucoma, depending on disease stage and risk factors Target IOP: Target IOP is based on the pressure reduction required to slow or stop disease progression; target IOPs set for disease severity with more aggressive targets in advanced disease

Key: OAG = open-angle glaucoma; RNFL = retinal nerve fiber layer; VF = visual field; IOP = intraocular pressure

The ophthalmic cholinergic agonists (acetylcholine and carbachol) are also labeled for use during ocular surgery to induce miosis. In some ophthalmic surgical procedures immediate constriction of the intact pupil may serve as an advantage. Prior to laser therapy, for example, a cholinergic agonist is helpful to induce pupil miosis and iris stromal thinning making the laser surgery more easily performed.[1,2] In addition, echothiophate iodide is indicated in the treatment of accommodative esotropia, which is a common type of strabismus (or crossed eye). In general, treatment of accommodative esotropia involves the use of eyeglasses or contact lenses to correct the patient's refractive error. Miotic agents, such as echothiophate iodide, may occasionally be used in addition to glasses or surgery in the treatment of esotropia.[13]

Pharmacology

The cholinergic agonists, also referred to as miotics, act directly on cholinergic receptors within the eye resulting in contraction of the iris sphincter (causing miosis), constriction of ciliary muscle (causing loss of accommodation) and decreased resistance to aqueous humor outflow (causing reduced intraocular pressure). The miotic ophthalmic agents include the direct acting cholinergic agents (acetylcholine, pilocarpine, and carbachol) and the indirect acting cholinergic agents (echothiophate). Ophthalmic acetylcholine is rarely used in the treatment of open-angle glaucoma due to its rapid inactivation. Instead, acetylcholine is used during ocular surgery for temporarily inducing miosis. Carbachol, also called carbaminoylcholine, is simply the substitution of carbamic acid for acetic acid on the acetylcholine molecule. This substitution results in increased resistance to cholinesterases and improved activity but also increased risk of adverse effects. Pilocarpine is an alkaloid of vegetable origin and is the most commonly used cholinergic agonist in the treatment of glaucoma.[14]

Methods

A literature search was conducted to identify articles evaluating the ophthalmic cholinergic agonist agents, searching the MEDLINE database (1950 – 2015), the EMBASE database, the Cochrane Library and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English, evaluating the comparative efficacy of the agents are included. Trials evaluating the agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Noncomparative trials and trials comparing monotherapy with combination regimens are excluded.[15-36] The following reports were excluded (note: some were excluded for more than 1 reason):

- Individual clinical trials which evaluated endpoints other than reduction of symptoms, such as pharmacokinetics[37], pharmacodynamics[38,39], oral use[29,40,41] or other outcomes unrelated to reduction of symptoms.
- Individual trials comparing the agents in dose-finding and placebo-controlled studies or in healthy volunteers.[42,43]
- Individual clinical trials evaluating agents or formulations not currently available in the US, protocol templates or clinical trials without access to the full article.[44-50]

Clinical Efficacy

The clinical evidence examining the efficacy of the ophthalmic cholinergic agonist agents is limited. A total of two comparative clinical trials, published in 1971 and 1972, evaluating the efficacy of acetylcholine and carbachol in round pupil cataract surgery were identified.[51,52] Many developments and improvements have been made to the management and administration of cataract surgeries since the 1970's and the outcomes reported by these trials likely are not important for today's cataract surgeries.[53] Several noncomparative and placebo controlled trials evaluating the agents in ocular hypertension and ophthalmic procedures are also

available for evaluation; a brief summary of this data is summarized below. No clinical trials evaluating the agents in the treatment of glaucoma are available for review.

One trial evaluating the efficacy pilocarpine 2% in patients with ocular hypertension is available. In 2001, Shaikh et al[22] published a randomized, controlled trial of 18 patients receiving pilocarpine in one eye and saline in the other eye three times at 10 minute intervals. After the dosing period, a significant reduction in IOP (p=0.001; median difference -4.25 mmHg; 95% CI, -5.85 to -2.40) and a significant increase in pulsatile ocular blood flow (p<0.001; median difference 4.60; 95% CI, 2.35 to 6.75) was demonstrated in the treated eye compared to the control eye. Adverse effects were not reported in the trial. According to this limited evidence, pilocarpine 2% may be an effective treatment option for treatment of ocular hypertension.

Four trials evaluating the efficacy of the cholinergic agonists in ophthalmic procedures and surgeries are available. In 2000, Wutthiphan et al[24] published a randomized, controlled trial of 30 patients receiving low-dose intracameral pilocarpine in sterile irrigation solution (0.13 mg/ml) in one eye and sterile irrigation solution alone in the other eye at the end of a phacoemulsification procedure to remove viscoelastic agents and induce pupil constriction to return to normal. Post-irrigation pupil size in the pilocarpine group was reported as 5.40 +/- 0.79 mm compared to 7.18 +/- 0.79 mm in the control group (no p-value provided). No differences in endothelial cell density, central corneal thickness and the average corneal thickness were reported between treatment groups. This evidence suggests intracameral pilocarpine may be effective in constricting the pupil post-procedure without adversely affecting corneal endothelium.

The three additional trials were published in 1996-1999. Cekic et al (1999)[28] conducted a randomized controlled trial comparing intracameral carbachol to sterile irrigation solution in 51 patients undergoing cataract extraction with phacoemulsification. IOP measurements were recorded at 8 hours, 24 hours and 7 days post-procedure. Statistically significant reductions in IOP were demonstrated with the carbachol group at 8 hours and 24 hours (12.4 +/- 3.4 mmHg and 13.1 +/- 4.5) compared to the control group (19.4 +/- 6.4 mmHg and 17.2 +/- 4.2 mmHg; $p < 0.05$). No differences in IOP values were reported at 7 days post-procedure. This evidence suggests carbachol produces early post-operative lowering of IOP but does not provide information on the clinical usefulness of this outcome. Solomon et al (1998)[30] conducted a randomized, controlled trial comparing intracameral carbachol 0.01% solution with placebo in 41 patients undergoing phacoemulsification and posterior lens implantation. Statistically significant reductions in IOP were reported with intracameral carbachol at 6 hours and 1 day post-procedure (15.9 mmHg and 15.0 mmHg) compared to placebo (20.4 mmHg and 17.6 mmHg; $p < 0.04$). In addition, improved visual acuity at 1 day post-procedure ($p = 0.0263$), quality of life parameters (attempt to descent stairs within one week post-procedure, $p < 0.04$) and improved depth of focus at 2 months post-procedure ($p = 0.025$) were reported with the carbachol treatment group compared to placebo. No differences in adverse event rates were reported between treatment groups. This evidence suggests early reduced IOP post-operatively may be associated with improved outcomes up to 2 months after phacoemulsification and posterior lens implantation. Laranjeira et al (1996)[32] conducted a retrospective study of 14 patients (16 eyes) who underwent radial keratotomy, developed hyperopia and received ophthalmic pilocarpine for 3 to 14 weeks (mean, 8.2 weeks) post-procedure. Patients were

followed for up to 49 weeks after treatment with pilocarpine and the authors concluded "pilocarpine effectively reduced overcorrections after radial keratotomy. After termination of treatment, the steepening of corneal curvature was maintained."

Adverse Drug Reactions

The ophthalmic cholinergic agonist agents are generally well-tolerated. The most common ocular adverse events reported with ophthalmic cholinergic therapy include myopia, eye pain, accommodative spasm and eye irritation.[1,2] Benzalkonium chloride is a preservative used in a number of the ophthalmic agents and is also associated with allergic reactions, corneal opacity and keratitis. Topical ophthalmic agents do not generally cause systemic adverse effects and systemic effects are rarely reported with the cholinergic agonists. Systemic adverse events that have been reported with ophthalmic cholinergic therapy include nausea, vomiting, bradycardia, diarrhea and increased salivation/perspiration.[7,8,14] To reduce the risk of systemic adverse events, patients should receive the lowest effective concentration of medication and receive instruction on proper method of topical administration. The cholinergic agonists are contraindicated in patients with acute inflammatory disease of the anterior chamber of the eye. Table 4 provides a summary of the adverse events reported with the individual agents, based on package labeling.

Adverse effects reported with carbachol therapy tend to occur more frequently and with higher severity compared to those reported with pilocarpine therapy.[54] In addition, carbachol is poorly absorbed through the cornea and is typically reserved for second-line therapy only if pilocarpine is ineffective.[14] Echothiophate is rarely used and reserved for use only when other glaucoma therapies are ineffective due to increased risk of systemic toxicity and more severe ocular adverse effects (cataract formation, retinal detachment and iris cyst formation) reported with echothiophate iodine therapy.

Table 4. Adverse Events Reported with Ophthalmic Cholinergic Agonist Therapies (frequency not defined)*[1,2]

Agent	Cardiovascular	Central nervous system	Gastrointestinal	Ocular	Respiratory	Miscellaneous:
Acetylcholine	Bradycardia, flushing, hypotension	Not reported	Not reported	Clouding, corneal edema, decompensation	Dyspnea	Diaphoresis
Carbachol	Arrhythmia, flushing, hypotension, syncope	Headache	Abdominal cramps, diarrhea, epigastric distress, salivation, vomiting	Bullous keratopathy, burning (transient), ciliary spasm, conjunctival injection, corneal clouding, irritation, postoperative iritis (following cataract extraction), retinal detachment, stinging (transient)	Asthma	Genitourinary: Urinary bladder tightness Diaphoresis
Echothiophate Iodide	Bradycardia, cardiac irregularities, flushing, hypotension	Not reported	Diarrhea, nausea, vomiting	Blurred vision, browache, burning eyes, ciliary redness, conjunctival redness/thickening, intraocular pressure increases (paradoxical), iris cysts, lacrimation, lid muscle twitching, miosis, myopia, latent iritis or uveitis activation, lens opacities, retinal detachment, stinging	Dyspnea	Neurologic & skeletal: Muscle weakness Diaphoresis, nasolacrimal canal obstruction
Pilocarpine	Hypertension, tachycardia	Not reported	Diarrhea, nausea, salivation, vomiting	Burning, ciliary spasm, conjunctival vascular congestion, corneal granularity (gel 10%), lacrimation, lens opacity, myopia, retinal detachment, supraorbital or temporal headache, visual acuity decreased	Bronchial spasm, pulmonary edema	Diaphoresis

*Rates obtained from package inserts and are not meant to be comparative

Summary

The ophthalmic cholinergic agonist agents are used most commonly to lower intraocular pressure in the treatment of glaucoma but are also used to induce miosis during surgery and to augment treatment in patients with accommodative esotropia. Current clinical practice guidelines do not list the cholinergic agonists as a preferred drug class for use in the treatment of glaucoma. Placebo-controlled clinical evidence available for the cholinergic agonists suggests the agents are effective in reducing IOP and constricting pupil size in patients with ocular hypertension and in those undergoing ophthalmic procedures and surgeries. Differences in frequency of adverse effects are observed with the agents but overall, the adverse effects reported with ophthalmic cholinergic agonists tend to be rare and mild in nature.

References

1. Lexi-Comp I, ed *Drug Information Handbook.* 21st ed. Hudson, OH: Lexi-Comp; 2015.
2. McEvoy GK, Snow EK, Kester L, Litvak K, Miller J, Welsh OH, eds. *AHFS 2015 Drug Information.* Bethesda, MD: American Society of Health-System Pharmacists; 2015.
3. AHFS Drug Information, ed *AHFS 2014 Drug Information.* Bethesda, MD: American Society of Health-System Pharmacists; 2014.
4. Phan TM, Nguyen KP, Giacomini JC, Lee DA. Ophthalmic beta-blockers: determination of plasma and aqueous humor levels by a radioreceptor assay following multiple doses. *Journal of ocular pharmacology.* Fall 1991;7(3):243-252.
5. Abshagen U, Betzien G, Kaufmann B, Endele G. Pharmacokinetics of metipranolol in normal man. *European journal of clinical pharmacology.* 1982;21(4):293-301.
6. Ophthalmology AAo. Primary open-angle glaucoma, preferred practice pattern. San Francisco2010.
7. Henderer JD, Rapuano CJ. Chapter 64. Ocular Pharmacology. . In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 12th ed. New York, NY: McGraw-Hill; 2011.
8. Salmon JF. Chapter 11. Glaucoma. In: Riordan-Eva P, Cunningham ET, eds. *Vaughan & Asbury's General Ophthalmology.* 18th ed. New York, NY: McGraw-Hill; 2011.
9. American Optometric Association. Care of the Patient with Open Angle Glaucoma St. Louis, MO: American Optometric Association; 2010.
10. Watson PG, Barnett MF, Parker V, Haybittle J. A 7 year prospective comparative study of three topical beta blockers in the management of primary open angle glaucoma. *The British journal of ophthalmology.* Aug 2001;85(8):962-968.
11. Sverrisson T, Gross R, Pearson J, Rusk C, Adamsons I. The dorzolamide/timolol combination versus timolol plus pilocarpine: patient preference and impact on daily life. United States Patient Preference Study Group. International Patient Preference Study Group. *Journal of glaucoma.* Oct 1999;8(5):315-324.
12. Ou Y, Goldberg I, Migdal C, Lee PP. A critical appraisal and comparison of the quality and recommendations of glaucoma clinical practice guidelines. *Ophthalmology.* Jun 2011;118(6):1017-1023.
13. Hiatt RL. Medical management of accommodative esotropia. *Journal of pediatric ophthalmology and strabismus.* Sep-Oct 1983;20(5):199-201.
14. Flach AJ, Fraunfelder FW. Chapter 22. Ophthalmic Therapeutics. In: Riordan-Eva P, Cunningham ET, eds. *Vaughan & Asbury's General Ophthalmology.* 18th ed. New York, NY: McGraw-Hill; 2011.
15. Leydolt C, Menapace R, Stifter EM, Prinz A, Neumayer T. Effect of primary posterior continuous curvilinear capsulorrhexis with posterior optic buttonholing on pilocarpine-induced IOL shift. *Journal of cataract and refractive surgery.* Nov 2012;38(11):1895-1901.
16. Kriechbaum K, Findl O, Koeppl C, Menapace R, Drexler W. Stimulus-driven versus pilocarpine-induced biometric changes in pseudophakic eyes. *Ophthalmology.* Mar 2005;112(3):453-459.
17. Findl O, Kriechbaum K, Menapace R, et al. Laserinterferometric assessment of pilocarpine-induced movement of an accommodating intraocular lens: a randomized trial. *Ophthalmology.* Aug 2004;111(8):1515-1521.
18. Bojic L, Mandic Z, Novak-Laus K, Sonicki Z, Karelovic D. A study of replacement of timolol-pilocarpine with latanoprost in pseudoexfoliation glaucoma. *Collegium antropologicum.* Dec 2003;27(2):729-734.
19. Martins A, Balachandran C, Klistorner AI, Graham SL, Billson FA. Effect of pupil size on multifocal pattern visual evoked potentials. *Clinical & experimental ophthalmology.* Aug 2003;31(4):354-356.
20. Toris CB, Alm A, Camras CB. Latanoprost and cholinergic agonists in combination. *Survey of ophthalmology.* Aug 2002;47 Suppl 1:S141-147.
21. Toris CB, Zhan GL, Zhao J, Camras CB, Yablonski ME. Potential mechanism for the additivity of pilocarpine and latanoprost. *American journal of ophthalmology.* Jun 2001;131(6):722-728.
22. Shaikh MH, Mars JS. The acute effect of pilocarpine on pulsatile ocular blood flow in ocular hypertension. *Eye (London, England).* Feb 2001;15(Pt 1):63-66.
23. Konstas AG, Lake S, Maltezos AC, Holmes KT, Stewart WC. Twenty-four hour intraocular pressure reduction with latanoprost compared with pilocarpine as third-line therapy in exfoliation glaucoma. *Eye (London, England).* Feb 2001;15(Pt 1):59-62.

24. Wutthiphan S, Hanutsaha P, Jenchitr W. Intracameral pilocarpine in topical phacoemulsification. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet.* Dec 2000;83(12):1452-1457.
25. Diestelhorst M. The additive intraocular pressure-lowering effect of latanoprost 0.005% daily once and pilocarpine 2% t.i.d. in patients with open-angle glaucoma or ocular hypertension. a 6-month, randomized, multicenter study. German Latanoprost Study Group. *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie.* May 2000;238(5):433-439.
26. Diestelhorst M, Nordmann JP, Toris CB. Combined therapy of pilocarpine or latanoprost with timolol versus latanoprost monotherapy. *Survey of ophthalmology.* Aug 2002;47 Suppl 1:S155-161.
27. Nordmann JP, Soderstrom M, Rouland JF, Malecaze F. Comparison of the intraocular pressure lowering effect of latanoprost and a fixed combination of timolol-pilocarpine eye drops in patients insufficiently controlled with beta adrenergic antagonists. French Latanoprost Study Group, and the Swedish Latanoprost Study Group. *The British journal of ophthalmology.* Feb 2000;84(2):181-185.
28. Cekic O, Batman C. Effect of intracameral carbachol on intraocular pressure following clear corneal phacoemulsification. *Eye (London, England).* Apr 1999;13 (Pt 2):209-211.
29. Strohmaier K, Snyder E, Adamsons I. A multicenter study comparing dorzolamide and pilocarpine as adjunctive therapy to timolol: patient preference and impact on daily life. *Journal of the American Optometric Association.* Jul 1998;69(7):441-451.
30. Solomon KD, Stewart WC, Hunt HH, Stewart JA, Cate EA. Intraoperative intracameral carbachol in phacoemulsification and posterior chamber lens implantation. *American journal of ophthalmology.* Jan 1998;125(1):36-43.
31. Spierer A, Zeeli T. Postoperative miotics for patients with infantile esotropia. *Ophthalmic surgery and lasers.* Dec 1997;28(12):1002-1005.
32. Laranjeira E, Buzard KA. Pilocarpine in the management of overcorrection after radial keratotomy. *Journal of refractive surgery (Thorofare, N.J. : 1995).* Mar-Apr 1996;12(3):382-390.
33. Bergea B, Bodin L, Svedbergh B. Primary argon laser trabeculoplasty vs pilocarpine. IV. Long-term effects on optic nerve head. *Acta ophthalmologica Scandinavica.* Jun 1995;73(3):216-221.
34. Bergea B, Bodin L, Svedbergh B. Primary argon laser trabeculoplasty vs pilocarpine. III. Long-term effects on visual fields. *Acta ophthalmologica Scandinavica.* Jun 1995;73(3):207-215.
35. Burr J, Azuara-Blanco A, Avenell A. Medical versus surgical interventions for open angle glaucoma. *Cochrane Database Syst Rev.* 2005(2):Cd004399.
36. Burr J, Azuara-Blanco A, Avenell A, Tuulonen A. Medical versus surgical interventions for open angle glaucoma. *Cochrane Database Syst Rev.* 2012;9:CD004399.
37. Place VA, Fisher M, Herbst S, Gordon L, Merrill R. Comparative pharmacologic effects of pilocarpine administered to normal subjects by eyedrops or by ocular therapeutic systems. *American journal of ophthalmology.* Oct 1975;80(4):706-712.
38. Yasuda A, Yamaguchi T. Steepening of corneal curvature with contraction of the ciliary muscle. *Journal of cataract and refractive surgery.* Jun 2005;31(6):1177-1181.
39. Lal A, Kataria V, Rajpal A, Khanna N. Pharmacodynamic effects of pilocarpine eye drop enhanced by decreasing its volume of instillation. *Indian journal of physiology and pharmacology.* Jul 1995;39(3):267-270.
40. Tsifetaki N, Kitsos G, Paschides CA, et al. Oral pilocarpine for the treatment of ocular symptoms in patients with Sjogren's syndrome: a randomised 12 week controlled study. *Annals of the rheumatic diseases.* Dec 2003;62(12):1204-1207.
41. Papas AS, Fernandez MM, Castano RA, Gallagher SC, Trivedi M, Shrotriya RC. Oral pilocarpine for symptomatic relief of dry mouth and dry eyes in patients with Sjogrens syndrome. *Advances in experimental medicine and biology.* 1998;438:973-978.
42. Leavitt JA, Wayman LL, Hodge DO, Brubaker RF. Pupillary response to four concentrations of pilocarpine in normal subjects: application to testing for Adie tonic pupil. *American journal of ophthalmology.* Mar 2002;133(3):333-336.
43. Edgar DF, Crabb DP, Rudnicka AR, Lawrenson JG, Guttridge NM, O'Brien CJ. Effects of dipivefrin and pilocarpine on pupil diameter, automated perimetry and LogMAR acuity. *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie.* Feb 1999;237(2):117-124.
44. Oostenbrink JB, Rutten-van Molken MP, Opdenoordt TS. The treatment of newly diagnosed patients with glaucoma or with ocular hypertension in The Netherlands: an observational study of costs and initial

treatment success based on retrospective chart review. *Documenta ophthalmologica. Advances in ophthalmology.* 1999;98(3):285-299.
45. Doe EA, Campagna JA. Pilocarpine spray: an alternative delivery method. *Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics.* Feb 1998;14(1):1-4.
46. Boles Carenini B, Brogliatti B, Dorigo MT, Vadala G, Protti R, Bellone A. Prepared association of metipranolol 0.1% + pilocarpine 2% and of timolol 0.5% + pilocarpine 2%. Comparison of clinical efficacy and topical tolerability in the treatment of patients affected by POAG tonometrically uncontrolled with beta-blocker alone (two-centre study). *Acta ophthalmologica Scandinavica. Supplement.* 1997(224):54-55.
47. Yuksel N, Elibol O, Caglar Y, Alcelik T. Short-term effect of apraclonidine on intraocular pressure in glaucoma patients receiving timolol and pilocarpine. *Ophthalmologica. Journal international d'ophtalmologie. International journal of ophthalmology. Zeitschrift fur Augenheilkunde.* 1997;211(6):354-357.
48. Tabandeh H, Thompson GM, Kon C, Bolton T. Phenylephrine and pilocarpine in the treatment of post-operative irido-corneal adhesion. *Eye (London, England).* 1995;9 (Pt 4):452-455.
49. Douglas GR. A comparison of acetylcholine and carbachol following cataract extraction. *Canadian journal of ophthalmology. Journal canadien d'ophtalmologie.* Jan 1973;8(1):75-77.
50. Romano JH. Double-blind cross-over comparison of aceclidine and pilocarpine in open-angle glaucoma. *The British journal of ophthalmology.* Aug 1970;54(8):510-521.
51. Beasley H. Miotics in cataract surgery. *Transactions of the American Ophthalmological Society.* 1971;69:237-244.
52. Beasley H. Mitotics in cataract surgery. *Archives of ophthalmology (Chicago, Ill. : 1960).* Jul 1972;88(1):49-51.
53. Kwitko ML, Kelman CD. *The History of Modern Cataract Surgery.* New York, NY: Kugler Publications; 1998.
54. Fiscella RG. Glaucoma medications: a drug-therapy review. *Managed care (Langhorne, Pa.).* Nov 2002;11(11 Suppl):25-31.