According to the national report Vision Problems in the U.S., 3.4 million adults are afflicted with vision impairment and blindness in the United States. The number of ophthalmic patients will double in the next 30 years. The report, published by the National Eye Institute in partnership with Prevent Blindness America, further estimates a cost burden to the nation that exceeds $4 billion annually in benefits and lost taxable income. Ocular medications and their managed use are a sizable portion of this total cost.

Ophthalmic agents are among the most commonly self-prescribed medications in today’s pharmaceutical marketplace. Ocular discomfort associated with dry eye may be the most common condition for which nonprescription ophthalmic products are used. Ocular discomfort may affect as many as 4.3 million people in the United States and 20% of all elderly people. In their prescribed forms, ophthalmic medications bring a number of challenges to the managed care organization. For example, this category of medications includes specially compounded products that are storage-sensitive and have certain sterility requirements. In the past decade, an explosion of new glaucoma medications and ocular allergy agents has entered the market. As a result, ocular pharmacology, traditionally one of the least-represented specialty groups in pharmacy, has attracted some attention but still remains one of the least-managed areas of pharmaceutical care by pharmacists.

As a profession, pharmacy will be expected to address these factors and to provide a redefined and proven relevance as a base source of ophthalmic drug experts. The intent of this article is to provide a baseline understanding of the ocular pharmacology specialty, as well as address the intricacies specific to the health professionals who provide ophthalmic pharmaceutical care. The information is presented in terms of the seven domains that make up managed care pharmacy, namely: Drug Distribution and Dispensing; Patient Safety; Clinical Program Development; Communication with Patients, Prescribers, and Pharmacists; Clinical and Formulary Considerations; Business Management; and Cost Management.

History

Ocular pharmacology has a rich heritage that includes a century of discovery and innovation. Modern managed care pharmacy of the ophthalmic patient originated with antibiotic recommendations proposed by Dr. K. Swan (1951) and Dr. Irving Leopold (1954). Within the full scope of use, ophthalmic medications are used for purposes that are therapeutic, diagnostic, surgically adjunctive, palliative, preventive, and cosmetic. The importance of the eye as an organ drug delivery pathway is seen by the plethora of drug manufacturers who exclusively develop and market the ophthalmics or who invest in subsidiary branches. Two fine historical reviews of 20th century ocular pharmacology have been written through the Thomas R. Lee Center for Ocular Pharmacology at Eastern Virginia Medical School and The Beckman Vision Center at the University of California at San Francisco Medical School.

Managed Care

Clinical ocular pharmacology is sometimes poorly addressed in managed care pharmacy services. This is not surprising, since ocular care is a small portion of managed care costs. Nonpharmacist health care professionals in the fields of ophthalmology and optometry have dominated the provisions for pharmaceutical care of the ophthalmic patient.

There is still a shortage of clinically relevant pharmacists specialized in ocular pharmacology. Because specialty areas such as dermatology or ophthalmology often comprise such a small portion of drug formularies, the amount of time that can be spent on reviewing “smaller ticket” items is limited. Often, many ophthalmic policies and procedures rely on ophthalmologists, and sometimes...
optometrists as drug therapy consultants. Although most ophthalmologists have excellent clinical skills, their knowledge of managed care plans, P&T committee formulary reviews, and pharmacoeconomics is often limited.

The challenge set forth to the profession of pharmacy is to create a new generation of oculocutaneous specialists who can bridge the gap between the expectations of emerging eye care treatments and the expectations of managed care pharmacists. This is a highly competitive cost-contained market. Pharmacists well versed and involved in the treatment plans of the ophthalmic patient will determine the relevance of the pharmacy profession in treating and managing eye disorders, infections, and cosmetics.

### Drug Distribution and Dispensing

Despite the handful of commercially prepared ophthalmic agents that fall within new medication categories, there has been little change over the years in the standard way drugs are delivered to the eye. The medication furnished is either commercially available in its final form or must be compounded through the services of a pharmacist.

The most serious eye conditions still require extemporaneously prepared formulations by a pharmacist. These compounded products have short stability periods and stringent storage requirements. A number of compounding formulas abound in the practice community—much of an institution’s practice standard is determined by the experiences and results taken from the medication prescribers. There is one published text written exclusively on ocular drug compounding.

When one considers some of the few recent advances in ocular pharmacology, technology in drug delivery is showcased. One such advance is seen with the use of carbopol gels. Drugs incorporated into gels have produced ocular products that are easily suspended, well tolerated, and less visually disrupting than previously used suspending agents, namely those using petroleum or lanolin as an ointment base. Products containing carbopol gels include Pilopine, Vexol, Betoptic S, and Azopt. Newer solvents, such as cyclodextrins, have improved the aqueous solubility, the stability, and the bioavailability of ophthalmic medications while also reducing ocular irritation. Fixed forms of drug delivery such as intraocular implants provide sustained intraocular drug levels of dexamethasone (Surodex) and ganciclovir (Vitrasert). Other intraocular implants are currently under investigation. Other advancements include gel-forming solutions, such as Timoptic-XE, that have the capability of forming gels in the tear film and provide for reduced dosing requirements due to a prolonged contact time to the drug-absorbing cornea. Further use of instrumentation in ophthalmology is seen in intravenous verteporfin (Visu-dyne) applied in conjunction with laser activation (photodynamic therapy or PDT), resulting in tangible benefit to patients with the wet form of age-related macular degeneration.

It is apparent from the complexities framing ophthalmic drug preparation and dispensing that the pharmacist is a necessary provider of information, education, and service.

### Drug Safety

The mere act of dispensing commercially prepared ophthalmic forms is riddled with challenges. Often, the patient must administer medications in a particular order and method. The pharmacokinetics of these agents are variable both in vitro and in vivo.

One such dilemma associated with commercially available oculardrugs is bio-equivalency. Recent problems with generic ophthalmic products suggest inequivalence to commercially branded products. The generic product of Pred Forte (prednisolone acetate 1%, Allergan), a potent corticosteroid for the treatment of ocular inflammation, has demonstrated caking of the drug and inadequate resuspension. A more extreme case involved generic 1% diclofenac sodium ophthalmic solution that was associated with approximately 200 cases of corneal toxicity, including superficial punctate keratopathy and corneal melting. The release of a generic timolol gel-forming solution with a different gel base and AB rating with no head-to-head study data and different retention times in the ocular tear film was of concern. Ophthalmic product “generic equivalence” must take into consideration particle size and other properties of suspensions, inert ingredients and preservatives, and different vehicles before true generic equivalency can be considered.

### Clinical Program Development

The disposition of ophthalmic agents is challenging as well. There are variations in absorption to the intended treatment site due to factors such as tissue integrity, lipophilicity, and chemical characteristics, to name a few examples.

Invariably, most ophthalmic patients present with one or more medical conditions. This brings forth several target populations that require special consideration in managed care, especially hypertensive, diabetic, and AIDS patients. In a popular textbook addressing ocular pharmacology, considerations of special patient populations are addressed.

In order to develop a managed care service in ocular pharmacology, there needs to be a source of expertise within the health care organization. For pharmacy, this requires a pharmacist who is willing and capable of taking on the additional steps necessary to acquire a specialist’s acumen of the subject. Most organizations that have an active pharmaceutical care program in ocular pharmacology still fail to provide hands-on clinical work with the patient.

Clinical program development must begin with access to knowledge. A managed care program in oculopharmacology should be centered on personnel that are budgeted, trained, and scheduled to provide services in this specialty area. The following information is a starting point to access information in the area of ocular pharmacology.

In addition to select schools of medicine, optometry, and pharmacy, there are excellent professional organization Web sites pro-
Ophthalmic Agents and Managed Care

TABLE 1  Eye Organization Web sites

- American Academy of Ophthalmology (www.AAO.org)
- American Optometric Association (www.AAOOPT.org)
- Association for Research and Vision in Ophthalmology (www.ARVO.org)
- National Eye Institute (www.nei.nih.gov)
- Prevent Blindness America® (www.preventblindness.org)

TABLE 2  Essential Texts


TABLE 3  Supplementary Texts


Ophthalmic pharmaceutical care information (see Table 1).

The medical literature has provided a steady but limited supply of ophthalmic pharmacology texts. The field of ophthalmology recognizes the text by Zimmerman, Koonere, Fechtner, and Sharir as the primary reference on ocular pharmacology. In similar fashion, the profession of optometry holds the Bartlett/Jaanus text as its source text. Pharmacy contributions to ocular pharmacology are mainly recognized through work published by the American Pharmaceutical Association. A pharmacy department's library should provide access to these ocular pharmacology references and others (see Tables 2 and 3).

Quick insight into ocular pharmacology can also be gained through a literature review on the treatment of the ophthalmic patient. Files of pertinent articles can provide timely and sufficient information to a managed care pharmacy program. Of broad ophthalmic interest, the authors provide a short list of review articles and chapters that have written within the context of their practice experiences (see Table 4, next page).

Medical journals continue to provide the most recent findings shared among ophthalmic medical professionals. A list of the most popular references is in Table 5 (next page).

Communications with Patients, Prescribers, and Pharmacists

With the numbers of experts in ocular pharmacology being scarce, program development in ocular pharmacy managed care becomes one of shared communications and unity of effort.

The patient has most access to a pharmacist at the exchange of medications during the drug counseling session. Within the university setting, ocular pharmacology specialists also provide valuable input to the treatment plan through participation in clinics, rounds, and advanced education and training.

If one were to compare the use of extemporaneous compounding formulations used among medical providers, a wide degree of variation would be found. As mentioned earlier, the authors are aware of only one textbook that is written entirely to reference common extemporaneously compounded eye regimens. The more common source material for compounded ophthalmic preparations is transferred by the experience and influence of the attending ophthalmologists and indexed historical files of copied protocols and recipes shared among hospitals in a given region.

Establishing liaison with local experts in this area is challenging also. It is estimated by the authors that there are fewer than a dozen practicing clinical ophthalmic specialists in the United States. For the profession of pharmacy, post-doctorate fellowships in ocular pharmacology are a rarity. The majority of specialists distinguished as ocular pharmacologists have a combined M.D./Ph.D. degree and are dispersed within academia. There are also small numbers of specialists found within the professions of pharmacy and optometry, but they, too, are almost exclusively in the university settings or sectors of the pharmaceutical industry. A high degree of success is found in a collaborative effort among the professions of
Strides are being made in bringing the profession of pharmacy into the spotlight for ocular pharmacy. Starting in May 2002, the American Pharmaceutical Association is sponsoring training for pharmacists and university educators on ocular pharmacy and self-treatment of ocular conditions. The training is being conducted by some of the authors of this article.

Clinical and Formulary Considerations

Many drug regimens use combinations that have questionable efficacy. At times, these “proven” regimens actually have counteractive effects. One such combination therapy is seen in the drug management of glaucoma using adrenergic agents, such as epinephrine, in combination with beta-blocker agents, such as timolol. Though this combination was fairly common at one time, the advent of new glaucoma therapies demonstrated improved efficacy, such as the topical ophthalmic carbonic anhydrase inhibitors first introduced to the market in 1995.

There are a number of commercially prepared combination glaucoma products that are being taken off production due to their limited utility. An example is the category of pilocarpine/epinephrine combination ophthalmic products (i.e., E-Pilo, P1E1, P2E1, etc.). In the past, these combination products were available from Novartis Pharmaceuticals and Alcon Labs. During the year 2001,
Historically, optometry was termed the “drugless” profession. Delivery of vision care by optometrists was originally based on “non-dilated” examinations, without the use of cycloplegic (fixing) and mydriatic (dilating) ophthalmic solutions. The rationale for this approach was that a better subjective refraction could be obtained using retinoscopy without cycloplegic medications. On the other hand, ophthalmologists performed routine ocular exams using medications and indirect ophthalmoscopy. As technology advanced, it became apparent that standard practice of care required the use of dilating agents in the completion of an ophthalmic examination. This led to a broad nationwide push to change optometry practice acts to include the use of mydriatic and cycloplegic eyedrops as part of the optometric scope of practice.

With these legislative changes, optometrists entered into the medical model of eye care, which included advanced examination procedures such as indirect ophthalmoscopy and biomicroscopy.

Optometry took the next evolutionary step in ocular pharmaceutical care as changes in health care insurance shifted individuals into third-party health care plans. It became apparent that if optometry was to maintain its claim of being “cost-effective” providers of basic “primary” eye care, it would require more than just mydriatics and cycloplegics. The inclusion of all legend drugs became the next goal. With this change in ideology, changes in optometry school curricula were made. The new curricula incorporated courses in general and ocular pharmacology, physical diagnosis, and ocular emergencies. In conjunction with the academic shift, an ongoing legislative effort was initiated to establish broad privileges for optometrists in the use of legend drugs in all 50 states. It took 20 years, but now all states allow the use of topical legend agents for the treatment of ocular allergy, infection, and inflammation, although some states prohibit the use of topical corticosteroids. All but four states allow the use of glaucoma agents, at least with topical antiglaucoma agents. The change in the scope of practice of optometry has met continued resistance from organized medicine. Optometrists have encountered difficulties in gaining access to hospital staffs, particularly in large urban areas. In addition, physicians often have significant influence on advising medical plans on the number and type of practitioners that should be included in a particular health plan. Despite the recent marked elevation in the standards of optometric education and mandatory proficiency examinations required for licensure, third-party insurers and major medical plans are still presenting optometrists with resistance in terms of blanket acceptance. Many insurance plans require medical-based requirements that are necessary to gain access to “panel” programs. This includes “board certification” and completion of a residency. While residency programs are available for optometrists to pursue, they are not required for licensure. Moreover, there is no formal “board certification” process available to an optometric clinician. Until insurance companies establish policies to allow access by optometrists in a category that is tailored to the educational standards of the optometry profession, it will be difficult for optometrists to gain access to many traditional physician-dominated health plans. Furthermore, the abundance of ophthalmologic providers, particularly in urban areas, has dampened efforts by optometrists to gain access to already overcrowded health care plans.

Optometrists have addressed this resistance to entry to traditional health care plans by forming their own eye health networks. The Vision Service Plan (VSP), for example, is primarily an optometric-based eye care plan that provides enrollees with eye examinations, contact lenses, and spectacles at reduced costs when they obtain services from participating providers. Companies such as Cole and Davis Vision run similar plans in both commercial retail optical stores and private optometric practices, respectively. Although these plans will pay for a “yearly examination,” they often do not provide for medical care, such as the treatment of glaucoma or other eye disorders.

Despite the difficulty optometrists encounter in gaining access and recognition from various insurance providers and hospitals, the accessibility and wide geographic distribution of optometrists allow them to be key triage points into the health care system. Optometrists are now able to diagnose and manage various disorders of the eye independently, thereby alleviating the need for additional patient costs as a result of an ophthalmologic referral. As optometrists gather continued expansion of their scope of practice, insurance providers may view optometric providers as cost-efficient alternatives to ophthalmologic care in select clinical scenarios.

Both companies made the decision to discontinue their entire product line due to a lack of market demand. As noted already, the use of these drugs both individually and in combination has markedly dropped off due to superior agents introduced within the past 10 years.

Combination antibiotic/anti-inflammatory products have also been a source of therapeutic scrutiny. Indiscriminate use of ophthalmic corticosteroid preparations may predispose patients to ocular side effects, including secondary infections, ocular hypertension, glaucoma, and even cataract formation. As an example, prolonged use of a combination product containing a corticosteroid and antibiotic without proper monitoring increases the potential for a secondary fungal or herpetic infection. Corticosteroids are contraindicated in herpes simplex epithelial keratitis and fungal keratitis since these infections can proliferate in the presence of the drug. In the case of herpes simplex stromal keratitis, specific corticosteroid therapy may be used under close monitoring in order to lessen the permanent scarring of delicate tissues of the cornea.

The American Academy of Ophthalmology states that corticosteroids have no role in the treatment of infectious conjunctivitis.
and that combination eye products containing antibiotics and corticosteroids are seldom, if ever, indicated for the treatment of any ocular inflammation. Furthermore, it is generally recommended that primary care clinicians not prescribe or use ophthalmic corticosteroids or their combination products in any ocular condition unless the case is referred to and followed by an ophthalmologist and/or an optometrist. The dangers of indiscriminate corticosteroid use were presented in a case study that documented bilateral cataract formation in a 24-year-old patient who applied 0.12% prednisolone acetate eye drops twice a day for a four-year period. Yet there may be exceptions to the practice of not using combination ophthalmics. Patients with low cognitive mental functions who receive short-term treatment following cataract extraction or glaucoma filtering procedures appear to be good candidates for a simplified medication regimen using combination drops.

It is a known fact that every medication introduced into the eye will have some degree of systemic absorption and possibly systemic side effects. Topically applied ocular drugs are primarily absorbed from the conjunctival sac into the systemic circulation through the conjunctival capillaries, from the nasal mucosa after passage through the lacrimal drainage system, or, after swallowing, from the pharynx or the gastrointestinal tract. Because topically applied drugs avoid the first-pass metabolic inactivation that normally occurs in the liver, these drugs can exert the same substantial pharmacologic effect as similar doses delivered parenterally. Each 50 microliter drop of a 1.0% solution contains 0.5 milligrams of the drug. This means that solutions applied topically to the eye may provide sufficient systemic absorption to exceed the minimum toxic systemic doses.

A more recent cause for alarm came from a drug manufacturer who reported several adverse cardiac events associated with excessive systemic absorption of a combination topical ophthalmic product used in routine eye exams. In the safety report, three patients were affected by the combination product of 1% hydroxyamphetamine hydrobromide with 0.25% tropicamide (Paremyd, Allergan). One patient died from myocardial infarction, another patient had a nonfatal ventricular fibrillation, and the third case involved syncope and bradycardia. Since then, the product has been withdrawn from the market due to manufacturing problems involved syncope and bradycardia. Yet another patient had a nonfatal ventricular fibrillation, and the third case involved syncope and bradycardia. Since then, the product has been withdrawn from the market due to manufacturing problems but will be returning back to production shortly. Systemic absorption of eye drops can be substantially reduced through the targeting of drug administration to the conjunctival cul-de-sac, positioning of the patient's head, and manual occlusion of the puncta. Detailed instructions on these techniques and the proper administration of ophthalmic medications is covered in textbook references already cited.

Drug therapy is a mainstay in ophthalmic conditions that warrant surgical intervention. Most ophthalmic patients require the use of medicines preoperatively, perioperatively, and postoperatively in corrective and cosmetic ophthalmic surgeries. Even with the evolving use of lasers, seen in corrective visual acuity procedures such as LASIK, glaucoma filtering procedures such as trabeculectomy, and diabetic retinopathy procedures such as panretinal photocoagulation, ophthalmic medications are commonly prescribed to enhance and maintain healthy vision.

Business management

The real issue to drug benefit is one of relevance. Are the services provided to the patient within the scope of one's given profession and do they provide meaning to successful treatment and reimbursement within the scope of medicine? In order to challenge the profession of pharmacy to invest in the managed care of ocular pharmacy, one must provide examples of successful insertion within an untapped field. Of all the professions that treat the ophthalmic patient, optometry has undergone the most significant changes in the past 20 years. The story of the optometry profession's journey into drug therapy is a noteworthy one (see box, previous page).

Cost management

A significant amount of time and effort is devoted to therapeutic application and control of the drug formulary. Ophthalmic agents as a group are not in the top drug classes by expenditure, but ophthalmics can have a high cost per patient. The pharmacy and therapeutics (P&T) committee is responsible for controlling drug access to its respective members. The role of the managed care pharmacist regarding rationale, clinical, and pharmacoeconomic drug analysis is critical to a major part of the success of any pharmacy benefit management (PBM) or health maintenance organization (HMO). Obviously, certain areas of clinical pharmacy, such as infectious disease, cardiology, peptic ulcer disease, etc., have many pharmacist practitioners that are well versed with product selection based on clinical superiority and cost analysis. Medication Utilization Evaluations (MUE) and Cost Containment Reports (CCR) remain vital to the cost management of ophthalmic medications.

Conclusion

Many changes in ocular therapy within the last decade have begun to hit the “radar screen” of managed care plans. New, more effective, therapies with perceived higher costs and new prescribers have definitely changed the face of ophthalmic pharmacotherapy. Especially with the advent of more expensive glaucoma therapy, managed care plans have begun to implement cost containment strategies within their perspective plans. Ocular allergy medication has also raised the level of interest due to expensive ocular allergy medications and direct-to-consumer advertising. However, pharmacoeconomic studies are underway to demonstrate the cost-effectiveness of such therapies, especially in the treatment of potentially blinding conditions like the glaucomas.

The finest efforts in managed care ocular pharmacy are attributed to members in the practice fields of ophthalmology, optometry, research, and industry. Until now, pharmacy impact has been present but rarely acknowledged.

Pharmacy as a profession is summoned to prove its relevance
in the area of ocular pharmacology as it applies to the managed care of our ophthalmic patients.

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