• Prevalence and economic implications
• Guidelines for treatment
• Drug-therapy review
• Pharmacoeconomic data
• Formulary status of glaucoma agents
• Benefits of disease management
• Adherence to therapy
• P&T survey results

Continuing education credit for physicians and pharmacists is sponsored by the University of Arizona Colleges of Medicine and Pharmacy at the Arizona Health Sciences Center, Tucson

This program is supported by an unrestricted educational grant from Allergan
As the American population ages, glaucoma prevalence rises—and will continue to do so—thus consuming greater medical and financial resources. For the first time, MCOs are attempting to understand ophthalmologic diseases, particularly glaucoma. Their interest is driven, in part, by the appearance in recent years of several new pharmaceutical products to treat glaucoma. The efficacy of these products has created demand and, in turn, a need for appropriate criteria for their utilization.

This peer-reviewed publication gives physicians and pharmacists who serve on pharmacy and therapeutics committees up-to-date information about the most efficacious and cost-effective medical treatments available. Relatively little published data exist in a centralized format about medical therapies for glaucoma, compared with information about other chronic conditions. This publication, a digest of existing knowledge and best practices, serves as a valuable tool for formulary decision makers and is an important contribution to the medical literature.

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INTRODUCTION
Glaucoma Arrives on Managed Care’s Doorstep

The appearance of competitive new prostaglandins and alpha2 agonists has offered patients, health plans, and physicians new treatment options. It also has produced a new cost driver in managed care organizations.
SHARAD S. MANSUKANI, MD

OVERVIEW
Glaucoma: Prevalence, Utilization, and Economic Implications

About 2.2 million Americans 40 and older — about 1.9 percent of this population — have primary open-angle glaucoma. Managed care organizations spend $1 billion annually to treat glaucoma.
MICHAEL D. DALZELL

DETECTION AND TREATMENT
Clinical Guidelines for the Treatment of Glaucoma

The AAO guidelines are considered the current standard. A task force working with NCQA to develop a glaucoma-related HEDIS measure may provide future direction in populationwide care.
LAWRENCE D. GOLDBERG, MD, MBA

PHARMACOTHERAPEUTIC OPTIONS
Glaucoma Medications: A Drug-Therapy Review

Today, clinicians have unprecedented versatility in the treatment of glaucoma. Choosing the optimal regimen hinges on knowledge about the capabilities and the limitations of currently available medications.
RICHARD G. FISCHELLA, RPh, MPH
COST-EFFECTIVENESS

Considerations in the Pharmacoeconomics of Glaucoma

Providing optimal glaucoma care requires planning, based not only on the historically relevant factors of drug safety and efficacy, but also on data relating to the value of medical treatments.

JAN D. HIRSCH, PhD

DECISION-MAKING FOCUS

Current Formulary Status of Glaucoma Agents

Data reported in this section reflect aggregate national formulary statuses of prescription glaucoma products, as well as trends with respect to the same.

DATA COMPILATION BY MEDI_MEDIA INFORMATION TECHNOLOGIES

BEYOND ACUTE TREATMENT

Constructing Disease Management Programs for Glaucoma

Glaucoma, which is associated with diabetes, hypertension, and hypothyroidism, is a good candidate for disease management. Clinicians and MCOs can benefit from establishing a DM program for glaucoma.

LAWRENCE D. GOLDBERG, MD, MBA

COMPLIANCE

Improving Adherence to Drug-Treatment Regimens for Glaucoma

Compliance with glaucoma therapy is relatively poor. Because glaucoma progresses slowly, long-term adherence is crucial to improving clinical and financial outcomes of treatment.

SHARAD S. MANSUKANI, MD

CONTINUING EDUCATION

Self-test

Pharmacist CE answer sheet/statement-of-credit request

OUTLOOK

P&T survey results

Cover art: Gino Severini, "Sea = Dancer" (Mare = Ballerina), January 1914. Oil on canvas, 105.3 x 85.9 cm, including artist's painted frame. Peggy Guggenheim Collection.
Continuing education is offered to physicians and pharmacists who read this publication, answer the self-test that begins on page 54, and fill out the appropriate evaluation form on either page 55 or 56.

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Expiration date: Nov. 29, 2003.

Course description

This activity is designed to educate physicians and pharmacists about screening, treatment, and management of glaucoma. This publication includes a series of review articles detailing current consensus thinking about screening and treatment guidelines; pharmaceutical therapeutic options; pharmacoeconomic considerations in selecting glaucoma therapy; and issues inherent in both managing the disease and in encouraging patient compliance with drug therapy. Additionally, current data are presented detailing the prevalence of glaucoma in the United States, its economic impact, and formulary status of medication therapies.

Educational needs assessment

As the American population ages, the prevalence of glaucoma is increasing and will continue to do so, thus consuming a greater share of medical and financial resources. Physicians and pharmacists seek knowledge about the most effective treatment approaches for glaucoma. These medical professionals want to be kept informed of the most current efficacious and cost-effective medical treatments available. Compared with other chronic conditions, relatively little published data exist in a centralized format to help these professionals make informed decisions. This peer-reviewed publication serves as a digest of existing knowledge and best practices for use by these professionals.

Target audiences

Medical directors; pharmacy directors; practicing primary care physicians, ophthalmologists, and pharmacists; members of pharmacy and therapeutics committees; and other senior managers in managed health care organizations.

Educational objectives

After reading this publication, the participant should be able to:

• Describe risk factors for glaucoma, the prevalence of the disease in the United States, and the economic impact it carries.
• Explain current consensus on glaucoma treatment, as well as appropriate methods of screening and prevention in high-risk individuals.
• Identify pharmacotherapeutic options for treatment of glaucoma, explain their mechanisms of action and relative effectiveness, and discuss contraindications for these products.
• Describe basic pharmacoeconomic principles that can help clinicians and managed care decision makers incorporate a value component into treatment determinations for glaucoma patients.
• Define appropriate roles for clinicians and managed care decision makers in developing a disease management approach to glaucoma.
• Illustrate the extent of and causes for non-adherence to glaucoma therapy and methods for improving the same.

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Glaucoma Arrives On Managed Care’s Doorstep

Sharad S. Mansukani, MD
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For the first time, managed care organizations are attempting to understand ophthalmologic diseases, particularly glaucoma. Their interest is driven by the appearance in recent years of several new pharmaceutical products to treat glaucoma. These new pharmacotherapeutic classes, including the prostaglandins and alpha2 agonists, are improving quality of life for people with glaucoma — preserving vision and halting progression of the disease more effectively than older products. Their efficacy has created demand for them and, in turn, a need for appropriate criteria for their utilization.

It wasn’t always this way. For years, glaucoma floated beneath the radar screens of most MCOs. The reason? Until recently, glaucoma was not a cost center. Medical directors’ agendas tend to be shaped by cost and utilization drivers that affect the bottom line: pharmacy, injectables, office visits, hospitalization, and emergency care. Most pharmacy directors will acknowledge that they actively monitor utilization of only the top 10 classes of drugs, including antihistamines, antidepressants, and antihypertensives. Traditionally, ophthalmologic agents rarely made the top 20, meaning that pharmacy directors weren’t overly concerned about them being significant contributors to expenses.

All the while, glaucoma continued its insidious assault on more than 2 million people, particularly the elderly, black, and Hispanic populations (NEI 2002). The second-leading cause of blindness in the United States, glaucoma is primarily associated with elevated intraocular pressure (IOP). Over time, IOP damages the optic nerve — destroying, at first, peripheral and then central vision — often silently, going unnoticed until its late stages. IOP can be controlled with medication, and, as the Ocular Hypertension Treatment Study demonstrates, early detection and treatment can prevent or delay onset of primary open-angle glaucoma, the most common form of the disease (Kass 2002). Argon laser trabeculoplasty, which aids fluid drainage from the eye and thus reduces IOP, is generally indicated after medications have been tried. End-stage glaucoma is often treated with conventional surgery after medication and laser-treatment failures.

The turning point in treatment — and what gained the attention of health plans and their pharmacy and therapeutics committees — was the development of powerful popular new prostaglandins and alpha2 agonists have brought about higher utilization, while their expense has produced a new cost driver in managed care organizations. The recent appearance of competitive products within these drug classes has offered patients, health plans, and physicians new treatment options.

1 Health Partners is a not-for-profit, 150,000-member Medicare and Medicaid HMO that is jointly owned by Philadelphia’s teaching hospitals. Mansukani, who attended Lehigh University and the Medical College of Pennsylvania, is an ophthalmologist by training, completing his residency in ophthalmology at the University of Pennsylvania and a fellowship in research and treatment of glaucoma at Wills Eye Hospital. He also served as a fellow in managed care/quality improvement at the University of Pennsylvania’s Wharton School of Business, is board certified in Medical Management by the American College of Physician Executives, and earned a Managed Care Executive degree from the Kellogg School of Business. He continues to practice ophthalmology and is on the faculty at both the University of Pennsylvania and Temple University School of Medicine.
ful new medication therapies. Specifically, two things occurred. First, the introduction of popular new prostaglandin and α₂ agonist products abruptly brought about higher utilization, while their expense relative to older therapies produced a new cost driver in managed care organizations. Second, the recent appearance of competitive products within these drug classes offered patients, health plans, and physicians new treatment options. Suddenly, there were choices to be made. Health plans will need assistance in dealing with these formulary options.

**OPPORTUNITY FOR PARTICIPATION**

Within managed care plans, P&T committees are beginning to think about guidelines for appropriate utilization of new glaucoma drugs. For most, this is terra incognita. Managed care executives traditionally are not ophthalmologists, and importantly, there are no ophthalmologists on P&T committees. Most P&T committees that render decisions about ophthalmologic agents do so based on manufacturer-provided research and U.S. Food and Drug Administration product reviews. In a minority of cases, these committees — astutely — are asking ophthalmologists for their input.

The situation is reminiscent of that 15 years ago, when managed care P&T committees began to wrestle with questions related to proper utilization of potent new antidepressants. The dynamics mirror those of today: a medical specialty that insurers didn’t fully understand; a group of providers who had little exposure to managed care; and an emerging new class of drugs rapidly gaining popularity. The novelty of it all created an opportunity for every party involved — MCOs, physicians, and pharmaceutical manufacturers — to shape the development of appropriate utilization guidelines.

Today’s players, too, are new at this. All three groups are trying to learn to work together in a way that improves care for glaucoma patients while managing rising pharmaceutical costs. The learning curve will be steep.

Ophthalmologists don’t have the experience their colleagues in other specialties possess with respect to influencing P&T committees. Until now, they have not had to interact with managed care payers about medical authorizations and formulary status — or, at least, not to the extent that other specialists and primary care physicians routinely do. Cardiologists, internists, and primary care physicians not only are more savvy about how to persuade P&T committees, but often they compose them.

Most manufacturers of newer products, meanwhile, are smaller pharmaceutical companies that are attempting to build relationships with MCOs, which themselves are struggling with this new therapeutic challenge. Not only is managed care relatively unfamiliar with the perspective of ophthalmology, so are hospitals and physician-provider organizations that are at risk for pharmaceutical expenditures. These groups all report increased utilization of new glaucoma agents, and they are asking for knowledgeable and objective guidance for their use.

Although the importance of advancing sound treatment protocols can no longer be ignored, neither can a truism of their development: Universal buy-in is crucial to the successful application of any guideline. The collective input of all three parties can result in evidence-based treatment standards, while mutual cooperation can foster a useful understanding of each others’ goals and how to work around each others’ limitations. Here’s where physicians, drug manufacturers, and MCOs all have roles — and opportunities.

For physicians, the role is that of educator. Managed care organizations want to forge standards for prostaglandin use, but they first must develop a better understanding of glaucoma and its treatment. This presents an immediate opening for ophthalmologists to define their importance to managed care — before their role is defined for them. With ophthalmology having been largely exempt from exposure to managed care and formularies, there is, understandably, some hesitancy in the specialty to be proactive with managed care. Whether ophthalmology likes it or not, however, most every other physician specialty has had to learn to deal with managed care, and the reality is that ophthalmologists will, too. The more active they are in educating MCOs about glaucoma treatment, the more it is to their advantage.

Drug manufacturers have invested in relationships with physician leaders and with MCOs. This creates an opportunity to work with both sides of the delivery system to develop appropriate utilization criteria that make sense from quality and cost perspectives. Pharmaceutical companies can do this most effectively by talking not about specific products but about the bigger picture: how prostaglandins can promote cost-effective care. To that end, inviting physicians and managed care medical and pharmacy directors to advisory boards to discuss glaucoma and its pathophysiology can be a valuable use of manufacturer resources. In the end, physicians and MCOs would get the same message. Equally important, health plans can then make educated decisions about treatment protocols and coverage, rather than creating policy in a vacuum.

Opportunities for cooperation extend to the managed care community, where health plans will need ophthalmology consultants on P&T committees. From a clinical perspective, medical and pharmacy directors who do not have a background in ophthalmology will need to acquire a basic understanding of it. From a cost standpoint, meanwhile, MCOs could play a valuable col-
ficiaries will not be disabled by blindness. The quality-of-life and social implications are staggering.

If glaucoma is not yet high among managed care’s priorities, two forces — one potential, one inevitable — could move it up the list. Now is the time for MCOs to reckon with glaucoma in a proactive way, rather than being obliged to react to it.

The first force — the wild card — is HEDIS. As discussed later in this publication, the National Committee for Quality Assurance is considering instituting a glaucoma screening measure in its Health Plan Employer Data and Information Set. HEDIS, NCQA, and quality measurement are enormous priorities for managed care organizations. A HEDIS glaucoma-screening measure would immediately put this disease at the forefront of health plans’ efforts to improve their members’ health.

DEMOGRAPHIC CONSIDERATIONS

The second force — a hands-down certainty — is America’s aging population. Glaucoma is an illness that primarily afflicts older people. As people age, glaucoma will become a greater cost driver in the health care system. Yet, so will every other disease state that already has managed care’s attention — hypertension, diabetes, depression, and others. So, what makes glaucoma special? The characteristics of the baby boom population, for one. In Age Power, demographer Ken Dychtwald, PhD, noted that because of this group’s “differences from earlier generations — its high level of education, its powerful women, its quirky character, and its willingness to try new things — [this generation] transforms each stage of life through which it migrates.” At a time when MCOs are developing strategies to deal with a burgeoning consumerism movement in health care, it’s important to understand that baby boomers — a generation that hasn’t truly tested the health care system yet — have never been shy about asking for what previous generations did not or could not have. “If you think this generation will wait two hours for an appointment; if you think it’s going to accept only one point of view; if you think it’s not going to want its health care customized,” Dychtwald wrote, “you are misunderstanding this generation” (Dychtwald 1999).

How that plays out with glaucoma is this: As a whole, baby boomers are better educated about health and dis-
ease and take a more active role in choosing their health care than previous generations. Awareness of glaucoma and guidelines for screening has improved in recent years. Public surveys, meanwhile, consistently indicate that blindness is one of the most frightening of all health conditions (GRF 2002). It can be expected that as baby boomers mature, they will demand treatments that preserve their vision, which enables them to enjoy to the fullest the freedom of activity that this generation always has cherished.

A second reason glaucoma will become a more pressing concern as the population ages is rooted in therapeutic compliance. As documented elsewhere in this publication, patients’ adherence to glaucoma-medication therapy is relatively poor. As with many other illnesses, glaucoma presents neither acute symptoms nor evidence of deterioration of health when the disease is controlled by medication. Physicians know well that when patients “feel good,” they often forget to take their medications or deliberately stop taking them to avoid untoward side effects. This, in turn, exacerbates illness and forces the cost of treatment to rise. With adherence to glaucoma therapy already lower than that of many other chronic conditions (Kass 1987, Kass 1986), any decline in persistence with therapy generates a more rapid rate of increase in aggregate treatment costs, compared with other conditions.

Any discussion of adherence to therapeutic regimens, particularly in the elderly population, inevitably turns into a discussion of public policy — a third reason for MCOs to pay attention to glaucoma care. As long as Medicare goes without an outpatient drug benefit, elderly people who are dependent on Social Security for a substantial portion of their incomes and who take several medications a day will be forced to choose from among those most critical to their survival. If, because of personal finances, someone must choose between filling a heart medication and the glaucoma prescription, he or she will choose the heart medication — particularly if there’s no noticeable loss of vision. Over time, the lack of adherence translates into higher downstream utilization of more costly therapies.

Health plans that serve Medicaid populations already know that per-member, per-month pharmacy expenses are roughly three times those of commercial payers. Black and Hispanic populations — who make up substantial portions of Medicaid plans’ memberships — experience high rates of glaucoma (Adams 1999, Quigley 2001). Developing a strategy for controlling the disease becomes imperative when one considers that Hispanics in particular are among the fastest-growing populations in the United States. The U.S. Census Bureau estimates that by 2050, half of the American population will be black, Hispanic, and Asian (U.S. Census Bureau 2000).

GLAUCOMA’S TURN

For more than 15 years, formularies have been mainstays of controlling the pharmacy benefit in MCOs. For the first time, this is being significantly played out for glaucoma. Physicians and MCOs should embrace this opportunity.

As a specialty, ophthalmology is lucky — this is a good time to become involved with managed care. Managed care is not going away, but it is being forced to conform more to public and professional realities. The industry is changing in ways that make physicians’ lives less burdensome. It faces constant pressures from employer groups and government payers to demonstrate quality of care. The result? Everyone is being called upon to work together to develop standards of care, which do one thing: They dictate what is appropriate care. Physicians who deviate from that must explain why they do. Guidelines also make health plans accountable, in that they compel plans to pay for appropriate care. They serve as a check and balance for both sides. The chapter “Clinical Guidelines for the Treatment of Glaucoma,” which begins on page 16, provides a more detailed look at how and why these standards are developing.

As new therapeutic options become available, making the effort to create standards for their utilization becomes not only necessary but imperative.

REFERENCES

Glaucoma: Prevalence, Utilization, And Economic Implications

Michael D. Dalzell
Editor, P&T Digest

Glaucoma is a group of diseases most commonly associated with elevated intraocular pressure (IOP), which causes irreversible damage to the optic nerve and retinal ganglion cells. Over time, this deterioration results in vision loss, which frequently goes unnoticed until a significant amount of damage has occurred. The National Eye Institute (NEI) estimates that half of all cases of glaucoma are undiagnosed. Most can be controlled and vision loss prevented with early detection and treatment (Kass 2002).

By far, the most common form of the disease is primary open-angle glaucoma. The most conservative estimates indicate that 2.2 million Americans 40 and older — about 1.9 percent of this population — have primary open-angle glaucoma (NEI 2002). Because glaucoma incidence rises sharply with advanced age, prevalence is likely to increase dramatically as the baby boom generation matures. This suggests that health plans that place an emphasis on glaucoma detection and treatment will see improved clinical and financial outcomes.

The next several pages provide a statistical snapshot of glaucoma: its prevalence, the demands it places on health care utilization, its economic implications for private health plans and government payers, and its effects on patients.

1 Michael D. Dalzell is also managing editor of Managed Care, a monthly peer-reviewed journal.

EXTENT OF DISEASE

Prevalence by age and sex
According to the 1996 National Health Interview Survey, about two thirds of glaucoma cases in the U.S. are in people 65 and older. Overall prevalence is slightly higher in women than men, though being female is not itself considered a risk factor.

By sex
Female (56%)
Male (44%)

By age
<45 (8%)
45–64 (21%)
≥65 (71%)

Number of cases
By age and sex (in thousands)

<45 45–64 65–74 ≥75 Total
Males
142 282 264 287 435 1,450
Females
72 264 572 542 1,146 1,186

SOURCE: Adams 1999
Prevalence does not differ significantly when broken down by geography or household income.

SOURCE: ADAMS 1999

**Prevalence by race**

After age, the most significant determinant in prevalence is race. On a per-thousand basis, blacks 65 and older have almost twice the rate of glaucoma cases (93.8) as whites (55.7).

**Cases per 1,000 people**

*By age and sex*

Although the high incidence of glaucoma in blacks has been known for some time, the first attempt to determine incidence in Hispanics — the fastest-growing racial group in the United States (Census Bureau 2000) — was not published until 2001. In this group, overall prevalence in people 40 and older is equivalent to that of the general population — 1.9 percent — but by old age, it reaches levels similar to those of the black population (12.6 percent in Hispanics 80 and older) (Quigley 2001).
OVERVIEW

UTILIZATION TRENDS

Office visits up sharply
Glaucoma was the primary diagnosis in 17.5 million visits to physicians during 1991 and 1992 (the latest years for which data are available), according to the National Ambulatory Medical Care Survey. This is equivalent to 3.5 visits per year per 100 persons. The average of 8.7 million annual visits was up 380 percent from 1975–76. For people 65+, the office-visit rate rose from 5.7 per 100 in 1975 to 19.9 per 100 in 1992.

While disease rates increased over this period, this is not assumed to be the cause of the substantial boost in glaucoma-related office visits. A contributing factor could be glaucoma-screening guidelines, which the NEI issued in 1991, that heightened awareness of the importance of early detection and treatment.

Highest return-visit ratio
Glaucoma was the fifth most frequent reason that patients returned to their physicians' offices in 1992 for previously treated problems — up from ninth in 1975. Expressed as a return-visit ratio — the number of return visits for each new-problem encounter — glaucoma ranked number 1, at 4.1:1.

Note: V-code visits for normal pregnancy and general medical examinations were not included in rankings.
Disparity in care
Expressed in terms of visits per 100 persons, the rate of visits involving a primary diagnosis of glaucoma is lower for blacks than whites. This is noteworthy, given that glaucoma is proportionally more prevalent in blacks than whites and is the most common cause of irreversible blindness in the black population (Danyluk 1991). These rates reported by Schappert, based on Census Bureau data, support the findings of Javitt (1991) that while glaucoma occurs much more frequently in the black population, older black Americans do not receive care for open-angle glaucoma at the same rate as white persons.

Medication tops therapeutic services
With glaucoma patients, almost 8 in 10 office visits end with a prescription being written, adjusted, or maintained. Medication therapy was recorded during 79.6 percent of glaucoma visits — by far, the most frequent therapeutic service mentioned. This is notably higher than for visits for all other primary diagnoses, for which medication therapy was indicated an average of 63.3 percent of the time.

Therapeutic service ordered or delivered at time of visit

In the U.S., the National Ambulatory Medical Care Survey found that ambulatory surgical procedures were performed during slightly more than 7 percent of office visits during 1991–92. When medications are administered or prescribed, more than half of patients are given more than one.

Number of new or continued medications

Ambulatory surgery during glaucoma visits

One caveat: These statistics are based on office visits in 1991–92. Since that time, several new topical agents have been introduced — the effect of which may well be an increase in the proportion of drug mentions. A Scottish study since has found that the availability of new agents has been associated with a large reduction in surgery rates among glaucoma patients (Bateman 2002).
ECONOMIC IMPLICATIONS

Managed care organizations spend $1 billion annually to treat glaucoma (GRF 2002). A 1998 study published in the *Journal of Glaucoma* pegged the per-patient cost of treating primary open-angle glaucoma in the United States, over a two-year period beginning with the initial diagnosis, at $2,109 (Kobelt-Nguyen 1998). There is evidence that when IOP can be controlled consistently over the long term, treatment costs decline thanks to reduced downstream utilization.

**Treatment cost varies with success**

Differences in the cost of treating patients with glaucoma are explained partly by the severity of disease at diagnosis, but all things being equal, evidence suggests that identifying appropriate therapeutic options early on can have beneficial effects on expenditures. A Dutch study found that the mean one-year cost of treating patients who had more than three adjustments in medication therapy was five times the cost of treating those who required no changes in therapy.

**Mean one-year cost of treatment**

<table>
<thead>
<tr>
<th>No changes in medication therapy</th>
<th>More than three adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>$347</td>
<td>$1,765</td>
</tr>
</tbody>
</table>

German researchers studying the direct cost of glaucoma management following initiation of medical therapy made an observation similar to that of their Dutch counterparts, noting that a high frequency of treatment changes are associated with higher costs. They postulated that new treatments that control IOP effectively over time could reduce the cost of patient management, and noted that reductions in surgical interventions could offset the cost of newer pharmaceutical agents (Kobelt 1998).

WHEN IS SCREENING COST-EFFECTIVE?

The cost of screening for glaucoma has been estimated to be about $850 per patient (Tuck 1997). British researchers concluded that the expense of screening can be justified if, over a lifetime, an equivalent amount of health care expenditure can be saved or if the personal economic impact on a patient would exceed $850. Considering the remaining life expectancy in people under 60, the authors wrote, screening people between ages 40 and 59 has about the same economic benefit as screening older patients, despite the lower prevalence in the younger age group.

The expenses associated with screening patients and the subsequent treatment of new cases raises the question of who is appropriate for screening. The most cost-effective screening programs, therefore, will target high-risk patients for early detection. An important implication of the Ocular Hypertension Treatment Study (Kass 2002) — which found that controlling IOP in patients who have elevated pressure but who are not diagnosed with glaucoma can prevent or delay onset of primary open-angle glaucoma — is that a well-designed screening strategy may prove more cost-effective than has been understood.

**Risk factors for glaucoma**

- Age >60
- Age >40 (blacks)
- Family history of glaucoma
- Extreme nearsightedness
- Diabetes mellitus

**Medication displacing surgery**

Over the last decade, the management of glaucoma has been altered significantly, thanks to the introduction of new pharmaceutical agents that have demonstrated clinical effectiveness. In a retrospective study of the correlation between use of these products and other methods to treat glaucoma, Scottish researchers noted sharp declines in utilization of older drugs and operation rates over a five-year period.

**Utilization patterns, Scotland, 1994–1999**

*Per 1,000 population*

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>New pharmaceutical products*</td>
<td>+24.9%</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>+6.4%</td>
</tr>
<tr>
<td>Miotics and older sympathomimetics</td>
<td></td>
</tr>
<tr>
<td>Surgical interventions</td>
<td>-47.7%</td>
</tr>
<tr>
<td>-Diuretics</td>
<td>-45.9%</td>
</tr>
</tbody>
</table>

*Topical prostaglandins, carbonic anhydrase inhibitors, alpha, agonists.

SOURCE: BATEMAN 2002
Blindness is the eighth-leading cause of disability in the United States. The NEI estimates that as many as 120,000 people are blind from glaucoma. For every 100,000 people over 40, the rate is 93 to 126 cases.

Leading causes of disability, age 15+

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Arthritis/rheumatism</td>
<td>17.1%</td>
</tr>
<tr>
<td>Back/spine problem</td>
<td>13.5%</td>
</tr>
<tr>
<td>Heart trouble</td>
<td>11.1%</td>
</tr>
<tr>
<td>Lung or respiratory trouble</td>
<td>6.8%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5.1%</td>
</tr>
<tr>
<td>Stiffness or deformity of limb</td>
<td>4.8%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.9%</td>
</tr>
<tr>
<td>Blindness/visual impairments</td>
<td>3.5%</td>
</tr>
<tr>
<td>Deafness/hearing difficulties</td>
<td>2.6%</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

SOURCE: CDC 1994

GLAUCOMA’S COST TO TAXPAYERS

The economic implications of glaucoma can be measured in ways other than the direct costs of utilization. In terms of Social Security benefits, lost revenues from income tax, and health care expenditures, blindness and visual impairments cost the U.S. government $4 billion per year (NEI 2002). The Glaucoma Research Foundation estimates that more than a third of this is attributable to glaucoma (GRF 2002).

Direct and indirect expense to U.S. government
Per year, in billions

<table>
<thead>
<tr>
<th>Glaucoma</th>
<th>Other visual impairments and blindness</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1.5</td>
<td>$2.5</td>
</tr>
</tbody>
</table>

Blindness is the eighth-leading cause of disability in the United States. The NEI estimates that as many as 120,000 people are blind from glaucoma. For every 100,000 people over 40, the rate is 93 to 126 cases.

Share of blindness due to glaucoma
U.S. cases of blindness, not including vision impairments

<table>
<thead>
<tr>
<th>Total cases: 1,046,920</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases of blindness</td>
</tr>
<tr>
<td>Glaucoma-related</td>
</tr>
<tr>
<td>All other causes</td>
</tr>
<tr>
<td>12%</td>
</tr>
<tr>
<td>88%</td>
</tr>
</tbody>
</table>

SOURCE: NEI 2002

REFERENCES


Clinical Guidelines
For the Treatment of Glaucoma

LAWRENCE D. GOLDBERG, MD, MBA

Goldberg, MD & Associates

SUMMARY
Several documents guide screening and detection of glaucoma. The AAO guidelines are considered the current standard. The VA has established the need for regular screening based on identified factors. Finally, a task force working with NCQA to develop a glaucoma-related HEDIS measure may provide future direction in populationwide care.

Glaucoma is a significant public health problem in the United States, particularly among blacks and the elderly, and is the second leading cause of legal blindness (EDGED 2002, Quigley 1997, Sommer 1991a). An estimated 4.2 million Americans have glaucoma, including about 2 million who are not aware they have the disease; another 5 to 10 million are believed to have elevated intraocular pressure (IOP) (EDGED 2002, Quigley 1997), which is known to be a risk factor for developing glaucoma.

The treatment of glaucoma is well established. Several trials have clearly shown that reducing IOP by treatment with topical ocular hypotensive medication can prevent or reduce the risk of progression of glaucoma (Collaborative Normal-Tension Glaucoma Study Group 1998, AGIS Investigators 2000, Lichter 2001). Moreover, the recently published Ocular Hypertension Treatment Study (Kass 2002) demonstrated that topical ocular hypotensive medication is effective in delaying or preventing the onset of glaucoma in patients with elevated IOP.

Yet until recently, there was neither public policy nor national guidelines encouraging early detection or prevention of this disease. Perhaps more importantly, millions of Americans at risk for glaucoma did not receive proper screening, diagnosis, or interventions to prevent progression to blindness.

To correct this shortcoming, several medical organizations and governmental agencies — including the American Academy of Ophthalmology (AAO), the Veterans Administration (VA), and the National Institutes of Health (NIH) — have developed consensus statements or guideline documents to serve as policy initiatives for early glaucoma detection and intervention (AAO 2000a, VA 2000, USPSTF 1996). Furthermore, the U.S. Centers for Medicare and Medicaid Services (CMS, formerly the Health Care Financing Administration) recently granted Medicare coverage of regular glaucoma screenings for at-risk individuals (Thomas 2000). Similarly, goals and strategies for optimal vision management have been incorporated into national disease-prevention programs, such as Healthy People 2010 and the Report of the U.S. Preventive Services Task Force (USPSTF 1996, Thomas 2000, NIH 2000a). It is hoped that the result of this mounting attention will be, according to Carl Kupfer, former director of the National Eye Institute, “to give vision a prominent place on the public health agenda” (NIH 2000b). It is only by this increased attention to and active implementation of glaucoma screening and management programs that the large number of patients at risk for glaucoma can be detected and appropriately treated.

1 Lawrence D. Goldberg, MD, MBA, is founder of Goldberg, MD & Associates, Battle Ground, Wash., a national health care consulting practice focused on medical management and marketing strategy, quantitative modeling and analysis, product development, clinical trials, disease management, regulatory compliance, reimbursement strategy, and technical advisory services. He is a former medical director for Humana Health Care Plans of Texas and a former associate medical director for United Healthcare of Louisiana. Trained in internal medicine, Goldberg received his MD and BA from Boston University. He earned his MBA from Louisiana State University.
at-risk individuals can be effectively controlled.

**Why intervene?**

Vision is an essential part of everyday life and is one of the basic senses that people depend on for learning, communication, and mobility. At its most basic level, vision enables people to orient themselves to their environment and to relate to other people with the unique advantages of visual contact and body language. In the bigger sense, vision enables people to learn through reading, become independent through driving, communicate with writing, and enjoy a special creativity associated with sight.

Glaucoma is a threat to this basic human capability. Glaucoma involves an increase in IOP that, over time, can lead to atrophy of the optic nerve and loss of vision (Quigley 1980). It is the second-leading cause of irreversible blindness in the U.S. and is the leading cause of blindness among blacks (Sommer 1991a, Leske 1983). In one report, it was shown that uncontrolled glaucoma can lead to blindness in up to 75 percent of affected individuals (Grant 1982). Furthermore, the quality-of-life impact of glaucoma has been proven to be significant, both on general health- and vision-related scales (Gutierrez 1997, Wilson 1998).

The economic impact of glaucoma is substantial as well. The increased health care expenditures related to glaucoma are enormous when one considers that the condition is responsible for 7 million office visits annually plus the costs of prescription drug fulfillment and surgical interventions (Schappert 1995). This is only among individuals diagnosed with glaucoma and related vision damage; additional costs ascribed to Social Security benefits, reduced productivity, and lost wages and the associated decrease in tax revenue also must be factored in. In the end, the potential costs are staggering.

Yet there is effective treatment for glaucoma. New research also identifies preventive measures that can preserve vision for people at risk of developing glaucoma.

The Ocular Hypertension Treatment Study (Kass 2002) demonstrated that topical ocular hypotensive medications can delay or prevent onset of glaucoma and progression of visual defects in people with elevated IOP (>21 mm Hg) but who have no evidence of glaucomatous damage. This study enrolled 1,636 individuals (including more than 400 of whom were black) with IOPs between 24 mm Hg and 32 mm Hg. Active treatment assigned to 817 individuals with elevated IOP (mean 24.9 ± 2.6 mm Hg) reduced IOP by 22.5 ± 9.9 percent compared with a decline of only 4.0 ± 11.6 percent among 819 untreated individuals. Eighty-seven percent of treated patients reached the IOP target of 24 mm Hg in both eyes; another 7 percent reached target in one eye. Perhaps the most significant result, however, is that at 60 months, the treated group saw a significant reduction in risk for developing glaucoma compared with the observation-only group ($P<0.0001$), and a reduced rate of both glaucomatous visual-field abnormalities and optic-disc deterioration.

Other studies have shown that the greater the reduction in IOP, the greater the reduction in risk for glaucomatous eye damage (Migdal 1994, Jay 1989, Glaucma Laser Trial Research Group 1995). This benefit of treatment has been observed even among patients with normal-tension glaucoma and early signs of ocular complications (Collaborative Normal-Tension Glaucma Study Group 1998). Among patients with unilateral or bilateral normal-tension glaucoma ($\leq 24$ mm Hg) with optic-disc abnormalities and visual field defects, optic-nerve damage developed in 35 percent of untreated patients and in only 12 percent of treated individuals who achieved a treatment-related reduction in IOP ($P<0.0001$).

These outcomes establish the importance of timely diagnosis and early and aggressive therapy to delay or prevent glaucoma and its sequelae. By extension, these find-
ings also highlight the need for screening targeted populations to identify patients with elevated IOP, who can then be appropriately managed for this high-risk finding.

GUIDELINES FOR GLAUCOMA SCREENING, DIAGNOSIS, AND MANAGEMENT

There are several documents that contribute to the current emphasis on regular screening and early detection in glaucoma. Although the AAO guidelines are considered by most ophthalmologists to be the current standard of care, the VA guidelines are important in establishing the need for regular screening based on identified risk factors.

Moreover, the recommendations of the Joint National Task Force for the Early Detection of Glaucomatous Eye Disease (EDGED), calling for the National Committee for Quality Assurance (NCQA) to develop a glaucoma-related Health Plan Employer Data and Information Set (HEDIS) measure may provide future direction in populationwide glaucoma care.

Veterans Administration

The Veterans Administration developed glaucoma-screening guidelines that are notable in that these were the first to focus on the importance of targeted screening in populations with risk factors for glaucoma (VA 2000). The VA screening recommendations are based on the concept that the most effective screening program identifies those individuals at greatest risk for developing glaucoma based on family history, age, and ethnicity. Individuals with a family history of glaucoma (a parent, sibling, or child), who are 65 or older, and/or who are black have additive risk for eye disease; based on this risk profile, the VA recommends a schedule for glaucoma eye examinations (Table 1). Other risk factors include hypertension, diabetes, and myopia. This concept of a high-risk population warranting more aggressive follow-up was subsequently adopted in the AAO’s guidelines, as reviewed next.

American Academy of Ophthalmology

The most widely accepted guidelines for screening and management of glaucoma are those distributed by the AAO (AAO 2000a, AAO 2000b). These recommendations are intended as a guide to providing quality eye care with consideration of the current environment of managed care and changing health care delivery norms. The concept of glaucoma detection and management put forth in these guidelines is modeled on a rational, evidence-based, and cost-efficient three-tier approach: 1) All individuals, but particularly the elderly and black populations, should undergo periodic screenings with a dilated-eye examination and a measure of IOP to identify those patients with ocular hypertension who are at risk for glaucomatous eye damage; 2) Individuals with elevated IOP then undergo further testing to determine baseline optic-nerve damage and go on to receive medication to reduce IOP; and 3) Patients with baseline optic-nerve damage are followed more aggressively using available diagnostic technology to assess success of treatment and control of glaucoma progression.

The AAO developed two documents, titled Preferred Practice Patterns, to assist practitioners in the identification, classification, and management of primary open-angle glaucoma (POAG), differentiated according to 1) >1 risk factor for glaucoma but with normal ocular findings on gonioscopy (glaucoma suspect), or 2) established POAG as evidenced by optic-nerve damage or visual-field limitation.

Glaucoma suspect

The guidelines for managing the glaucoma suspect, aimed at individuals who are at high risk for glaucoma,
seek to preserve visual integrity by encouraging vigorous monitoring, early detection of ocular hypertension, and active treatment to reduce IOP. The main thrusts of the glaucoma suspect Preferred Practice Pattern are early detection of elevated IOP and identification of individuals with elevated risk factors for developing glaucoma. Age and race are the two most compelling risk factors for glaucoma, and these determine the recommended schedule for screening examinations (Table 2). In addition, however, glaucoma screening, according to the guidelines, should be part of every comprehensive adult eye examination (AAO 1996), and should include assessment of these risk factors (age and race), as well as family history, health status, and IOP and dilated-eye examination findings. This first screening will identify the large portion of the population with no risk factors and normal IOP, then exclude it from therapy or further examination. The remaining patients are considered glaucoma suspects, and are examined for baseline glaucomatous optic-nerve damage and treated according to POAG guidelines, below.

Primary open-angle glaucoma

The document on established POAG is intended, according to its drafters, “to enhance [the] patient’s health and quality of life by preserving visual function without causing untoward effects of therapy” (AAO 2000a). It was designed as a guide to optimal diagnosis and treatment of adults with clinical evidence of POAG or related ICD-9 classifications, including low-tension glaucoma, residual stage open-angle glaucoma, and glaucomatous atrophy of the optic disc. The goals of the recommended care program are defined in Table 3.

Detection. Early detection is imperative to the control of glaucomatous eye damage and disease progression. Yet, IOP alone may not be a sufficient test for identifying patients with glaucoma. Several studies have indicated that optic-nerve damage may be present at IOP levels below the usual screening cutoff2, (Dielemans 1994, Mitchell 1996), while other studies have proven that some individuals with elevated IOP may never develop glaucomatous damage (Mitchell 1996, Sommer 1991b). The POAG Preferred Practice Pattern, therefore, recommends assessment of optic-nerve status as part of screening examinations (See “Ophthalmic Procedure Review,” page 21).3 In general, however, the most practical method for conducting widespread screening of targeted populations — before glaucoma suspects are subjected to these additional evaluative techniques — is to identify risk factors, assess IOP, and perform a dilated-eye examination with attention to the optic disc.

Examination. A complete eye-care evaluation should include a history and physical examination, comprehensive eye assessment, plus review of specific factors related to POAG (e.g., status of the optic nerve, visual field, and IOP). This may require up to three visits (AAO 2000a). The eye examination should always include a dilated-eye exam and IOP assessment, but a definitive examination for glaucoma should focus on the following techniques (refer to Figure 1, page 17): 1) pupil examination for reactivity and afferent pupillary defect; 2) slit-lamp biomicroscopic examination for secondary glaucoma, such as pseudoexfoliation, pigmentary dispersion, or inflammation; 3) measure of IOP in each eye, preferably with a Goldmann-type applanation tonometer; 4) gonioscopic evaluation of the anterior-chamber angle to exclude angle

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2 The AAO does not describe a concrete IOP “cutoff” (mm Hg) for screening. For this type of glaucoma, low-tension glaucoma, the AAO recommends that practitioners set a target IOP of 20 to 30 percent below baseline IOP, with periodic adjustments as needed based on progression of optic-nerve damage after reaching goal.

3 Whereas disk examination and visual-field testing have such limitations as cumbersome technique and variable sensitivity (Johnson 1983, Kosoko 1986, Quigley 1982, Sommer 1991c, Zeyen 1993), they are the only available optic-status evaluation techniques. The AAO recognizes that these may not be efficient as populationwide screening techniques, but holds that they are indicated and cost-effective for high-risk populations. Frequency-doubling technology demonstrates promise and has sensitivity for moderate glaucomatous eye damage (Quigley 1998a).
DETECTION AND TREATMENT

closure or secondary causes of elevated IOP; 5) magnified stereoscopic visualization of the optic-nerve head and red-free illumination plus direct ophthalmoscope or biomicroscope to assess the nerve-fiber layer; 6) documentation of optic-nerve head appearance; 7) examination of the fundus through dilated pupil; and 8) visual-field evaluation via automatic static threshold perimetry or manual combined kinetic and static threshold testing.

Management Plan. The AAO developed an algorithm to guide eye-care providers in decision making when confronted with a patient with POAG (Figure 2, below). The first step in the plan is to identify a target IOP, or upper limit of IOP expected to slow or stop optic-nerve damage (Anderson 1989, Jampel 1997). Standard target pressures are 20 to 30 percent below baseline value, but categories of glaucoma severity are highlighted in Table 4.

**FIGURE 2** AAO guidelines: algorithm for managing patients with primary open-angle glaucoma

![Algorithm Diagram](image-url)
The technology supporting glaucoma assessment and optic-nerve head analysis has evolved rapidly in the last decade. The potential applications of these new diagnostic and screening tools are compelling, but may not be cost-efficient as populationwide practices. The appeal of technology advancement, therefore, has been at odds with the practical aspects of patient management, creating rifts in the ophthalmologic community. The American Academy of Ophthalmology has generated several documents that summarize and evaluate the safety, effectiveness, and clinical utility of these new procedures (AAO 1999; Assessment Committee in press). The table below outlines the key clinical findings of the AAO's technology assessments for automated perimetry and optic-nerve head and retinal nerve-fiber layer analysis. For a complete review of the processes and outcomes of the ophthalmic technology and procedure assessments, see the full articles referenced here.

The AAO reported that for routine use, none of the techniques evaluated can be rigorously supported by available literature as accurate and reliable monitors of glaucoma, disease progression, or optic neuropathy. However, each technique has specific advantages that support its utility in certain clinical applications, and physicians must individualize their applications based on combined features of a specific case, availability of technology, reliability profile, and cost considerations.

### New ophthalmic technologies: AAO assessment summary

<table>
<thead>
<tr>
<th>Technology</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automated perimetry</td>
<td>• Early detection of glaucomatous loss</td>
<td>• Long and challenging test (14–18 min.)</td>
</tr>
<tr>
<td>SWAP (Short-wavelength automated perimetry)</td>
<td>• Reduced testing time</td>
<td>• Sensitive to blur and media opacities</td>
</tr>
<tr>
<td>FDT (Frequency-doubling technology perimetry)</td>
<td>• Not affected by blur and pupil size</td>
<td>• Lack of longitudinal studies</td>
</tr>
<tr>
<td>HPRP (High-pass resolution perimetry)</td>
<td>• Detects early glaucomatous loss</td>
<td>• Sensitive to media opacities and blur</td>
</tr>
<tr>
<td>MAP (motion-automated perimetry)</td>
<td>• Strongly predictive of visual-field loss, particularly early loss</td>
<td>• Difficult procedure</td>
</tr>
<tr>
<td></td>
<td>• Resistant to blur and media opacities</td>
<td>• 15-minute test</td>
</tr>
<tr>
<td></td>
<td>• High sensitivity, especially in early-moderate glaucoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optic-nerve head</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rodenstock</td>
<td>• Less labor intensive than manual stereophotogrammetry</td>
<td>• Technically complex</td>
</tr>
<tr>
<td></td>
<td>• Requires wide pupillary dilation and clear media</td>
<td>• Requires a reference plane</td>
</tr>
<tr>
<td>Heidelberg retinal tomography</td>
<td>• Images can be gained via undilated pupil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Uses low light</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Real-time image</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Better axial resolution than Rodenstock</td>
<td></td>
</tr>
<tr>
<td>Retinal nerve-fiber layer analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nerve-fiber analyzer</td>
<td>• Quicker and more objective than visual fields</td>
<td>• Polarizing structures of eye [cornea, lens] may change retardation values</td>
</tr>
<tr>
<td></td>
<td>• Higher sensitivity than Glaucoma Hemifield test</td>
<td>• Peripupillary atrophy and chorioretinal scarring may increase retardation values</td>
</tr>
<tr>
<td>Optical coherence tomography</td>
<td>• No reference plane required</td>
<td>• Procedure difficult in posterior subcapsular and cortical cataracts</td>
</tr>
<tr>
<td></td>
<td>• Independent of optical resolution of eye</td>
<td>• Requires pupillary dilation</td>
</tr>
<tr>
<td></td>
<td>• Not affected by refractive state or axial length of the eye</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Not affected by changes in nuclear sclerotic cataract density or similar media opacities</td>
<td></td>
</tr>
</tbody>
</table>

DETECTION AND TREATMENT

With a target pressure in mind, treatment can be selected, and may include medical therapy, laser surgery (argon laser trabeculoplasty), and/or incisional surgery (filtering surgery). Topical medication is, in most cases, indicated as first-line therapy, with trabeculectomy recommended generally only after medical therapies fail to control IOP. To determine the effectiveness of therapy, the practitioner must distinguish between the impact on IOP of a prescribed agent and the patient’s normal IOP background fluctuations. Prostaglandin analogs, topical adrenergic derivatives, and topical miotics increase aqueous outflow. Alpha₂-adrenergic agonists, carbonic anhydrase inhibitors, and beta-adrenergic antagonists (beta blockers) decrease aqueous outflow. The AAO does not recommend a specific agent as first-line therapy, though it does suggest that when a drug fails to reduce IOP, it be discontinued in favor of another before the original agent is supplemented by other medications. For a full review of the medication options for glaucoma treatment, see “Drug-Therapy Review,” on page 25.

The ultimate therapeutic selection (medication or surgery) will be the option that offers the greatest potential benefit when risk, cost, and quality of life are considered. Each option will carry some potential for adverse effects and complications. The individual patient’s perception of these risks will influence the choice of intervention.

Follow-up. Follow-up is arguably the most important aspect of glaucoma management, the point at which the success of assigned treatment is determined, progression of optic-nerve disease is evaluated, and approaches are changed to improve treatment outcomes. The general follow-up intervals are based on whether target pressure is achieved, whether there has been any progression to eye damage, and how long IOP has been controlled (Table 5). When planning follow-up intervals, one might make adjustments based on the stage of disease, the IOP relative to target pressure, and the presence of other risk factors for optic-nerve damage. At the time of follow-up, a decision may be made to alter the therapeutic regimen based on the factors outlined in Table 6.

Gonioscopy is always indicated as part of the initial evaluation of glaucoma suspects, but should also be performed when there is suspicion of anterior-chamber abnormalities and in patients who are phakic (i.e., who have not undergone cataract surgery and retain the eye’s natural internal lens) if lens changes are present.

Counseling/Referral. When questions about treatment preferences arise or when a patient is refractory to assigned treatment, the AAO recommends consultation with or referral to an appropriate subspecialist. The primary care ophthalmic provider may also refer a patient with unusual or complicated disease to an ophthalmologist with extensive experience in that particular indication. Further, there are many support groups, counseling providers, and social services available to patients whose quality of life is impaired by glaucoma.

Overall, the Preferred Practice Patterns provide guidance for the pattern of practice, not for the care of any particular individual. Eye-care professionals are advised to use individual judgment.

### Table 4: Severity of glaucoma damage

<table>
<thead>
<tr>
<th>Degree</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Characteristic optic-nerve abnormalities are consistent with glaucoma but with normal visual field</td>
</tr>
<tr>
<td>Moderate</td>
<td>Visual-field abnormalities in one hemifield and not within 5 degrees of fixation</td>
</tr>
<tr>
<td>Severe</td>
<td>Visual-field abnormalities in both hemifields and within 5 degrees of fixation</td>
</tr>
</tbody>
</table>

SOURCE: AAO 2000a

### Table 5: AAO guidelines: recommended follow-up intervals for general, optic-nerve head, and visual-field evaluation

<table>
<thead>
<tr>
<th>Target IOP achieved?</th>
<th>Progression of damage</th>
<th>Duration of control (months)</th>
<th>Follow-up interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>&lt;6</td>
<td>General: 1–6 months</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>&gt;6</td>
<td>3–12 months</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>n/a</td>
<td>1 week–3 months</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>n/a</td>
<td>2 days–3 months</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>n/a</td>
<td>2 days–1 month</td>
</tr>
</tbody>
</table>

SOURCE: AAO 2000a
DETECTION AND TREATMENT

EDGED Task Force

The Joint National Task Force for the Early Detection of Glaucotamous Eye Disease (EDGED Task Force), of which the author served as chair, comprised a panel of experts charged with developing a consensus document in support of a HEDIS measure designed to “effectively educate and elevate awareness with respect to glaucomatos eye disease in high-risk populations” (EDGED 2002). The goal was to promote the early identification of patients with or at risk for glaucoma through the development of objective and well-regarded outcomes measures. The rationale for this panel and for its submission to NCQA, which administers HEDIS, was to promote a glaucoma measure via the support of its member organizations — which include the NEI, the VA, the Glaucoma Foundation, the AAO, and others — to make glaucoma management a more visible priority.

Based on supportive scientific evidence establishing the risks of uncontrolled ocular hypertension, the need for early detection, the preventive efficacy of early detection, and the proven effectiveness of active treatment for elevated IOP in preventing or delaying vision loss (Gutierrez 1997, Kass 2002, Migdal 1994, Glaucoma Laser Trial Research Group 1995, Hiller 1975, Shields 1995, Sponsel 1995, Quigley 1998b, The Fluorouracil Filtering Surgery Study Group 1996), the panel’s recommendations focused on the assumption that glaucoma fits the profile required for a new HEDIS measure: a significant disease burden, an identified high-risk population, and availability of effective care measures. The EDGED Task Force subsequently submitted a “concept” document in support of a glaucoma HEDIS measure to NCQA. The document addressed all of the desirable attributes (as outlined in Table 7) of well-designed HEDIS measures. At the time of this printing, NCQA’s Geriatric Measurement Advisory Panel has convened a technical subgroup to develop a glaucoma HEDIS measure and to present the draft measure to NCQA’s Committee for Performance Measurement for consideration.

CONCLUSION

Based on the data available today, glaucoma is a disease of significant morbidity but one that can be effectively prevented and/or treated in most patients. Regular screening, particularly among such high-risk individuals as the elderly and black populations, enables early detection and intervention with the intent of controlling IOP. This, in turn, has been shown to reduce the risk of optic-nerve deterioration and/or glaucomatous visual-field loss. As stated in Healthy People 2010, “Blindness and visual impairment from most eye diseases and disorders can be reduced with early detection and treatment. Early intervention through regular vision exams is imperative to maintaining eye health (NEI 2000a).”

In the past, the responsibility of physicians was to treat illness, but today the standard is to deter disease through preventive measures and risk-factor management. According to the United States Department of Health and Human Services, clinicians must take every opportunity to increase the proportion of patients undergoing vision screening and to deliver preventive care (USPSTF 1996). For glaucoma, this involves regular screening of target populations and further evaluation of glaucoma suspects.

Glaucoma remains the second-leading cause of ir-

<table>
<thead>
<tr>
<th><strong>TABLE 6</strong></th>
<th>AAO guidelines: factors determining need for adjustment to treatment plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Target IOP not achieved</td>
<td></td>
</tr>
<tr>
<td>- Continued optic-nerve damage progression after achieving target IOP</td>
<td></td>
</tr>
<tr>
<td>- Stable optic-nerve status and low IOP over prolonged period on pressure-lowering medications</td>
<td></td>
</tr>
<tr>
<td>- Intolerant or nonadherent patient</td>
<td></td>
</tr>
<tr>
<td>- Contraindications to patient’s medications</td>
<td></td>
</tr>
</tbody>
</table>

**SOURCE:** AAO 2000a

<table>
<thead>
<tr>
<th><strong>TABLE 7</strong></th>
<th>Desirable attributes of HEDIS measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relevance</strong></td>
<td></td>
</tr>
<tr>
<td>- Meaningful</td>
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<tr>
<td>- Health importance</td>
<td></td>
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<tr>
<td>- Financial importance</td>
<td></td>
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<tr>
<td>- Cost effectiveness</td>
<td></td>
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<tr>
<td>- Strategically important</td>
<td></td>
</tr>
<tr>
<td>- Controllability</td>
<td></td>
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<tr>
<td>- Variance among systems</td>
<td></td>
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<tr>
<td>- Potential for improvement</td>
<td></td>
</tr>
<tr>
<td><strong>Scientific soundness</strong></td>
<td></td>
</tr>
<tr>
<td>- Clinical evidence</td>
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<tr>
<td>- Reproducible</td>
<td></td>
</tr>
<tr>
<td>- Valid</td>
<td></td>
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<tr>
<td>- Accurate procedures</td>
<td></td>
</tr>
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<td>- Case-mix adjustment/risk adjustment</td>
<td></td>
</tr>
<tr>
<td><strong>Feasibility</strong></td>
<td></td>
</tr>
<tr>
<td>- Precisely defined</td>
<td></td>
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<tr>
<td>- Reasonable cost</td>
<td></td>
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<td>- Logistically feasible</td>
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<td>- Confidential</td>
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<td>- Auditable</td>
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**SOURCE:** NCQA 1998
DETECTION AND TREATMENT

reversible blindness in the United States and the leading cause of blindness in the black population. The trend of greater public policy support and increased advocacy should contribute to reducing the prevalence of this disease. With increased awareness of the dangers of uncontrolled ocular hypertension and more aggressive screening and management programs, it may be possible to stop the progression of glaucoma and reach the goal of preventing blindness from this disease.

REFERENCES


Glucoma Medications: A Drug-Therapy Review

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SUMMARY

Today, clinicians have unprecedented versatility in the treatment of glaucoma. Early detection, prevention, and control are promises inherent in the expansion of the pharmacological glaucoma armamentarium. Choosing the optimal regimen hinges on knowledge about the capabilities and the limitations of currently available medications.

Many new antiglaucoma medications have reached the market in recent years. New classes of glaucoma pharmacotherapies — including prostaglandin/prostamide combinations, alpha₂ agonists, and topical carbonic anhydrase inhibitors (tCAIs) — started to receive approval from the U.S. Food and Drug Administration (FDA) and began to appear on the market about seven years ago.

As the newer drugs — the prostanoid products, the tCAI/nonselective beta-blocker combination dorzolamide hydrochloride/timolol maleate, and the alpha₂ agonist brimonidine tartrate — have gained larger shares of the glaucoma market, clinicians have become less reliant on older products. (A trade-name conversion chart for generic medications can be found in Table 1 on page 26.) Many practicing ophthalmologists already have embraced prostaglandins and alpha₂ agonists as first-line therapies, though on a broader scale, the specialty at large is debating the abandonment of beta blockers — long the standard of treatment — as primary therapy for chronic open-angle glaucoma (Goldberg 2002). American Academy of Ophthalmology treatment guidelines are not prescriptive in terms of classes of medications indicated for first-line therapy.

Today, clinicians have unprecedented versatility in the medical treatment of glaucoma. Early detection and prevention, as well as control of the disease, are promises inherent in the expansion of the pharmacological glaucoma armamentarium. The key to choosing the optimal regimen for each glaucoma patient and glaucoma suspect is knowledge. This article concentrates on the clinical aspects of glaucoma medications; its goal is to provide the clinician with the information needed to make informed choices.

NEWER AGENTS

Topical carbonic anhydrase inhibitors

Although systemic CAIs (sCAIs) are more potent, the topical CAIs — used three times daily as monotherapy or twice a day as adjunctive therapy — effectively reduce intraocular pressure (IOP) and generate fewer and milder side effects (SEs). Carbonic anhydrase (CA) is an enzyme that catalyzes the reversible hydration of carbon dioxide and the dehydration of carbonic acid, affecting fluid transport in various cell systems, including the kidneys, choroid plexus, and the eye. In the eye, both dorzolamide and brinzolamide work through the reversible and noncompetitive binding of CA. By decreasing bicarbonate formation, sodium and fluid movement into the posterior chamber decline and less aqueous fluid is generated, thus reducing IOP.

Richard G. Fiscella, RPh, MPH

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Dorzolamide 2 percent solution, the first tCAI developed for clinical use, penetrates the cornea, effectively inhibiting two of the seven CA isoenzymes — CA II and CA IV, which are found in the corneal endothelium, ciliary processes, retina (CA II), choriocapillaris (CA IV), and lens (both) — and may reduce the secretion of aqueous humor by as much as 50 percent. Although it appears that dorzolamide does not reduce IOP as effectively as either timolol 0.5 percent (a beta blocker) or sCAIs, this agent rarely induces systemic SEs (sSEs). The most common ocular SE (oSE) associated with its use is eye stinging; sSEs include bitter taste and digestive system problems, such as diarrhea, nausea, and gastroenteritis.

Brinzolamide 1 percent, available in a carbomer gel base, displays IOP-reducing efficacy similar to that of dorzolamide; it causes some blurry vision, but less stinging than dorzolamide, perhaps because its pH is different.

Contraindications associated with the use of tCAIs include hypersensitivity to any of their pharmaceutical excipients, hypersensitivity to sulphonamides, severe renal impairment, and hyperchloraemic acidosis. The most common adverse effects associated with tCAIs, aside from a few reports of gastrointestinal distress and formation of renal stones, are ocular allergies, severe renal impairment, and hyperchloraemic acidosis. The most common adverse effects associated with tCAIs, aside from a few reports of gastrointestinal distress and formation of renal stones, are ocular allergies, severe renal impairment, and hyperchloraemic acidosis.

Nasolacrimal duct occlusion and eyelid closure decrease absorption into the blood and, possibly, reduce local side effects. Ideally, the patient should close his or her eyes for 5 minutes after the drop is instilled; 1 minute is the bare minimum, and 3 minutes is an acceptable compromise (Bendel 2001).

### Alpha, agonists

Although these selective alpha-adrenergic agonists have some affinity for alpha, receptors, their main affinity is for alpha, receptors. In the eye, they work by activating presynaptic alpha, receptors, thus inhibiting the release of norepinephrine. This, in turn, reduces the amount of norepinephrine available for activation of postsynaptic beta receptors on the ciliary epithelium, thereby reducing the formation of aqueous humor. Medications in this class are generally taken two or three times daily.

Apraclonidine, a polar derivative of clonidine developed for ophthalmic use, is hydrophilic and a relatively selective alpha, agonist; some alpha, activity — such as mydriasis, conjunctival blanching, and eyelid retraction — has been associated with its use. It reduces IOP by decreasing aqueous humor.

Apraclonidine 0.5 percent solution, taken two or three times daily, is primarily indicated for short-term (30-day) adjunctive therapy for patients who require additional reduction of IOP. Because it does not cross the blood-brain barrier, it causes very few sSEs. One of the most common sSEs associated with this agent is dry mouth, but long-term (90-day) use can result in severe ocular allergy and tachyphylaxis (IOP drift). Apraclonidine 1 percent solution is primarily used following anterior-segment laser surgery to control pressure spikes and angle-closure attacks.

Brimonidine, a highly selective alpha, agonist, demonstrates a relative affinity for alpha, receptors that is 23 to 32 times greater than that of apraclonidine, and causes little or no mydriatic/vasoconstrictive alpha, activity. Similar to clonidine — a systemic, centrally acting hypertension medication — brimonidine is more lipophilic than apraclonidine. Its primary route of delivery is through the cornea and it has two mechanisms of activity,
not only decreasing aqueous humor but also increasing uveoscleral outflow.

Although brimonidine has been associated with potential neuroprotective properties in animal models, this has not been demonstrated in humans. No tachyphylaxis has been demonstrated with brimonidine. Ocular SEs include allergies, burning, and stinging; sSEs include dry mouth, some fatigue, drowsiness, and headache.

Brimonidine 0.2 percent can be used to treat chronic glaucoma, and has been shown to be as effective as timolol and betaxolol (a beta blocker) in reducing IOP. Although the package insert indicates three-times-daily dosing, it is used twice daily in most regimens.

Brimonidine 0.15 percent — a 25-percent-milder version of the drug, received FDA approval in March 2001. This product has been shown to reduce IOP as efficaciously as brimonidine 0.2 percent, probably because of improved bioavailability. Brimonidine 0.15 percent causes fewer sSEs, such as drowsiness and fatigue, than brimonidine 0.2 percent. With a pH of 7.2, which is close to that of natural tears, brimonidine 0.15 percent is associated with a 40-percent lower incidence of ocular allergies; its preservative is a stabilized oxychloro complex, which breaks down to sodium chloride and water on exposure to ultraviolet light and which is not retained in ocular tissues. The preservative used in most topical glaucoma medications, benzalkonium chloride (BZK), has been known to cause ocular allergy and fibrosis and to contribute to the failure of glaucoma-filtering surgery.

Apaclonidine and brimonidine are contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy. Because of reports of apneic episodes and cyanosis, brimonidine should not be prescribed for infants or small children.

**Prostaglandins and prostanamides**

Prostaglandins — analogues of the hormone prostaglandin F<sub>2</sub> beta — are thought to reduce IOP by improving uveoscleral outflow. Prostaglandins can cause eye inflammations and may pose problems for patients with concomitant conditions, but generally they cause few sSEs and mild oSEs.

The first of the prostaglandins to be FDA-approved was latanoprost 0.005 percent solution, which entered the United States glaucoma market in 1996 and is now the most frequently prescribed primary open-angle glaucoma (POAG) treatment in the world. Latanoprost is at least as effective as timolol (Hedman 2000), and tends to foster patient adherence to therapy because it is taken only once daily. Early reports suggested that best results were achieved with bedtime dosing, but subsequent evidence suggests that time of day does not matter as long as the drug is administered at the same time each day. Although latanoprost is used as first-line therapy or monotherapy outside the United States, it is currently indicated in the United States as adjunctive treatment for open-angle glaucoma patients who cannot tolerate or have not responded to other therapeutic agents. Latanoprost should be refrigerated until dispensed. Once it is opened, it expires after 6 weeks at room temperature.

A few cases of migraine headache and exacerbation of herpes simplex keratitis have been reported, and there have been rare reports of upper-respiratory-tract infections, joint or muscle pains, nonocular allergy, or eczema, but most latanoprost SEs are ocular: iris discoloration, pigmentation changes around the eyelids, and lengthening and thickening of the eyelashes. Conjunctival hyperemia has been reported to be more common among latanoprost users than among timolol users, with 1 percent of latanoprost users discontinuing therapy as a result (as reported on the package insert).

Also reported were cases of mild punctate corneal epithelial erosions and, typically in predisposed patients, iritis and cystoid macular edema (CME). CME often is associated with a prior event, such as rupture of the lens capsule, complication of ocular surgery, or a history of CME. No causal relationship has been established between latanoprost use and herpes simplex, migraine, or CME.

Iris discoloration is reported in between 7 and 12 percent of cases, almost always affecting mixed-color irises, most often green/brown or blue/grey-brown. Typically, discoloration, usually darkening of the iris, is noticed between 18 and 26 weeks after latanoprost therapy begins. It is irreversible, the result of an increase in the amount of melanin within the melanocyte, rather than an increase in the number of melanocytes, as had been raised previously as a potential concern (Wistrand 1997).

Unoprostone isopropyl is a docosanoid, which may activate the F<sub>2</sub> alpha receptor at higher doses. Its suspected mechanism of activity is the increase of aqueous humor through the uveoscleral pathway and/or the trabecular meshwork. Unoprostone 0.15 percent solution, approved for use in the United States in 2000, is taken twice daily. Studies from Europe and Latin America report that it is substantially less effective than either timolol or latanoprost at reducing IOP (Novack 2002). Like latanoprost, unoprostone rarely causes SEs (most often, flu syndrome), and its oSE profile is similar to that of latanoprost, but with less incidence of iris discoloration.

Travoprost 0.004 percent solution and bimatoprost 0.03 solution received FDA approval in March 2001. Travoprost targets the same prostanoid receptor that latanoprost does, and reduces IOP by increasing drainage of aqueous humor. Because glaucoma is more prevalent among blacks than in other populations, it may be clinically significant that, unlike the other prostaglandins,
travoprost has demonstrated some greater effectiveness in black patients (Netland 2001). However, this potential advantage still needs to be more thoroughly studied.

Generally, travoprost exhibits the same level of IOP-reducing ability that latanoprost does. Ocular hyperemia is much more prevalent with travoprost than with latanoprost, but travoprost may cause fewer incidences of iris discoloration. Once the patient removes travoprost from its foil pouch and opens the bottle, the drug has a 6-week shelf life at room temperature. Clinicians should warn contact-lens wearers to remove their lenses before administering travoprost, because the lenses may absorb the Bzk used as a preservative.

Bimatoprost lowers IOP by increasing aqueous humor outflow through both the trabecular meshwork and by the uveoscleral route. An ocular hypertensive lipid classified as a prostamide (a synthetic structural analogue of a prostaglandin), it selectively mimics the effects of naturally occurring prostamides, but does not appear to act on the F, alpha receptor.

In Phase III trials, 64 percent of subjects receiving bimatoprost achieved the target IOP of 17 mm Hg or less, compared with 37 percent of subjects receiving timolol twice daily (Sherwood 2001). At six months, bimatoprost reduced IOP by 33 percent, compared to timolol’s 23 percent. The most prevalent oSE was conjunctival hyperemia. Patients may develop red eye, especially during the first day or two of treatment, and that the condition may lessen within one or two weeks. Other oSEs include lengthening and thickening of eyelashes, ocular pruritus, blurred vision, dry eye, eye pain, and foreign-body sensation. Compared with the Phase III studies with latanoprost, fewer patients reported iris discoloration.

Selective beta blockers

At this time, betaxolol 0.25 percent solution is the only beta-adrenergic antagonist or beta blocker that is beta, selective and cleared for use in the United States. By minimizing beta2 inhibition, it is pulmonary-sparing and cardioslective. Beta blockers represent the industry standard against which other IOP-reducing medications are measured. Timolol 0.5 percent, twice daily, a nonselective beta blocker, reduces IOP effectively and, for Phase III trials of other IOP-reducing drugs, its performance provides the benchmark. They reduce adenylyl cyclase activity, which, in turn, reduces the production of aqueous humor.

Although nonselective beta blockers may be more efficacious in lowering IOP, selective beta blockers appear to be better tolerated systemically, particularly in patients with chronic obstructive pulmonary disease (COPD, such as emphysema, chronic bronchitis, or chronic asthma, individually or in combination), and may have less effect on blood pressure (Stewart 1998).

combination therapy

One product combines a tCAI with a beta blocker: dorzolamide hydrochloride 2 percent/timolol maleate 0.5 percent, which can be applied twice daily; rather than three times, while delivering similar IOP-reduction power. Further, combining these agents gives the patient one set of eye drops to use, rather than two, and this simplification should promote patient adherence to therapy. One sSE associated with this product is taste perversion; oSEs include ocular burning and stinging, conjunctival hyperemia, blurred vision, superficial punctate keratitis, and eye itching. This medication is contraindicated in patients with bronchial asthma or a history of the disease, severe COPD, sinus bradycardia, second- or third-degree atrioventricular block, overt cardiac failure, cardiogenic shock, or allergy to either component.

Clinical effectiveness of newer medications

Although head-to-head trials of various IOP-reducing drugs are not always available, it is interesting to consider the reported mean IOPs and changes from baseline in Phase III trials (Table 2). Comparing Phase III trial data, latanoprost and travoprost appear to be similar with respect to the proportion of patients who achieve IOPs of 17 mm Hg or less, with bimatoprost slightly more effective than both. Bimatoprost also was equally effective in Phase III trials among black and white populations. There are some data to suggest that travoprost may be more effective than latanoprost in blacks, though this needs further study.

OLDER AGENTS

Until 1995, patients would receive epinephrines, topical beta blockers, systemic CAIs, or cholinergic blocking agents to treat glaucoma. Since the FDA’s approval of the newer products (topical CAIs, alpha agonists, prostaglandins, and combinations), these older products have been losing ground steadily in the marketplace.

Cholinergic blocking agents (miotics)

Direct-acting cholinergics stimulate the parasympathetic muscarinic receptor site to increase aqueous outflow through the trabecular meshwork; however, the intensive dosing regimen, combined with a significant side-effect profile, make patient adherence difficult. Among the oldest glaucoma drugs, cholinergic agents have been used to reduce IOP for more than a century. Pilocarpine, a direct-acting cholinergic and the archetypical agent in this class, effectively reduces IOP when used four times daily. Pilocarpine can provoke miotic responses, such as pupillary constriction, which can restrict patient responses in poor lighting. It can also cause eye pain, brow ache, or accommodative spasms. Systemic ad-
verse effects, although rare, include nausea and/or vomiting, pulmonary edema, bradycardia, diarrhea, perspiration, salivation, and bronchial secretion. In rare instances, retinal detachment has been associated with its use.

Indirect-acting cholinergics, or anti-cholinesterase inhibitors (AChls), promote the accumulation of acetylcholine at the muscarinic receptors, stimulating increased aqueous outflow. Echothiophate iodide, physostigmine, and demecarium are AChls. Side effects, in addition to those associated with the direct-acting miotics, include cataracts, iris cysts, and corneal toxicity.

Carbachol, given two or three times daily, is similar to pilocarpine, but more potent and can induce SEs that are a bit more pronounced. In particular, brow ache tends to be more severe. A synthetic molecule, carbachol has both direct- and indirect-acting mechanisms.

In patients receiving succinylcholine during general anesthesia, miotics prevent the body from inactivating the anesthetic, greatly extending its effect and risking respiratory failure and cardiovascular collapse. The combination of miotics and angiotensin-converting enzyme (ACE) inhibitors or calcium-channel blockers can worsen headache, increase vasodilation, and cause hypotension.

Nonselective alpha-adrenergic agonists

Drugs in this class, such as epinephrine and its prodrug, dipivefrin, have both alpha- and beta-adrenergic activity; the former results in decreased aqueous production, while the latter increases it and may also stimulate conventional and uveoscleral outflow (Bendel 2001). Therefore, these agents provide poor IOP control;

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Comparison of clinical trial data of newer glaucoma agents</th>
</tr>
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<tbody>
<tr>
<td><strong>Product</strong></td>
<td><strong>dosing</strong></td>
</tr>
<tr>
<td>Baseline IOP (mm Hg)</td>
<td>25.2</td>
</tr>
<tr>
<td>Mean IOP (mm Hg), 6 months</td>
<td>18.5</td>
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<tr>
<td>Mean IOP ∆ (mm Hg)</td>
<td>–6.7</td>
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<tr>
<td>Mean % ∆</td>
<td>27</td>
</tr>
<tr>
<td>% patients ≤17 mm Hg IOP, 12 months</td>
<td>49.5</td>
</tr>
<tr>
<td>Mean IOP, blacks (mm Hg)</td>
<td>18.6</td>
</tr>
<tr>
<td>Mean IOP, nonblacks (mm Hg)</td>
<td>18.6</td>
</tr>
<tr>
<td>Hyperemia (%)</td>
<td>5~15</td>
</tr>
<tr>
<td>% patients discontinued</td>
<td>1</td>
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<tr>
<td>Iris pigmentation (%), 6 mo. 12 mo.</td>
<td>6.7</td>
</tr>
<tr>
<td>Stability</td>
<td>2.5</td>
</tr>
<tr>
<td>Size (ml)</td>
<td>6 weeks, room temp.</td>
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<tr>
<td>Drops per bottle</td>
<td><del>90</del>95</td>
</tr>
<tr>
<td>Average wholesale price †</td>
<td>$53.00</td>
</tr>
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</table>

* Not six months.
† As of September 2002.

when taken twice daily, they demonstrate the weakest ef-
fact among all classes of IOP-reducing agents.

Adverse effects include considerable stinging and tear-
ing, brow ache, black conjunctival spots, and soft contact lens staining, as well as CME in aphakic (lensless) and lens-implant patients. These drugs are associated with conjunctival deposits and also discolor on exposure to heat or light. Topical epinephrine rarely causes SEs, but hypertensive crisis, nervousness, headache, palpitations, and increased heart rate have been reported. Because of their limited efficacy and considerable side effects, these products are seldom used today.

At one twentieth the concentration of epinephrine, dipivefrin results in generally milder adverse SEs; however, long-term use often results in follicular conjunctivitis and hyperemia. Dipivefrin is converted to active epinephrine after it is absorbed through the cornea into the eye.

Probably, neither of these agents should be prescribed for patients with hyperthyroidism or cardiac disease or those taking MOA inhibitors or tricyclics (Bendel 2001).

Systemic CAIs

Agents such as acetazolamide; methazolamide, taken two or three times daily, and dichlorphenamide, taken once to three times daily, are highly effective at reducing IOP by inhibiting the formation of aqueous humor; however, sCAIs may cause extremely severe SEs, including paresthesias; gastrointestinal disturbances, such as anorexia, nausea, and a metallic or otherwise altered taste; and central nervous system (CNS) problems, such as lethargy, malaise, and depression.

As weak diuretics, sCAIs may produce electrolyte disturbances, such as transient hypokalemia; they can produce metabolic acidosis, which may exacerbate COPD; and, in rare cases, they may cause renal calculi, blood dyscrasias, or dermatitis. Because CAIs are sulfonamides, clinicians should use them with caution when treating patients with sulfà allergies, as they have also been associated, in rare cases, with fatal aplastic anemia.

The most commonly used sCAI, acetazolamide, is seldom prescribed for chronic glaucoma; its injectable form can be used to treat acute glaucoma. Although its structure is similar to that of acetazolamide, methazolamide is more lipid soluble and causes less systemic acidosis, diuresis, gastrointestinal problems, and paresthesias, but may produce more CNS SEs. Dichlorphenamide is rarely used because its SE profile, which is similar to that of acetazolamide, is much more pronounced, and patients may also experience anorexia and confusion.

Nonselective beta blockers

Nonselective beta blockers — including timolol maleate, levobunolol, carteolol, and metipranol — may decrease aqueous humor production by 50 percent, and are generally about 15 percent more effective than selective beta blockers at reducing IOP. They are typically applied twice daily. Timolol 0.5 percent solution is a highly effective IOP-reducing agent. As a solution that forms a gel upon application, timolol may be administered once daily, which may increase IOP activity and reduce SEs. Carteolol has intrinsic sympathomimetic (partial agonist) activity and has a milder SE profile.

Beta blockers likely lower IOP by reducing adenylyl cyclase activity, thus diminishing aqueous production. Ocular SEs are generally minor, and include stinging, burning, and, rarely, allergic conjunctivitis. Like systemic beta blockers, topical agents can cause sSEs by their unintended direct absorption through the nasopharyngeal mucosa into the vascular supply.

Systemic SEs associated with beta blockers include bradycardia, aggravation of congestive heart failure, heart block, increased low-density lipoprotein cholesterol, decreased high-density lipoprotein cholesterol, bronchospasm in asthma patients, and CNS SEs, including impotence, hallucinations, and depression. These drugs can also mask signs of hypoglycemia and have been associated with lowered blood pressure.

Clinicians should select topical medications carefully when prescribing beta blockers and calcium-channel blockers, diuretics, cardiac glycosides, or ACE inhibitors, or when prescribing both topical and systemic beta blockers (Bendel 2001).

THERAPEUTIC CONSIDERATIONS

In a published debate about the abandonment of beta blockers as first-line monotherapy for chronic open-angle glaucoma, A. Anton of the Instituto Oftalmobiologica Aplicada at the Universidad de Valladolid, in Spain, and G.L. Skuta, of the Dean A. McGee Eye Institute at the University of Oklahoma, presented their beta blocker views in a recent issue of the British Journal of Ophthalmology (Goldberg 2002).

“It seems reasonable,” Anton concluded, “to use beta blockers only as second- or even third-line treatment when other drugs are not tolerated, are unable to lower IOP in a particular patient, or are contraindicated. Why should we use beta blockers first if there are medications available that are at least as effective, at least as easy to use, cause significantly fewer systemic side effects, and have similar or only slightly worse local side effects?”

Skuta admitted that treatments have improved and that the newer agents have provided welcome options for patients intolerant of beta blockers. “However,” he wrote, “beta blockers are highly effective ocular hypotensives with well-known side effects. Generally, they are well tolerated, have a very low rate of ocular allergy, may be
used in children when necessary, and are more cost-effective than many other newer alternatives."

Geriatricians are investigating the safety and efficacy of the newer glaucoma medications. In the Journal of the American Geriatric Society, Novack and colleagues (2002) suggested that glaucoma be considered a disease of the aging eye. “Most medications used to treat glaucoma are in topical eyedrop form and may cause numerous untoward systemic effects in older persons,” they warned, adding that geriatricians should acquire comprehensive knowledge about the newer medications “because there is a growing trend by ophthalmologists to lower intraocular pressure aggressively.” Their article focuses exclusively on the newer drugs.

Glaucoma is a spectrum of related diseases, and POAG is the most prevalent form of it; congenital, narrow-angle and secondary glaucoma account for only a combined 10 percent of cases. Because POAG is a silent disease — visual-field changes are rarely evident in their early stages — screening those individuals at risk is essential to early detection, which, in turn, can delay or prevent onset.

Screening to detect early-stage glaucoma depends on optic-nerve head changes — examples of which can include optic-disc cupping, disc hemorrhage, or nerve-fiber layer changes. Persons without elevated IOP may suffer from normal-tension glaucoma; those who have elevated IOP but without optic-nerve head changes can be considered ocular hypertensives or glaucoma suspects.

In a landmark report published in June, the Ocular Hypertension Treatment Study (OHTS) researchers demonstrated what clinicians have long suspected: topical hypotensive medication can delay or prevent the onset of POAG (Kass 2002). They studied 1,626 higher-risk subjects, age 40 to 80 with no evidence of glaucomatous damage but with an IOP of 24 to 32 mm Hg in one eye and between 21 and 32 mm Hg in the other. Subjects were randomly placed in observation or treatment groups. Treatment consisted of commercially available ocular hypertension medication.

The treatment goal was to reduce IOP by at least 20 percent and to achieve an IOP of 24 mm Hg or lower. At the end of the five-year study, the cumulative probability of developing POAG was 4.4 percent in the treatment group and 9.5 percent in the observation group. The OHTS group discovered little evidence of increased systemic or ocular risk associated with the glaucoma eye drops. The researchers concluded that although their results do not imply that all patients with elevated or borderline IOP should receive medication, clinicians should consider treating ocular hypertensives who are at moderate or high risk to develop POAG.

CONCLUSION

When constructing a treatment regimen for a glaucoma patient, the clinician will use all the tools available, including guidelines, recommendations, and most importantly, his or her own experience and knowledge of the condition in general and that of the patient. The purpose of this chapter has been to assist in this process by providing the clinician with basic knowledge about glaucoma pharmacotherapeutic options, the variety of which has increased sharply within the last several years.

REFERENCES


Considerations in the Pharmacoeconomics of Glaucoma

JAN D. HIRSCH, PhD
Director of Clinical Research, Prescription Solutions

SUMMARY
Pharmacoeconomic research identifies, measures, and compares the costs and consequences of pharmaceutical product and service utilization. Providing optimal glaucoma care requires planning, based not only on the historically relevant factors of drug safety and efficacy, but also on data relating to the value of medical treatments.

Throughout the health care industry, providers and administrators are striving to improve both the overall quality and efficacy of medical care, including that for patients with glaucoma, while working within restrictive financial boundaries.

Pharmacoeconomic analysis provides the framework for achieving this goal. Providing optimal glaucoma medical care requires planning, based not only on the historically relevant factors of drug safety and efficacy, but also on data relating to the value of medical treatments. The science of pharmacoeconomic research has evolved to provide these data.

Researchers first applied pharmacoeconomic analysis to treatments for higher-prevalence chronic conditions, such as migraine headache and asthma, to identify the regimens that offer the best value. Because glaucoma is relatively silent and practically asymptomatic in its early stages, investigators have only recently considered applying pharmacoeconomic assessment to glaucoma treatments.

For any pharmacoeconomic analysis to be useful, the multidimensional concept of medical-treatment value must be accepted. This requires the investigator to assess and balance the factors that determine total treatment costs and clinical benefits. This article considers only the pharmacoeconomic analysis of drug therapy for glaucoma. To retain that focus, conventional surgical, laser surgery, and complementary and alternative treatments for glaucoma will not be discussed here, although the same principles would apply.

Among the systems designed for the pharmacoeconomic assessment of medical treatments is the ECHO (Economic, Clinical, and Humanistic Outcomes) model, proposed by Kozma (1993), which focuses on economic, clinical, and humanistic outcomes. Economic outcomes in the ECHO model include direct medical costs, such as the costs of the drug, administration, and treatment of adverse effects; direct nonmedical costs, such as patient transportation; indirect costs, such as lost work days, lost earnings, and decreased productivity; and intangible costs related to pain and suffering. Clinical outcomes include efficacy, onset of action, percentage of patients who become free of symptoms, symptom recurrence, and adverse effects. Humanistic outcomes include health-related quality of life, return to normal functioning, and patient satisfaction with therapy. Some variables may relate not only to patients, but also to caregivers and significant others.

1 Jan D. Hirsch, PhD, is the director for post-launch clinical research at Prescription Solutions, a Costa Mesa, Calif.-based pharmacy benefit management company. Hirsch leads the clinical research group’s Real World Prospective Outcomes Research program, which evaluates the value, safety, and effectiveness of FDA-approved medications and devices in actual patient care settings and focuses specifically on such managed care environments as HMOs, IPAs, medical groups, and integrated health systems. A pharmacist by initial training, Hirsch has authored book chapters in multiple pharmacoeconomic texts and has written numerous journal articles on the value of specific pharmaceutical agents. She earned her PhD from the University of South Carolina.
The clinical characteristics of a disease determine the relevance of each type of outcome. For example, lost work days are more relevant in the evaluation of asthma or migraine, which can temporarily debilitate sufferers, but less relevant to glaucoma. More relevant to glaucoma would be, for example, the cost of noncompliance, because once the disease is diagnosed, glaucoma patients typically use medication for years. Noncompliance brings a risk of greater downstream costs associated with more invasive therapies.

Because glaucoma is a chronic disease for which the number of medical therapies recently has expanded, pharmacological treatment of glaucoma has attracted the attention of outcomes researchers. This article describes the basic pharmacoeconomic principles that can be used to help clinicians incorporate a value component into their decisions about treating glaucoma patients.

**PHARMACOECONOMIC RESEARCH**

Pharmaceutical research identifies, measures, and compares the costs and consequences of pharmaceutical product and service utilization. In this definition, *costs* refer to resources consumed; the *consequences of using* pharmaceutical products and services are considered to be the outcomes defined in the ECHO model. At the core of this research are evaluations estimating the value of the economic, clinical, and humanistic outcomes resulting from different treatments, which are compared systematically to help the clinician determine an optimal therapeutic approach.

**Pharmacoeconomic analysis methods**

*Cost minimization, cost effectiveness, cost benefit, and cost utility* are the basic types of pharmacoeconomic analyses. Each assesses the resources consumed and the clinical, economic, and humanistic outcomes produced by various therapies. Each type of analysis expresses resources consumed in terms of monetary units, but uses a different unit to express the outcome.

Cost minimization is the simplest of these analyses, because it assumes that the outcomes of the therapies being compared have been proven equivalent among treatment groups. This reduces the analysis to a monetary comparison of resources consumed.

A cost-effectiveness comparison of two or more treatments analyzes the dollars spent in consumed resources and the clinical outcomes derived from this expenditure. Because it uses natural units of medical outcomes (e.g., life-years gained; mm Hg blood pressure reduction) to compare medical treatments, this type of pharmacoeconomic analysis — more than any — parallels the medical thought process and is intuitively accepted within the medical community as reasonable. That is why, in medical-decision making, cost effectiveness is the most commonly performed of the four analyses. A cost-effectiveness evaluation, however, cannot be used to compare treatments with dissimilar outcomes. For example, consider the outcomes goals for a group of patients with glaucoma, a chronic disease, and a group of patients with bacterial keratitis (BK) infection, an acute disease. The former goal is quantified as lowering mean intraocular pressure (IOP), while the latter goal is quantified as curing the infection. These goals are not directly comparable in a cost-effectiveness analysis.

In a cost-benefit analysis, the outcomes of two dissimilar treatment groups, inherently expressed in dissimilar natural units, can be defined in terms of monetary units. This conversion allows the investigator to compare dollars with dollars: dollars spent in consumed resources with the dollar value gained in clinical outcomes. Thus, a cost-benefit analysis allows the investigator to compare costs and outcomes of unrelated health care strategies, such as eye care and orthopedic programs.

A cost-utility analysis evaluates the effect of treatment on societal outcomes, typically expressed in terms of quality-adjusted life-years — in effect, expanding the cost-benefit analysis. A cost-utility evaluation allows the investigator to include the humanistic outcomes of patient preferences or quality of life when comparing products or programs with dissimilar outcomes measures.

In the evaluation of drug therapies for glaucoma, cost-minimization and cost-effectiveness assessments have been reported most frequently. Cost minimization is used to compare treatments with similar safety and efficacy, while cost effectiveness seeks to compare two treatments when one has a safety or efficacy advantage and the acquisition price of each differs.

**Resource consumption in glaucoma**

In a pharmacoeconomic analysis, it is vital to account for the complete cost of the treatment. Identifying and measuring the resources consumed in treatment can be time-consuming, tedious, and perhaps confusing. To obtain the true value of the resources used, the investigator must start with the price of the medication used in a treatment regimen, but also must consider other, often overlooked, resources consumed.

Depending on the regimen, such factors might include compounding by a pharmacist, costs associated with the administration of the medication (e.g., if the drug must be delivered intravenously, then the syringe, IV bags, and nurse time), monitoring the patient for adverse effects, and the costs of dealing with complications. If the patient incurs expenses for travel to the treatment site or must take time off from work because of disease symptoms, these costs should also be considered.
In glaucoma, both disease severity and corresponding treatments drive the total disease cost, as demonstrated in a retrospective study by Siebert (2000). Costs — including diagnostic tests, physician visits, loss of income, and ancillary support — increase as the disease progresses, and later-stage pharmaceutical and surgical interventions are most responsible for this increase. The Siebert group reviewed the charts of 40 patients, estimating medication costs using local pharmacy prices and office-visit and test costs using the 1998 Medicare fee schedule.

Using visual-field and optic disc criteria, these researchers defined the stages of disease progression as $0 = $normal$, $1 = $suspected damage$, $2 = $questionable damage$, $3 = $definite or moderate damage$, $4 = $marked damage$. Average annual costs of medication and average annual total costs per patient are shown in Table 1.

The authors noted that this study has its limitations: Not all costs can be captured in a retrospective study; the sample size is small, indirect costs were not measured, geographic variances might be significant, and having only five stages of disease progression may not be sufficient. Regardless, Siebert effectively, if basically, demonstrated that total costs do correlate and rise with disease progression in glaucoma.

A similar relationship between costs and disease progression was also demonstrated in a large multinational observational study (Jönsson 1999). The U.S. results illustrated a progression of treatment costs, related to disease severity; the mean cost per patient (including drugs, tests, surgery, hospital, and physician visits) was greater for patients with primary open-angle glaucoma (POAG) than for patients with only ocular hypertension.

Factors affecting pharmacoeconomic evaluations of glaucoma drugs

In glaucoma, a number of factors relevant to both the disease and the treatment can determine what resources are consumed, what outcomes are achieved, and what a pharmacoeconomic analysis should consider. This section discusses several key factors related to glaucoma.

Diagnosis and disease progression. Early treatment of elevated IOP in higher-risk patients can delay or prevent the onset of glaucoma (Kass 2002) and avoid associated treatment costs. Earlier detection requires aggressive screening and may result in earlier treatment, which increases resource consumption during early stages of disease but can obviate the need for more aggressive — and, as Siebert and colleagues demonstrated, more expensive — therapeutic intervention later.

Treatment costs. Glaucoma medications vary — sometimes substantially — in efficacy, side effects, and acquisition cost. Although these factors deserve consideration in a pharmacoeconomic evaluation, acquisition cost — at first

### Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Total costs mean (SD), $P=0.0156*$</th>
<th>Medication costs mean (SD), $P=0.0007*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$200 ($106)</td>
<td>$36 ($71)</td>
</tr>
<tr>
<td>1</td>
<td>$374 ($193)</td>
<td>$60 ($70)</td>
</tr>
<tr>
<td>2</td>
<td>$483 ($183)</td>
<td>$186 ($119)</td>
</tr>
<tr>
<td>3</td>
<td>$605 ($116)</td>
<td>$72 ($61)</td>
</tr>
<tr>
<td>4</td>
<td>$836 ($409)</td>
<td>$195 ($107)</td>
</tr>
</tbody>
</table>

*SD = Standard deviation. $P$-value based on analysis of variance (ANOVA).

| Source: Siebert 1999 |

### Table 2

<table>
<thead>
<tr>
<th>Hypothetical 100 patients initiated on drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>75% succeed initial therapy</strong></td>
</tr>
<tr>
<td>Path 1</td>
</tr>
<tr>
<td>80% experience no adverse effects (60% of total)</td>
</tr>
<tr>
<td>Path costs</td>
</tr>
<tr>
<td>$20.00</td>
</tr>
<tr>
<td>Path 2</td>
</tr>
<tr>
<td>20% experience adverse effects (15% of total)</td>
</tr>
<tr>
<td>Path costs</td>
</tr>
<tr>
<td>$70.00</td>
</tr>
<tr>
<td><strong>25% fail initial therapy</strong></td>
</tr>
<tr>
<td>Path 3</td>
</tr>
<tr>
<td>70% experience no adverse effects (17.5% of total)</td>
</tr>
<tr>
<td>Path costs</td>
</tr>
<tr>
<td>$80.00</td>
</tr>
<tr>
<td>Path 4</td>
</tr>
<tr>
<td>30% experience adverse effects (7.5% of total)</td>
</tr>
<tr>
<td>Path costs</td>
</tr>
<tr>
<td>$130.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cumulative percentage costs (Path cost multiplied by cumulative percentage of patients in the path)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$12.00 ($10.50 + $14.00 + $9.75 = $46.25)</td>
</tr>
</tbody>
</table>

| Average expected cost per patient: |

$12.00 + $10.50 + $14.00 + $9.75 = $46.25
assessment, the easiest factor to calculate — may actually be more difficult to assess than expected due to variations in product and use characteristics, such as bottle size, drop size, and dosing regimen.

Adherence. Noncompliance with a prescribed drug regimen can decrease the efficacy of the therapy and increase treatment costs, especially in the long term. Glaucoma treatment is prophylactic. Because glaucoma is virtually asymptomatic, with neither pain nor vision loss in the early stages, there is a risk that patients’ persistence with therapy will decrease, allowing their disease to advance more rapidly to the more costly disease stages.

Cost of failure

In performing pharmacoeconomic evaluations, it is necessary to bear in mind that treatment failure must be considered explicitly. Pharmacoeconomic assessments are made from the population perspective of medical decision making, not the one-on-one perspective inherent in the traditional physician–patient relationship. No treatment can be expected to be effective in all cases; a percentage of patients will fail, some because the treatment is ineffective and others because adverse effects prohibit continuation of the therapy.

From the population perspective, treatment failures can generate substantial cost. The expected average cost per patient of a drug therapy should include the additional cost of failure. A simplified algorithm (Table 2) illustrates how therapy failure can affect the cost of therapy from the overall population perspective. Assume that 100 patients initiate drug therapy, the price per patient of the initial drug therapy is $20, the cost to retreat a patient who fails initial therapy is $60, and the expense of treating a patient who suffers an adverse effect is $50.

In this scenario, of 100 patients who initiate therapy, 75 percent succeed initial therapy and 25 percent fail. Of those who succeed, 80 percent experience no side effects (path 1), while 20 percent subsequently suffer an adverse effect (path 2). Of those who fail initial therapy, 70 percent have no adverse effect (path 3), while 30 percent do (path 4).

The cost per patient in each path: 1 = $20, or only the price of the initial therapy; 2 = $70, the initial therapy plus treatment of the adverse effect ($20 + $50); 3 = $80, the initial therapy plus retreatment ($20 + $60); 4 = $130, initial therapy plus retreatment, plus adverse effect ($20 + $60 + $50).

Path 1 is least expensive and path 4 is most expensive. From the population perspective, however, the expected average cost per patient should include the resources consumed by the patients in all the paths, not just the ones who succeeded initial treatment with no side effects. The average cost per patient in this population of 100 patients is determined by adding the cumulative percentage costs, which, in this scenario, is $46.25 — more than double the $20 for initial drug therapy.

The more patients who take paths 2, 3, and 4, the higher the average expected cost. In a population perspective, omitting the costs of failure can lead to average cost estimates that are much lower than the actual average costs would be in reality. This underestimation would reduce, perhaps greatly, the usefulness of the average cost estimate when making medical decisions.

An example of the importance of considering the incidence of failure in specific groups of patients is the selection of a first-line therapy in glaucoma. This is an important cost-control factor because, as many researchers have discovered, the percentage of therapy failures due to lack of efficacy and/or adverse effects differs across medications and often across types of patients. For example, in a randomized, masked, prospective study, DuBiner (2001) compared twice-daily brimonidine 0.2 percent, a highly selective alpha2 adrenergic agonist, with once-daily latanoprost 0.005 percent, a prostaglandin, as glaucoma monotherapy, assessing efficacy and tolerability as first-line agents. Overall, more patients in the brimonidine group (80 percent) vs. the latanoprost group (74 percent) achieved the targeted IOP reduction of greater than 20 percent. However, when patients’ prior therapy was considered, the results differed. In treatment-naive patients, a higher percentage was successful when started on brimonidine vs. latanoprost (88 percent vs. 59 percent, respectively), but in previously treated patients this was reversed and a higher success rate was observed for latanoprost (88 percent) vs. brimonidine (74 percent).

Considering the success rate within specific patient groups is important from a cost perspective, because first-line therapies that generate a higher responder rate (i.e., lower failure rate) will generate fewer follow-up visits and have a pharmacoeconomic advantage. In general, agents that reduce disease severity, slow progression, generate fewer failures, or show a more advantageous safety profile will offer potential cost savings to the health care system.

GLAUCOMA PHARMACOECONOMIC EVALUATIONS

The two types of pharmacoeconomic analyses most commonly applied to glaucoma treatments have been cost minimization and cost effectiveness. Examples that illustrate the approaches to each are presented below. These examples have been selected from published literature — of which there is relatively little for the newer agents — available about products approved for use in the United States (a generic/trade-name conversion chart can be found on page 26).
Cost minimization

Many published studies have focused on the daily costs of using glaucoma medications, assuming basically equivalent safety and efficacy profiles, but using a variety of costing methodologies. A typical example of a cost-minimization study is by Fiscella (1999), who compared the costs of 19 glaucoma medications commonly used at the time, including beta blockers, topical and systemic carbonic anhydrase inhibitors (CAIs), an alpha_2 agonist (brimonidine), a prostaglandin (latanoprost), and a combination product (dorzolamide plus timolol). Fiscella measured the actual volume of each bottle of eye drops for all commercially available sizes of the product from all manufacturers, averaging the results of five bottles of each. He compared drops per milliliter and the daily costs of the manufacturer-recommended dosage schedules, calculating average wholesale prices according to the 1999 Drug Topics Red Book.

Most products delivered the minimal volume stated on the label, but the number of drops per milliliter ranged from 19.7 (levobunolol) to 33 for Bausch & Lomb’s timolol. In some cases, two same-size containers from the same manufacturer, with identical volume, yielded different numbers of drops. For example, two bottles of Schein’s generic timolol 0.5 percent, from different lots, each contained 15 ml, as labeled, but one bottle yielded 443 drops and the other yielded 382 drops. Daily costs of bilateral application ranged from 30 cents for Falcon’s once-daily timolol 0.5 percent gel-forming solution to 81 cents for Allergan’s twice-daily levobunolol. Of the topical CAIs, three-times-daily dorzolamide costs $1.02 per day, while three-times-daily brinzolamide costs 96 cents per day. The most expensive medication tested was a systemic CAI, neptazane 50 mg tablets, at $1.90 or $2.85 per day, depending on regimen.

The large multinational observation study by Jönsson (1999) also compared costs of medications using a different method that is common in pharmaco-economic evaluations. Jönsson and colleagues used a simulation model to estimate a total cost per patient (including costs for drug therapy, medical visits, tests, trabeculectomy, and surgery) based on the retrospective data collected in the study. Their results revealed an annual cost per patient that ranged from lowest to highest for latanoprost, brimonidine, and dorzolamide, respectively.

In a smaller experiment with newer agents, Frenkel (2002) compared the monthly costs of bimatoprost 0.03 percent, latanoprost 0.005 percent, and travoprost 0.004 percent for bilateral treatment to reduce IOP. Frenkel counted the number of drops in each bottle of medication, averaging the results of two bottles for each drug. He determined the average price for each medication using purchase prices charged by one independent pharmacy, five chain drug stores, and one Internet pharmacy. Frenkel determined bimatoprost to be the most economical of the three drugs, the other two each being about 30 percent more costly (Table 3).

### Cost effectiveness

Cost-effectiveness assessments are appropriate for comparisons of two treatments when one has a safety or efficacy advantage. The large observational study by Jönsson (1999) supports the rationale that the IOP-reducing effect of treatments, along with the initial IOP level, are the drivers of total cost: “Results indicate clearly that the IOP at the start of

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Average cost of therapies, by bottle and monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Drops*</td>
</tr>
<tr>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td>Bimatoprost</td>
<td>124.0</td>
</tr>
<tr>
<td>Latanoprost</td>
<td>85.5</td>
</tr>
<tr>
<td>Travoprost</td>
<td>92.5</td>
</tr>
</tbody>
</table>

*Average number of drops per 2.5 ml bottle, at room temperature. SOURCE: FRENKEL 2002

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Costs by types of practice pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern</td>
<td>Average annual treatment cost per eye</td>
</tr>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Common practice</td>
<td>$733.85</td>
</tr>
<tr>
<td>Best practice</td>
<td>$732.09</td>
</tr>
<tr>
<td>Difference</td>
<td>+ $1.76, CPM†</td>
</tr>
</tbody>
</table>

*Estimated by expert Delphi panel. † Common-practice management. ‡ Best-practice management. SOURCE: EVANS AND CASCIANO 2001
treatment and the IOP-lowering effect at treatment start have positively and negatively significant effects on costs” (Jönsson 1999). Despite this support, examples of head-to-head cost-effectiveness evaluations for glaucoma drugs are not common in current literature.

One drug-comparison study, by Evans and Doyle (2001), evaluated the effectiveness and cost effectiveness of a prostamide (bimatoprost 0.03 percent), and a prostaglandin (latanoprost 0.005 percent), given once daily. Clinical success was defined as reducing IOP to 15 mm Hg or less after three months. The success rate for bimatoprost was 29 percent, and 14 percent for latanoprost. This difference translated to a cost-effectiveness rate (medication cost/efficacy) at trial’s end of $517 for bimatoprost and $1,071 for latanoprost. Thus, from this study’s perspective, it cost twice as much to achieve a successfully treated patient with latanoprost as it did with bimatoprost.

This same type of framework can also be used on a much broader basis to compare practice patterns and compare classes of drugs. An example of this is by Evans and Casciano (2001), who used a decision-tree analysis to compare the total, drug, and medical-care costs of common-practice management (CPM) and best-practice management (BPM) of POAG. They convened a Delphi panel of ophthalmologists specializing in glaucoma to define the treatment characteristics of the typical community practice (CPM pattern) and of the ideal specialized practice (BPM pattern). Evans and associates used a decision-analytic approach to depict and economically quantify the clinical sequelae under each pattern. Percentage likelihood of drug usage was based on panel consensus. Drug-efficacy rates were based on published data. Typical drug-dosing regimens and the number of physician visits, as established by panel consensus, were the basis for treatment-cost estimates.

The researchers found a higher percentage of medical care costs were attributable to surgery in BPM as compared to the CPM model. However, they also found, perhaps unexpectedly, that the total average treatment cost per eye of the CPM pattern and BPM pattern were virtually identical (Table 4).

Evans and Casciano also concluded that increased use of alpha2 agonists and decreased use of nonselective beta blockers in first-line POAG management, combined with the increased use of surgical procedures in their model of glaucoma management, could improve outcomes at no additional cost, thus improving cost effectiveness.

**CONCLUSION**

The pharmacoeconomic methods most applicable to glaucoma drug therapy are cost minimization and cost effectiveness. Several examples of their use have been presented in this article; however, such analyses are relatively new to the literature, and the newest medications available to the practitioner are sparsely represented to date. In addition, because various methods are used to calculate costs and outcomes in pharmacoeconomic studies, readers should carefully evaluate the data, assumptions, and methods when assessing the results of a study or when making comparisons of published studies. Further studies are needed to give clinicians and health care systems treating glaucoma patients the relevant economic-value information they need to make informed medical and coverage decisions.

**REFERENCES**


The data reported in this section reflect aggregate national formulary statuses of prescription glaucoma products, as well as trends with respect to the same. The data are current as of August 2002. This information is supplied by Yardley, Pa.-based MediMedia Information Technologies, which collects it from managed care plans and pharmacy benefit managers.

Formulary status is reported several ways. First- and second-tier status, also known as “approved” products, are self-explanatory. Drugs labeled third tier are those that are explicitly listed on formularies’ third tiers. The health plan will pay for these so-called nonformulary drugs, but the member is usually responsible for a higher out-of-pocket copayment or coinsurance fee than for first- and second-tier prescription products.

Where a drug is categorized as not listed/reimbursed, it is not assigned to a specific formulary tier, although the health plan will bear at least some financial responsibility for the product if a physician writes a prescription for it.

Two categories are referred to herein as “negative formulary status”: not reimbursed and prior authorization. Products categorized as not reimbursed are, simply, products that a health plan or PBM’s pharmacy and therapeutics committee has chosen not to cover. Prior authorization, in this case, refers to prescription drugs that are not covered unless medical necessity is established on a case-by-case basis.

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1 MediMedia Information Technologies, a division of MediMedia USA Inc., collects, standardizes, aggregates, and disseminates pharmaceutical information about managed care drug formularies (through such resources as Formulary Compass, Infoscan Formulary Database, and FormTrak Cards), as well as hospital-based diagnosis-and-treatment information (Hospital Diagnosis and Therapy Audit, or HDTA). MediMedia Information Technologies also conducts primary market research on behalf of clients through its proprietary web-based information service, PharmScope. Formulary Compass is a registered trademark of MediMedia Information Technologies.
FORMULARY STATUS AT 5 SELECTED PBMs

Figure 1 compares glaucoma agents’ aggregate formulary status at five major PBMs in 2000 with that of 2002. Older products refers to prescription drugs introduced before 1995. 1995–1999 products represent four medications introduced during this period: Alphagan (brimonidine tartrate 0.2%), Azopt (brinzolamide), Trusopt (dorzolamide hydrochroride), and Xalatan (latanoprost). The graphics for recent launches depict formulary acceptance in 2002 of three products first marketed after 2000: Alphagan P (brimonidine tartrate 0.15%), Lumigan (bimatoprost), and Travatan (travoprost).

Comparisons of 2000 and 2002 tend to gain more positive formulary status within two years of introduction. As their safety, efficacy, and financial outcomes become established over time, they gradually displace older medications as preferred products. That many older products moved from lower tiers in 2000 to the third tier in 2002 may also be, in part, a reflection of increased use of three-tier formularies during this period.

FIGURE 1 2000–2002 formulary-status comparisons among PBMs
Percent of PBM formularies

<table>
<thead>
<tr>
<th>Older products</th>
<th>2000</th>
<th>2002</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>96.7%</td>
<td>71.4%</td>
</tr>
<tr>
<td>1995–1999 products</td>
<td>89.4%</td>
<td>90.0%</td>
</tr>
<tr>
<td>Recent launches</td>
<td>60.0%</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

Example: Older products were listed on the first or second tier of 96.7 percent of the five PBMs’ formularies in 2000. First- or second-tier listings for these products fell to 71.4 percent in 2002.

FORMULARY STATUS AMONG HMOs

Figure 2 indicates current HMO formulary status of seven glaucoma products introduced since 1995. These HMOs administer pharmacy benefits for 98.5 million covered lives. Products are listed in order of introduction.

FIGURE 2 2002 HMO formulary status

Example: As of August 2002, Lumigan was listed on the first or second tier for 46.3 percent of HMO members, and on the third tier for an additional 18.1 percent. Formularies covering 27.4 percent of HMO members do not list Lumigan, meaning it is covered but the conditions of coverage are unspecified. Prior authorization is required in 5.0 percent of cases, while 3.2 percent of members are specifically denied a pharmacy benefit for this product.

3 MediMedia Information Technologies captures formulary data from 98 percent of HMOs in the U.S. Among these HMOs, MediMedia counts the number of covered lives for approximately 90 percent of them.
HMO Formulary Status (continued)

Figure 3 provides a more detailed analysis of the nature of the negative formulary statuses indicated in Figure 2. About 12.8 million of the 98.5 million people (13 percent) covered by the HMOs in Figure 2 are enrolled in benefit plans that invoke either prior authorization or not-reimbursed status for 1 or more of these 7 medications. For this subset of covered lives, the share of formularies that require prior authorization versus those not reimbursing for the product at all are indicated in Figure 3.

**FIGURE 3  Analysis of negative formulary status, by status**

% of covered lives

- **Prior authorization:**
  - Trusopt: 41%
  - Xalatan: 48%
  - Alphagan: 29%
  - Azopt: 30%
  - Travatan: 17%
  - Lumigan: 61%
  - Alphagan P: 8%

- **Not reimbursed:**
  - Trusopt: 59%
  - Xalatan: 52%
  - Alphagan: 71%
  - Azopt: 70%
  - Travatan: 83%
  - Lumigan: 39%
  - Alphagan P: 92%

**Example:** Among HMOs whose formularies give negative status to Lumigan, 39 percent of their members (in the aggregate) are denied reimbursement for its use; the remainder require prior authorization as a condition of coverage.

Another way of analyzing negative formulary status is depicted in Figure 4. More than half of HMO formularies (based on a calculation of covered lives) single out only 1 of the 7 glaucoma medications for negative formulary status. About 4 in 9 formularies (based on a calculation of covered lives) assign negative status to more than one product.

**FIGURE 4  Analysis of negative formulary status, by number of products**

Share of covered lives

- More than one product with negative formulary status (44%)
- One product (56%)
FORMULARY TRENDS AND PROJECTIONS

As indicated in Figure 1, products tend to gain positive formulary status over time. Manufacturers seeking formulary acceptance for newer products initially face considerable hurdles, such as cost-and-rebate considerations and the need to demonstrate to P&T committees that these brand-name medications are more clinically effective than the older products they are intended to replace.

The improvement in formulary status that often comes with time is indicated in Figure 5. The graphics depict formulary status in 2000 and in 2002 for Azopt, which was launched in 1999. A year after launch, Azopt was a first- or second-tier medication for 52 percent of HMO members. By 2002, three years after the product’s launch, approved status had risen to 71 percent — even while the use of three-tier formularies became widespread.

Using 2000/2002 formulary trends for Azopt as an example, one can make educated projections about how formulary statuses could change for three products introduced in 2001. Figure 6 depicts one-year post launch statuses for Travatan, Lumigan, and Alphagan P. The fact that each of these three products currently resides on upper formulary tiers to a greater extent than Azopt did in 2000 does not necessarily reflect a poor reception by health plans; rather, it could be an outgrowth of today’s trend of managed care plans giving in to member demands — to the extent that members are willing to pay more for their choices.
Constructing Disease Management Programs for Glaucoma

LAWRENCE D. GOLDBERG, MD, MBA

SUMMARY

Glaucoma, which is associated with diabetes, hypertension, and hypothyroidism, is considered to be a good candidate for disease management. This article explains to clinicians and administrators who are interested in the identification and treatment of glaucoma what they should know about disease management and how they might benefit from establishing a DM program for glaucoma.

Disease management (DM) is a term that has been used, misused, misunderstood, and pondered by clinicians since it first came into use by managed care organizations and pharmaceutical corporations in 1993. It has since become increasingly pervasive through the remainder of the decade and into the 21st century.1

But the term itself is somewhat misleading, because the goal of DM is not to manage a disease, but to improve the health of a specific patient population by taking a unified and coordinated team approach to the entire spectrum of care: identifying a target patient population; diagnosing the disease; selecting and applying a treatment protocol that promises good economic, clinical, and societal results; monitoring treatment; and outcomes assessments, which, ideally, are used to improve the process.

The concept behind the term is not as definite as it might appear. What any entity using the term might mean by it depends on the relevance of DM to the entity. Basically, the function drives the concept. Functionality is subjective.

1 Although the term disease management was first coined by Boston Consulting Group in a report it developed for Pfizer Inc. (the report, commissioned in 1991, was released in 1993), in a sense, the DM movement was launched in 1992 when HEDIS introduced its first asthma standards.

Besides MCOs and drug companies, others — including employers, pharmaceutical benefit management companies (PBMs), insurers, professional associations, and specialty organizations — have invested substantial financial and human resources in DM, and have their own subjective definitions. MCOs and others are primarily interested in DM as a way to share financial risk with payers and providers. Although their perspective has broadened substantially since, pharmaceutical manufacturers first became interested in DM programs to demonstrate the effectiveness of their medications to MCOs; it was certainly to their advantage to demonstrate that increased use of a pharmaceutical therapy may decrease the overall cost of care for a specific patient population. Other groups, meanwhile, have other unique motivators — needs that are met through the provision of rational and systematic care delivery. Such motivators include the need to manage overall health costs (government and private purchasers); to stay within capitation allowances (practitioners), and to maintain health (patients), among others (Couch 1997).

The Disease Management Association of America (DMAA) defines DM as “a system of coordinated health care interventions and communications for populations with conditions in which patient self-care efforts are significant. Disease management supports the physician or practitioner/patient relationship and plan of care, emphasizes prevention of exacerbations and complications utilizing evidence-based practice guidelines and patient empowerment strategies, and evaluates clinical, humanistic, and economic outcomes on an ongoing basis with the goal of improving overall health” (DMAA 2002).

Although the DMAA definition generally refers to vendor-driven DM programs that contract with MCOs to focus on those plans’ most common high-cost/high-prevalence diseases, other DM programs are internal or physician group-driven systems and may be just as likely to produce savings through a reduction in the total cost of care. The purpose of this article is to explain to clinicians interested in the identification and treatment of glaucoma what they should know about DM and to address how they might benefit from establishing a DM program.
CLINICIAN PERSPECTIVE

Most physicians instinctively believe that they have been managing patients appropriately — and thus, managing disease — for years. Yet, there is a subtle but definitely profound difference between the traditional physician’s focus on providing each patient the care needed to resolve a specific medical problem and the DM-based goal of providing optimal care to a specific patient population, particularly when “optimal care” means prevention, treatment, and patient education intended to produce not only clinical improvement but also positive economic outcomes and societal impact. (See “Considerations in the Pharmacoeconomics of Glaucoma” on page 32 for more discussion of outcomes assessment.)

Success for the clinician, in this context, may require a shift in mindset from experience-based to evidence-based medical practice. Only a few years ago, some managed care experts cautioned physicians who still harbored reservations about DM to forget their “rugged individualist” perspective on medical practice and embrace the basic patient-oriented concept of DM: improving patient care by taking a comprehensive approach to managing patient populations, rather than individual cases, and applying a global approach to care, rather than the ad hoc, fragmented approach fostered by traditional fee-for-service medicine (Wynn 1996). Table 1 offers a key-point comparison between traditional medical practice and disease management.

Today, the majority of clinicians realize the benefits of working as part of a care team. Practice guidelines, which leading physicians helped to develop and that reflect the most effective and efficient protocols in use, already form the basis for optimizing patient care in many eye care practices. Glaucoma treatment remains fragmented, to the extent that it does, not because of clinician reluctance or resistance, but because integrated data systems are nonexistent or lacking, and because physicians have little real-time access to pertinent patient-care information needed to help them manage the millions of uncoordinated bits of data required to make optimal medical recommendations.

Guidelines answer the question, “What is the best way to treat glaucoma patients?” DM programs answer the question, “How are glaucoma treatment goals most effectively achieved?” The best clinician perspective on DM is to use this powerful tool to provide the best possible care, most effectively, to help patients achieve their health care goals.

DM programs have become common because they are natural extensions of the integrated health care delivery models favored by MCOs. Clinicians, increasingly, have come to favor these models because, while they typically require the physician to share some financial risk, they also offer financial rewards to physicians who meet financial, clinical, and societal outcomes goals. Entering into a glaucoma DM program will require eye care professionals to become partners with other entities — MCOs, carriers, pharmaceutical firms, and primary care physicians — each of which brings financial means, tools, expertise, or dedicated information- and human systems that, when put together, will enable efficient and effective management of glaucoma.

Through DM, clinicians will be much better able to perform the tasks necessary to improve clinical, financial, and societal outcomes: identifying persons at risk to develop glaucoma, detecting it as early as possible, prescribing the most clinically effective treatment protocol, and working with the other members of the care team to

<table>
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<td><strong>Traditional medical practice</strong></td>
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<td>Disease components are managed singly</td>
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<td>Providers and payers address only what they are responsible for treating or reimbursing</td>
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to ensure the best possible outcomes — in particular, educating and encouraging both glaucoma patients and glaucoma suspects to become active participants in the DM process.

**6 COMPONENTS OF A DM PROGRAM**

To be most effective, a DM program must be comprehensive, involving all the entities necessary to provide cost-effective, standardized, evidence-based care designed to generate optimal outcomes. In the case of glaucoma, participants might include a primary care physician, optometrist, ophthalmologist, nurse or physician assistant, pharmacist, hospital, lab, MCO and drug manufacturer. The successful DM program relies on comprehensive, sophisticated data collection and analysis to track patients’ progress, to determine what works best for most patients, and to figure how much the total course of treatment will cost — including not only the expenditure on initial therapy, but also the costs associated with retreatment, multiple-level treatment courses, adverse effects, office visits, lost wages, and other costs to the patient, the health care system, and society.

According to the DMAA, a full-service DM program includes the following six components: population-identification processes; evidence-based guidelines; collaborative practice models; patient self-management education; process- and outcomes measurement, evaluation, and management; and a routine reporting/feedback system, which may include practice profiling and communication with patients, physicians, health plans, and ancillary providers (DMAA 2002).

Simply stated, under a DM program, a health care team applies a care plan using evidence-based practice guidelines and measures the outcomes. A care team, in the case of glaucoma, may include an optometrist or family physician, who is likely to discover the initial evidence of glaucoma; an ophthalmologist, who diagnoses or confirms the condition (often with the help of a laboratory) and recommends a treatment regimen; a pharmacist, who prepares medication and educates patients about its use, side effects, and contraindications; a nurse or physician assistant, who educates the patient about glaucoma, instructs the patient about the treatment protocol, and monitors compliance and complications; the patient, who self-mediates; DM program personnel, who, in some plans, independently monitor when prescriptions are filled; a drug manufacturer, which supports and provides patients and providers by distributing educational materials; and an MCO orchestrating the whole system.

**FOCUS ON GLAUCOMA**

Although glaucoma is associated with such comorbid conditions as diabetes and hypertension, making it seem appropriate for integrated care, DM was first applied to higher-cost, higher-prevalence, chronic diseases that require complicated care-management protocols. Congestive heart failure, diabetes, and asthma initially were chosen for DM primarily because of the perceived financial savings and the ability of these programs to document the quality improvements sought by National Committee for Quality Assurance (NCQA) and other accreditation bodies. Health plans and clinicians who work within DM programs seek to apply prevention and treatment protocols that will provide the most effective care to the covered patient population at the optimal cost.

Except in the context of managing eye care “carveout” arrangements, improving glaucoma care has been, mostly, a low MCO priority. Generally, medical directors have little direct experience with eye care, and outside of the Medicare population, eye care receives little MCO attention. Recently, however, the DM phenomenon has reached what may be considered the second wave. Simultaneously, glaucoma has received much recent attention in the medical press, and is now considered to be a good candidate for the development of DM programs, given the glaucoma-prevalence statistics and economic implications detailed earlier in this publication. Furthermore, considering that 2 percent of Americans age 40–50 and 6 percent of those over 70 have elevated intraocular pressure (or IOP, a known risk factor for glaucoma); that glaucoma is the leading cause of preventable blindness in the United States and is the second most prevalent cause of all blindness; that glaucoma is the leading cause of blindness among blacks and is 6 to 8 times as common in this population as among white Americans; and that some glaucoma patients may have to use IOP-reducing drugs for decades (GRF 2002), a DM approach makes sense intuitively.

Three recent developments, detailed in the following paragraphs, would appear to lay the foundation to support more widespread adoption of DM programs for glaucoma.

1. The Medicare, Medicaid, and State Children’s Health Insurance Program Benefits Improvement and Protection Act (which took effect Jan. 1, 2002), provides new coverage for screening individuals who are determined to be at high risk for glaucoma, have a family history of glaucoma, or have diabetes (NEI 2002, CMS 2001). Moreover, according to *Healthy People 2010*, a set of health objectives prepared by the federal government under the leadership of the U.S. Department of Health and Human Services, particularly the National Institutes of Health (NIH), the nation’s new vision-health policy objectives include a focus on glaucoma (NIH 2000). Also, the National Eye Health Education Program (NEHEP), established in 1988 by the National Eye Insti-
Defining a population’s needs
Couch (1997) recommends that DM be considered as a process that flows, almost naturally, starting with the identification of the patient population to be served. In his DM model, the creation of a knowledge base with two components provides the basis for all that follows. The first component outlines the requirements of each stakeholder — purchasers (primarily employers), payers (insurers and MCOs), providers (hospitals, clinics), practitioners (primary care physicians, optometrists, ophthalmologists, pharmacists, nurses, and others), policy makers (governmental and private), product producers (pharmaceutical manufacturers), and patients. Their needs and goals vary but overlap. Their concerns include managing overall health care costs, improving quality of care, improving outcomes and satisfaction (for patients, employees, providers, and others), decreasing per-member, per-month costs, keeping plan premiums low, decreasing resource utilization (particularly in a capitated arrangement) and readmission rates, rationalizing and standardizing diagnosis and treatment, and helping patients become and remain healthy.

Factors vary from covered population to covered population, and thus no mix of health care team members and their responsibilities will exactly match those of any other. Defining these needs accurately is the first step to developing a successful DM program.

The next step, according to Couch, is developing the medical requirements knowledge base, which will be shaped by the stakeholders’ knowledge base. Once the program’s knowledge base is established, the steps that follow, in order, are goal setting/team development, risk stratification and intervention planning, communicating the necessary interventions, behavior modification, clinical process/environment redesign, and outcomes measurement and management.

A systems approach
Another popular model (Eichert 1996) suggests beginning with a shared vision, to consolidate stakeholders’ points of view about DM and what the organization’s program should look like. Similarly, a “shared reality” should be established, so everyone understands where the organization stands in terms of how it manages glaucoma today.

The system then can be improved by taking the following steps:
- Understand and share key beliefs or assumptions about how much DM can improve quality of care and reduce costs.
- Identify barriers to change, such as insufficient knowledge, misaligned incentives, poor communications, and lack of cooperation among members of the care team.
- Develop strategic options to decide what can and should be done to implement improvements.
- Identify leverage options to establish patient-care points at which the most beneficial changes can be accomplished with the least expenditure of resources.
- Identify critical outcomes to measure the impact of the program. Doing so could challenge your vision and key beliefs.
- Learn and improve. Incorporate data collection and analysis to evaluate your efforts, and apply continuous-quality-improvement (CQI) principles.

Advanced case management
Powell (2000) offers a six-step DM program development model that focuses on the functional:
- Define the target population.
- Organize a multidisciplinary, cross-functional team to collect baseline data for post-intervention comparisons; develop ongoing care-team member training; and identify and eliminate system, patient, provider, and economic barriers to success.
- Define the core components and treatment protocols of the DM program, and determine how best to monitor and evaluate the program.
- Pilot the program on a small scale.
- Measure the outcomes produced by the program. Once these first five steps have been completed, the program can be fully implemented and CQI processes can be developed that enable the program to deliver consistently better outcomes.

References
BEYOND ACUTE TREATMENT

tute, a branch of the NIH, has been working to educate the public about the importance of early glaucoma detection.

2. The Ocular Hypertension Treatment Study (OHTS), published in June 2002, estimates that more than 130,000 Americans are legally blind from glaucoma, that between 3 and 6 million people are at risk for developing primary open-angle glaucoma (POAG) because of elevated IOP, and that fewer than half of all people with glaucomatous visual-field loss have been appropriately diagnosed or treated (Kass 2002). Generally, it is more advantageous to treat almost any disease earlier, rather than later, because the later the diagnosis, the more complex and expensive the necessary therapy becomes. The OHTS indicates that topical ocular hypotensive medications can delay or prevent the onset of POAG in persons with elevated IOP. Glaucoma patients do not exhibit symptoms until later in the progression of the disease, when they start to lose vision. Simply stated, the results of the OHTS underscore the health policy imperative of properly identifying and treating the millions of Americans at risk for glaucoma.

3. NCQA is now considering adding a standard to promote the early detection of glaucoma in high-risk populations through its Health Plan Employer Data and Information Set (HEDIS). Should this proposed HEDIS measure be adopted by NCQA, the issue of identifying glaucoma in targeted populations will be of significantly greater importance for both MCOs and their provider networks. For more information about this initiative, see “Clinical Guidelines for the Treatment of Glaucoma,” on page 16.

SYSTEMATIC APPROACH TO GLAUCOMA CARE: A PARTNERSHIP

Although 46 percent of patients in this country have chronic diseases and conditions, including glaucoma, such ailments account for 76 percent of health care expenditures (Whelan 2002). Several studies suggest that the development of a systematic approach to caring for these patients can improve outcomes.

After a decade of watching the DM movement grow, now is the time — in the spirit of enlightened self-interest — for eye care clinicians to be proactive and adopt a DM approach. Perhaps the easiest and surest way for the eye care group to do so is to approach the MCO and explain that the group can excel at glaucoma DM, but needs a partnership with the MCO to do it.

The right mindset is vital. It is necessary to realize that both the clinical team and the MCO exclusively can contribute equally important components of DM. The MCO is best able to help to identify glaucoma suspects, educate them about the importance of early diagnosis and treatment of glaucoma, and send them to providers who are most able to treat them. Reducing the incidence of reversible eye disease is the forte and the exclusive responsibility of the eye care professional. This merger of abilities is the key to a successful glaucoma DM program.

It may help to allay clinicians’ concerns about the motivation of a given MCO to know that, in a survey conducted in 2000, DM decision makers’ most emphatic stated goal was to improve quality of care, as 95 percent of all respondents rated this objective as very important. In decreasing order of importance, they also valued higher patient satisfaction, reduced costs of treatment, and adherence to national standards, such as those in HEDIS (Whelan 2002).

Certainly, all members of the eye care team are involved in the DM process — performing their natural functions, accepting their proper responsibilities, sharing negotiated risk, and acquiring rewards commensurate with their success — but the MCO is the entity with the most to gain from successful glaucoma DM in terms of clinical, economic, and societal outcomes; the most to lose if it fails to prove HEDIS compliance or these outcomes worsen; and, as the entity capable of obtaining both clinical and financial information, the most to contribute to the implementation of the plan. The MCO also has the most comprehensive inherent focus on overall DM and, in all probability, will be the entity that drives the vehicle.

According to Gurnee and Da Silva (1997), while the onus for making the DM program work will rest squarely on the shoulders of the physicians, the MCO should be expected to provide “a computer system with accurate, detailed, and summarized medical and pharmacy claims data for a period of at least 12 months,” and “should be willing to share demographic and specific enrollment data (such as details about the patient, the managed care plan, the PBM, the amount of copayment and the formula) with its partners.”

In addition to supplying the requisite informational systems and data, the MCO should also be primarily responsible for overseeing the system’s public-awareness campaign, aligning benefits, and conducting systemwide continuous quality improvement.

BUILDING A GLAUCOMA DM PROGRAM

Although commercial vendors custom-design DM programs for buyers, it may be more advantageous to develop a glaucoma program in-house, with any needed external help coming from academic experts or professional consultants. DM program vendors tend to focus on higher-cost health care areas; they may, for instance, be hired to design cardiac care programs to produce significant reductions in annual per-patient costs for mem-
bers with moderate to severe heart failure — an expense currently estimated at $10,000 to $20,000 (O’Connell 1994). In contrast, the annual per-patient costs of providing glaucoma care to nonsurgical patients are about $1,055 (Kobelt-Nguyen 1998). In light of the potential savings — small, in terms of typical commercial DM efforts — a glaucoma DM program purchased from a commercial DM vendor may be relatively expensive and, perhaps even more importantly, unnecessary for most eye care groups.

Many organizations that responded to the 2000 survey chose to set up their DM programs internally and suggested establishing an internal champion to oversee each program or the array of programs established. The decision makers placed a high level of importance on the roles of primary care physicians, case managers, specialists, and pharmacists within the DM program. The survey also pointed out that there are no universal standards or models for DM programs, although the sponsoring party and program scope proved to be two virtually universal program-defining characteristics.

A modular DM plan for glaucoma might be most appropriate. Here, relevant modules would be “installed” for primary care physicians, optometrists, ophthalmologists, the MCO, and others. Each module would outline responsibilities and options, based on the resources, expertise, and position in the process that each member of the eye care team occupies.

About half of those with glaucoma have not been diagnosed. Finding those people is integral to glaucoma DM and is at its core. A progressive, three-phase patient-selection and treatment process — identify the population at high risk, screen for suspects, and diagnose/treat patients — ensures that all those, but only those, who need intensive glaucoma therapy receive it as early as possible, and therefore makes the process cost-effective.

In this first phase, it is primarily the MCO’s job to reach out to members in high-risk categories (e.g., blacks 40 and older; all individuals who are 60 or older; and those with a family history of glaucoma, diabetes, high blood pressure, nearsightedness, loss of peripheral vision, or serious eye injury) about the importance of early glaucoma detection and the risks associated with missed diagnosis, and get them into the system.

Virtually every managed care plan offers enrollees eye care benefits, yet most people do not self-refer to eye care specialists. It should be made clear to every lay person that he or she holds the ultimate responsibility for preventing glaucoma and must initiate the discovery process by visiting an eye care specialist regularly; if he or she suspects a vision problem or is at risk for glaucoma, an immediate visit is vital.

The second phase in the process, screening, is the responsibility of the primary care physician or optometrist who provides the educated potential consumer his or her first contact with the system. The MCO should detail for these clinicians the optimal strategy of comprehensive early detection, including IOP measurement and dilated-eye examination of the optic nerve, because structural alterations of the optic nerve or nerve-fiber layer frequently occur before visual defects or visual-field abnormalities can be detected. The MCO must also establish the necessary referral protocols for the primary care physician to send at-risk persons to the optometrist or ophthalmologist, or for the optometrist to send patients to the ophthalmologist for the third phase of the selection process.

In the third and final phase, the ophthalmologist is able to perform or arrange for comprehensive testing, pre-
should be full partners in a DM program. According to Gurnee and Da Silva (1997), the drug company should use its “size, resources and experience” to perform services, including determining the total cost of an untreated illness; the natural history of a disease, and the cost of treatment, conduct outcomes research in the target population, design patient-education and compliance programs (regardless of drug-use particulars), help to develop and promote materials that help to inform health care professionals, and supply providers and patients with education and communications materials. (From a credibility standpoint, such informational materials are best written in a way that helps the patient understand the condition and the nature and importance of therapy, as opposed to being product-specific.) The PBM’s role is to collect and analyze data, and to select nonadherence and other specific drug-use patterns it detects for the basis of educational programs.

The business agreement connecting the health plan, physicians, PBM company, and other partners in the DM program, Gurnee and Da Silva continue, should have at least three cost drivers, which may include “all of the drugs or therapeutic classes of drugs that are specifically employed in the treatment of the specified disease; all therapeutic devices and adjuncts to therapy; all hospital days with ICD-9 discharge codes for the disease, as well as surrogate markers for the disease and its complications; all ER visits coded for a particular diagnosis or complication; and all laboratory and other diagnostic costs associated with the disease.”

Several DM models are available for consideration, three of which are summarized in the accompanying article, “Three DM Program Models,” on page 45.

CONCLUSION

Glaucoma is a serious, insidious, and pervasive disease — actually, a spectrum of eye diseases — that is costly, especially in the latter stages, and exacts a heavy toll on society. To manage glaucoma both effectively and cost-effectively is more complicated than many potential members of a glaucoma DM team may believe.

Taking a systematic, coordinated, care-team approach with the right mindset and the correct partners will serve as the best path to significant improvement in quality of care, cost reduction, and providing substantial benefits to individuals with glaucoma and to those at risk for developing this serious condition.

REFERENCES


Improving Adherence To Drug-Treatment Regimens For Glaucoma

Sharad S. Mansukani, MD

SUMMARY

Compliance with glaucoma therapy is relatively poor. Because glaucoma progresses slowly, long-term adherence is crucial to improving clinical and financial outcomes of treatment. Physicians must consider several factors before steps can be taken to promote correct use of medications.

Patient adherence to therapeutic regimens long has been an issue in clinical practice. As the quantity and availability of medications to treat chronic and progressive diseases continues to expand, it becomes increasingly important that patients follow their pharmacotherapeutic regimens. The success of therapy relies heavily on their compliance.

Across diseases and conditions, the economic and health consequences of nonadherence are profound. Failure to take medications as prescribed has been estimated to cost the U.S. economy $100 billion per year. Of this, $30 billion is in direct medical costs due to increased morbidity and mortality (Shorter 1993).

Compliance — or more accurately, the lack of it — is especially common with glaucoma therapy. Treatment for this disease includes administration of topical medications and surgery to increase aqueous outflow and/or reduce intraocular pressure (IOP). Most ophthalmologists embrace drug therapy as first-line treatment for glaucoma, a trend that has heightened the importance of patient compliance. Yet, depending on the medications used, adherence is poor in at least one third of glaucoma patients (Kass 1987, Kass 1986).

Because glaucoma progresses slowly, patients’ long-term adherence to their prescribed regimens is crucial to the success of their treatment. Nonadherence can be difficult to detect, however, and many physicians feel powerless to help noncompliant patients persist with medication regimens. In reality, physicians have several strategies for improving compliance.

For the balance of this article, the word adherence is used as a synonym for compliance. To many, compliance suggests patients are subservient to the physician. In actuality, a healthy doctor-patient relationship is the first strategy in improving adherence to therapy (Dezii 2000).

NONCOMPLIANCE ISSUES

Several factors contribute to nonadherence to glaucoma therapy. Some of these are controversial and include gender, side effects, and the presence of several interrelated psychosocial factors. In 1977, a study published in the British Journal of Ophthalmology found that glaucoma patients who did not adhere to drug-treatment regimens lacked education about the effects of their disease (Bloch 1977). Numerous studies since have corroborated Bloch’s findings (Lee 2000, Rotchford 1998, Busche 1997, Cooper 1996, Gurwitz 1993).

To ensure that patients take their prescribed medications as directed, physicians must consider several factors. First, has the patient’s history been thoroughly reviewed to determine that a drug is appropriate (a) for the type of glaucoma being treated and (b) in light of other medications on the patient’s therapy schedule? Second, has the patient been fully educated about glaucoma and its progression, the therapy that he or she will undergo, and the administration of the drug or drugs in that regimen? Third, what are the safety and side-effect profiles of the chosen medications? Finally, is this patient capable of following the treatment regimen? A physician must be aware of the patient’s ability to self-administer a particular medication.

Patient history

When choosing a drug for treatment, the ophthalmologist must gather a complete patient history. Age and comorbidities must be considered. Elderly patients are more likely than younger patients to take several medications; often, they already are involved in frequent...
and difficult dosing regimens by the time they begin glaucoma treatment. More important, there is always the possibility that a patient who is taking other prescription medications might have contraindications to certain glaucoma therapies. It is crucial that the prescribing ophthalmologist have access to this information, whether it is obtained directly from the patient, the primary physician, or the pharmacist.

Understanding a patient’s tolerance level and ability to comprehend the treatment regimen also is important in gauging the potential for adherence. For patients who have symptoms of dementia, the dosing regimen must be simple enough so that doses are not confused or completely forgotten; otherwise, the instructions must be communicated to their caregivers. Similarly, depression has been identified as a significant risk factor for non-adherence. Patients with depression — which is relatively common in the elderly — are three times as likely as patients without depression to fail therapeutic adherence (DiMatteo 2000).

**Patient education**

When an ophthalmologist diagnoses glaucoma in a patient, it is critical that the patient fully understands the condition, its effects, and the best ways to slow its progression. Patients must be educated that in glaucoma, irreversible damage occurs to the optic nerve, and that visual-field loss and eventual blindness will occur if the condition goes untreated. They also should know that glaucoma is a lifelong condition, that a lack of obvious symptoms does not mean that the disease is “cured,” and that they should continue to take their medications even when they are feeling good.

A general connection can be made between patients not understanding the rationale for therapy and non-adherence. A California health plan, for instance, studied why members failed to pick up a prescription at the pharmacy after having it filled. Investigators found that one of the most common reasons patients abandoned the prescription was that the physician was difficult to understand (Lash 1995).

One-on-one counseling for patients during office visits is an effective way to approach patient education. A frank discussion in which a patient feels comfortable with the terminology is the first step to ensuring adherence. A patient who fully understands the implications of the disease is less likely to take risks by skipping doses or quitting drug regimens. Similarly, a patient who feels comfortable asking questions will be more likely to discuss concerns about side effects or dosing difficulties. This patient will be more honest when reporting compliance (Gottlieb 2000), which helps the physician to determine whether a switch to a more suitable regimen should be made.

Most ophthalmologists maintain busy practices, which makes it challenging to find time to answer all of the questions patients raise. This is compounded by the fact that glaucoma is a disease that, more often than not, affects elderly patients. This population tends to require more time in consultation. A knowledgeable ophthalmic technician can assume the role of the patient consultant. The most important factor is that patients’ questions and concerns are addressed in a thorough manner.

Another way to educate patients about glaucoma and treatment is through brochures supplied by the practice. Such material has numerous advantages. Information is provided in a clear and succinct manner. It can be taken home to reinforce messages delivered during the office visit. It can be digested by the patient at his or her own pace. It prompts them to ask informed questions. But it is important to add that such material should not take the place of the initial consultation, but complement it by opening the door to further discussion.

Finally, the office staff must be cognizant of where to refer patients who want more information. The Internet is an important educational resource. Some useful Web sites include the Glaucoma Research Foundation «http://www.glaucoma.org», the Glaucoma Foundation «http://www.glaucoma-foundation.org», the Glaucoma Service and Foundation at Wills Eye Hospital «http://www.wills-glaucoma.org», and the American Academy of Ophthalmology «http://www.aao.org».

**Pharmacology**

Glaucoma treatment has undergone several changes over the past seven years. Historically, patients have had few medication options for reducing IOP. Since 1995, a significant amount of medical literature has detailed side effects, efficacy, and mechanisms of action for newer drug therapies.

The traditional medical treatment for reducing IOP has been the beta blocker, which has a long history of suc-
cess in treating glaucoma. However, patients with certain pulmonary or respiratory conditions often cannot tolerate these agents. Their side effects can lead to nonadherence. Some common cardiopulmonary side effects associated with beta-blocker use include low blood pressure, low pulse rate, heart palpitations, and, in patients with asthma or other respiratory conditions, shortness of breath (Sica 1999). Other side effects, such as impotence, depression, fatigue, along with other systemic side effects, negatively affect quality of life. This, too, influences adherence (Stefan 2001, Serle 2002).

Carbonic anhydrase inhibitors (CAIs) reduce IOP by inhibiting the production of aqueous fluid. Side effects associated with systemic CAIs include frequent urination, tingling sensations in the extremities, and indigestion. Some patients may develop kidney stones from prolonged use of CAIs, while others suffer from sexual dysfunction. Given that a major factor in nonadherence is patient discomfort, these issues must be considered when prescribing CAIs. Oral CAIs are no longer widely prescribed to treat primary open-angle glaucoma because of their systemic side effects and because of the availability of more effective topical agents.

Alpha-agonists are highly effective, showing responses similar to those of beta blockers. However, dosing may be an issue with these drugs. The recommended dosing is three times daily (though approximately 90 percent of brimonidine use is twice daily (Fiscella 2002a)). For some patients, this can be inconvenient; for others, it lends itself to forgetfulness. Either has an adverse effect on adherence (Stefan 2001, Serle 2002).

Prostaglandins compose a relatively new therapeutic class for glaucoma treatment. These agents reduce IOP by increasing aqueous humor outflow. A significant advantage with prostaglandins is that they are taken once a day, which improves patient adherence (Stefan 2001, Serle 2002, Whitson 2002). At present, once-a-day dosing is the best available solution to adherence problems.

Prostaglandins have revolutionized the treatment of glaucoma and have reduced the need for trabeculectomy and other surgical alternatives (Bateman 2002). Although the side effects associated with prostaglandins — excess lash growth, iris pigmentary changes, cystoid macular edema, and uveitis — can be significant, they are, from a long-term health perspective, no worse than or better than other glaucoma medications. Unfortunately, some prostaglandin products are largely unavailable through managed care plans because they are not universally listed on formularies. Because of this, it is important for physicians and pharmaceutical companies to stress to MCOs the important role that these drugs play in treating glaucoma (Stefan 2001, Serle 2002, Whitson 2002).

Dealing with nonadherence

When measuring the success of a therapeutic regimen, the causative factors for nonresponsiveness should be determined. Before switching therapy, it should be ascertained whether adherence is an issue. The challenge for physicians is to initiate a conversation that will elicit answers as to how well patients are following their prescribed therapy.

Some personal experience may serve as an example. When I talk with a patient about adherence, I start the conversation in a nonthreatening manner so that the patient does not feel as if he or she has “done something wrong.” Otherwise, patients may not be fully honest, making therapy arduous to maintain and its effectiveness difficult to gauge. I have found that it is best to say to a patient, “I know how tough it is to stick to these medications. Have you had difficulties with taking them? Do you find that you forget to take the medications?”

This helps to put the patient at ease and, thus, more open to conversation. Once this discussion has been initiated, it is essential to review the side effects of these medications, as this often is the reason that patients stop taking them. Frequently, opthalmologists and other physicians are uncomfortable discussing such side effects as sexual dysfunction, but doing so can greatly improve adherence and the probability of positive clinical outcomes.

PRESCRIBING HABITS

Another factor that contributes to nonadherence is American physicians’ prescribing habits. In the United States, the convention when treating glaucoma is to add medications to a regimen. About half of glaucoma patients are prescribed more than one medication to control IOP, even though there are relatively few published data about the efficacy of polypharmacy. In Europe, however, it is more common to switch to another drug before trying multiple medications. Prescribing fewer medications has a dual benefit: The fewer agents a patient has to take, the better the chances for adherence and the lesser the threat of drug interactions. Ultimately, this will minimize the cost of therapy for both the patient and the health plan.

Several studies have documented that, over time, simpler drug regimens are more effective in patients’ overall treatment. In each, the primary reason for a regimen’s success was a direct result of how easily patients could administer their medications. Such studies have been performed across disease states, such as diabetes, coronary artery disease, and behavioral illnesses, with similar results (Jackevicius 2002, Morris 2000, Durbano 2002).

If a patient does not respond to a particular glaucoma therapy, and if nonadherence is eliminated as a cause for
the lack of response, one option that should be considered is to replace the therapy — instead of adding one or more drugs to the patient’s regimen. Just as more-than-once-a-day dosing can discourage adherence, so can a complex treatment regimen involving drug combinations that, often, must be administered in a specific order and at precise intervals.

In determining whether it is appropriate to change medications or add one to an existing regimen, most physicians establish a target IOP for a patient, then determine whether pressure has been reduced from baseline as a direct result of that therapy. If so, the addition of a second medication, working in conjunction with the first, may bring about even further reduction in IOP. If, however, no change from baseline can be documented, switching to another medication is warranted.

Similarly, ophthalmologists monitoring changes in visual-field loss in their patients will look for evidence that a medication has halted progression of field loss. If visual-field loss continues, then a switch to another medication could be more advantageous than initiating adjunct therapy.

A strategy for identifying the best medication for unresponsive patients is to engage the patient in one-eye trials. In this method, the physician administers the medication to one eye and then checks IOP and for side effects at frequent follow-up visits. This avoids subjecting the patient to therapy with ineffective medications, while giving the physician and patient an opportunity to discuss any difficulties the patient may be having with the medication.

Monotherapy will not always be the most appropriate treatment strategy for a certain percentage of patients whose conditions do not respond to prescribed therapy. The promise of improved adherence, however, compels the ophthalmologist, whenever possible, to try to limit the number of medications that a patient must take for glaucoma.

COST CONSIDERATIONS

Several studies have documented a connection between patients’ costs and adherence. This is an important issue that ophthalmologists are finding to be more common as the elderly population increases and as more individuals become reliant on health care programs funded by the federal and state governments.

It may be helpful for patients to know how to get the most value for their money. One study compared several different formulations on a cost-per-day basis. The difference in the cost showed that on a daily basis, the seemingly more expensive therapies — such as the combination timolol 0.5 percent/dorzolamide 2.0 percent (Cosopt) or the prostaglandin latanoprost (Xalatan) proved to be less expensive than three-times-daily doses of a CAI and beta blockers (Fiscella 1999). At the 2001 American Academy of Ophthalmology annual meeting, Fiscella presented similar findings that suggest that bimatoprost (Lumigan) and travoprost (Travatan) are less costly than beta blockers on a per-day basis (Fiscella 2001).

Out-of-pocket expense is an access barrier for some patients, resulting in decreased utilization and noncompliance (Joyce 2002, Cox 1998, Horn 1996). There are many strategies for minimizing this burden. Benefit plans, for instance, may grant patients access to a large bottle for the same copayment as a small bottle. Some may offer 90-day supplies of prescriptions through mail-order pharmacies for a single copayment. Recommending either tactic to patients can help them reduce cumulative out-of-pocket expense. For patients without a pharmacy benefit, it may be worthwhile for them to shop for best price. Fiscella (2002b) noted a $15 difference for the same prostaglandin product at various Chicago-area pharmacies.

Many states have programs for patients who might not qualify for Medicaid but who still are unable to afford glaucoma medications. A listing of such programs can be found by contacting state health departments, departments of public welfare, or like agencies. Finally, some manufacturers offer programs that provide medications at little or no cost to fixed-income elderly people who lack a pharmacy benefit of any kind.

WHAT PHYSICIANS, PHARMACISTS, AND MCOs CAN DO

An ophthalmologist who has collaborative relationships with patients will be able to monitor patients’ adherence effectively. Having a patient’s complete history to supplement the clinical measures of efficacy creates an atmosphere that facilitates positive results.

The direction of current research in glaucoma treatment continues to be toward earlier treatment, patient-friendly drug regimens, and more satisfied and healthy patients. It is crucial that physicians and administrators at health plans gain a full understanding of emerging therapies that, ultimately, encourage adherence.

This implies that MCOs, too, share a responsibility for ensuring adherence among their members. PBM data can help health plans determine when medications for glaucoma are not being refilled. The health plan, in turn, can develop programs that educate members about the importance of taking their medications as directed.

Some such programs might encourage members to ask a pharmacist how to use the medication properly (e.g., applying topical solutions) if they are having difficulty doing so. As the health care provider with whom patients have the most frequent contact, pharmacists bear an im-
important role in helping patients adhere to therapy. By educating patients about proper administration and storage techniques, pharmacists can help patients get the most out of their medications and their money. Pharmacists should advise patients who pick up prescriptions to wait the appropriate amount of time between eye drops. This avoids the “washout effect,” thus improving the effectiveness of two or more concurrent medications. Another technique is to remind patients to refrigerate eye drop solutions, so that patients can feel the drop entering the eye. This reduces waste of medication. The move to once-a-day medications and the improved efficacy of single-drug therapy will help to improve adherence to glaucoma therapies. Before the first medication is prescribed, however, communication with patients and educating them about their disease are important first steps to facilitating adherence and to improving outcomes.

REFERENCES


Fiscella RG. Personal communication with Allergan Inc., Irvine, Calif., 2002a.
Fiscella RG. Personal communication with the author, 2002b.
CONTINUING EDUCATION SELF-TEST
P&T Digest
Glaucoma

**Directions:** Please tear out the combined answer sheet/assessment form on page 55 (physicians) or 56 (pharmacists). On the answer sheet, place an X through the box of the letter corresponding with the correct response for each question.

1. **About how many cases of glaucoma in the United States are undiagnosed?**
   - a. One fourth.
   - b. One third.
   - c. One half.
   - d. Two thirds.

2. **The Ocular Hypertension Treatment Study (Kass et al.) demonstrated that:**
   - a. Topical hypotensive medications can delay or prevent onset of glaucoma in patients with elevated IOP (>21 mm Hg) but who have no evidence of glaucomatous damage.
   - b. Topical hypotensive medications can delay or prevent onset of glaucoma in patients with slightly elevated IOP (17–21 mm Hg) but who have no evidence of glaucomatous damage.
   - c. Prostaglandins are more effective than beta blockers in patients with elevated IOP.
   - d. Clinical outcomes for medication therapy are, at minimum, equivalent to surgical therapies.

3. **As a specialty, ophthalmology is debating the abandonment of beta blockers as primary therapy for primary open-angle glaucoma. Many practicing ophthalmologists, however, already have embraced prostaglandins and alpha₂ agonists as first-line therapies.**
   - a. True.
   - b. False.

4. **As a method of pharmacoeconomic analysis, cost minimization:**
   - a. Analyzes the dollars spent in consumed resources and the clinical outcomes derived from this expenditure.
   - b. Expresses the outcomes of two dissimilar treatment groups in terms of monetary units.
   - c. Evaluates the effect of treatment on societal outcomes, typically expressed in terms of quality-adjusted life years.
   - d. Assumes that outcomes of therapies compared have been proven equivalent among treatment groups.

5. **The goal of disease management is to:**
   - a. Encourage physicians to manage patients — and thus, the disease.
   - b. Improve the health of a specific population using a team approach to the spectrum of care.
   - c. Foster use of experience-based, rather than evidence-based, medicine.
   - d. Reduce office visits for chronic conditions.

6. **Patients’ nonadherence to medication regimens is thought to cost the U.S. economy ______ per year:**
   - a. $15 billion.
   - b. $30 billion.
   - c. $76 billion.
   - d. $100 billion.

7. **In black patients 65 and older, the prevalence of glaucoma (on a per-thousand basis):**
   - a. Is almost double that of the white population.
   - b. Is about one-third higher than that of the white population.
   - c. Is slightly higher than that of the white population.
   - d. Is roughly equivalent to that of the Asian population.

8. **The Veterans Administration schedule for glaucoma eye examinations, subsequently adopted in AAO guidelines, recommends that:**
   - a. Individuals with one risk factor be screened every other year.
   - b. Individuals with two or more risk factors be screened annually.
   - c. Individuals with three risk factors be screened every six months.
   - d. Answers “a” and “b.”

9. **Alpha₂ agonists:**
   - a. Increase formation of aqueous humor.
   - b. Reduce formation of aqueous humor.

10. **In an experiment involving newer glaucoma agents, Frenkel found that the average cost of monthly therapy was lowest for:**
    - a. Travoprost.
    - b. Latanoprost.
    - c. Bimatoprost.

11. **Glaucoma treatment remains fragmented to the extent that it does because:**
    - a. Integrated data systems are lacking or nonexistent.
    - b. Physicians have little real-time access to pertinent patient-care information.
    - c. Physicians need help to coordinate various data required to make optimal medical recommendations.
    - d. All the above.

12. **Adherence to drug therapy is thought to be poor in about what share of glaucoma patients?**
    - a. One eighth.
    - b. One fourth.
    - c. One third.
    - d. One half.
CONTINUING EDUCATION ANSWER SHEET/CERTIFICATE REQUEST
P&T Digest
Glaucoma
CME Credit for PHYSICIANS
See page 56 for answer sheet for pharmacists

EXAMINATION: Place an X through the box of the letter that represents the best answer to each question on pages 54 and 57. There is only ONE answer per question. Place all answers on this answer form:

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PROGRAM EVALUATION: So that we may assess the value of this self-study program, we ask that you please fill out this evaluation form.

Overall activity rating

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Were the educational objectives met?

A great deal 5 4 3 2 1
Not at all

Will this activity benefit you and improve patient care?

Very much 5 4 3 2 Very little 1

What other topics would you like to see addressed?

______________________________________________________________
______________________________________________________________

Give an example of what you will do differently in your practice as a result of participating in this activity:

______________________________________________________________
______________________________________________________________

Did you detect any bias in this presentation?

Yes ___ No ___

If yes, explain: ______________________________________________

Comments: __________________________________________________
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Physician — Maximum of 3.5 hours in category 1 credit. This learning module may be used for category 1 credit through Nov. 29, 2003.

Complete answer sheet/evaluation form, enclose with a check for $15 payable to the University of Arizona, and mail to:

Continuing Medical Education
University of Arizona College of Medicine
PO Box 245121
Tucson, AZ 85724-5121

Credit will be awarded upon successful completion of assessment questions (80 percent or better) and completion of program evaluation. If a score of 80 percent or better is not achieved, no credit will be awarded and the registrant will be notified.

Please allow up to six weeks for processing.
CONTINUING EDUCATION ANSWER SHEET/REQUEST FOR STATEMENT OF CREDIT
P&T Digest
Glaucoma

CE Credit for PHARMACISTS

Sponsored by the University of Arizona College of Pharmacy at the Arizona Health Sciences Center

First name, M.I. ______________________

Last name __________________________

Specialty___________________________

Address____________________________

__________________________________

__________________________________

City _______________________________

State _________________ ZIP__________

Daytime tel. ________________________

E-mail _____________________________

Pharmacist — This program is approved for 3 contact hours (0.3 CEU).

ACPE program number: 003-999-02-077-L01
Release date: Nov. 29, 2002.
Expiration date: Nov. 29, 2003.

Complete answer sheet/evaluation form, enclose with a check for $6 payable to the University of Arizona Foundation, and mail to:

Office of Continuing Education
University of Arizona College of Pharmacy
PO Box 210207
Tucson, AZ 85721-0207

Please allow up to six weeks for processing.

EXAMINATION: Place an X through the box of the letter that represents the best answer to each question on pages 54 and 57. There is only ONE answer per question. Place all answers on this answer form:

A. B. C. D. E. | A. B. C. D. E.
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Credit will be awarded upon successful completion of assessment questions (70 percent or better) and completion of program evaluation. If a score of 70 percent or better is not achieved, no credit will be awarded and the registrant will be notified.

PROGRAM EVALUATION: To receive pharmacy credit, please provide all information requested below. This will assure prompt and accurate issuance of your continuing education credit.

Please rate this program as follows:

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<th>Overall quality of program</th>
<th>Excellent</th>
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How long did it take you to complete this continuing education activity?

hours _____ minutes _____

Requested topics/skills to address in future programs:

__________________________________________________

Comments:

__________________________________________________

Did you detect any bias in this presentation?

Yes ____ No ____ If yes, please explain:

__________________________________________________
13. A Scottish study (Bateman et al.) that attempted to discern the relationship between rising utilization of newer pharmaceutical agents and rates of glaucoma surgery found that surgical interventions have:
   a. Decreased 20 percent.
   b. Decreased 25 percent.
   c. Decreased 35 percent.
   d. Decreased 45 percent.

14. AAO guidelines for managing glaucoma suggest that clinicians identify a target IOP that, depending on the severity of disease, is about:
   a. 10 to 20 percent below baseline value.
   b. 15 to 25 percent below baseline value.
   c. 20 to 30 percent below baseline value.
   d. 30 to 40 percent below baseline value.

15. Prostaglandins are thought to reduce IOP by:
   a. Improving uveoscleral outflow.
   b. Decreasing uveoscleral outflow.

16. Which of the following does Hirsch identify as the most prominent factor affecting pharmacoeconomic evaluations of glaucoma medications?
   a. Disease progression.
   b. Treatment costs.
   c. Adherence.
   d. Cost of failure.
   e. None; Hirsch does not necessarily weigh any single factor more strongly than another in evaluating the pharmacoeconomic value of a therapy.

17. The Disease Management Association of America identifies which of the following as components of a full-service DM program?
   b. Evidence-based practice guidelines.
   d. A routine system of feedback, such as physician-practice profiling.
   e. All the above.

18. Of the following factors that negatively influence adherence to glaucoma therapy, which was the first to be documented in the literature, in 1977?
   a. Lack of education among patients about their disease.
   b. Side effects of medications.
   c. Complicated drug regimens.
   d. High out-of-pocket cost.

19. One of the following is not a risk factor for glaucoma. Which one?
   a. Family history of glaucoma.
   b. Extreme farsightedness.
   c. Age >40 (blacks).
   d. Age >60.
   e. Diabetes mellitus.

20. With respect to medication therapies, AAO guidelines:
   a. Favor alpha2 agonists over beta blockers as first-line therapy.
   b. Do not recommend a specific agent as first-line therapy.
   c. Suggest that when a drug fails to reduce IOP, it be discontinued in favor of another before the original agent is supplemented by other medications.
   d. Both B and C.

21. Which of the following statements about clinical trials involving newer glaucoma agents is/are true?
   a. When compared with timolol, bimatoprost achieved target IOP reductions in a greater percentage of subjects, 64 to 33 percent.
   b. In terms of mean percentage change from baseline, travoprost and latanoprost generally exhibit the same level of IOP reduction.
   c. Brimonidine has been shown to be as effective as timolol and betaxolol in reducing IOP.
   d. All the above.

22. In terms of pharmacoeconomic analysis, a cost-effectiveness comparison of two or more treatments:
   a. Analyzes the dollars spent in consumed resources and the clinical outcomes derived from this expenditure.
   b. Expresses the outcomes of two dissimilar treatment groups in terms of monetary units.
   c. Evaluates the effect of treatment on societal outcomes, typically expressed in terms of quality-adjusted life years.
   d. Assumes that outcomes of therapies compared have been proven equivalent among treatment groups.

23. Goldberg proposes a modular DM plan for glaucoma that assigns responsibility to:
   a. MCOs, for reaching and teaching people in high-risk categories about the benefits of early detection.
   b. Primary care physicians, for providing appropriate interventions to consumers who are making their first contact with the health care system and knowing when it is appropriate to refer to a specialist.
   c. Ophthalmologists, for arranging for comprehensive testing, prescribing a treatment regimen, and performing any necessary surgery.
   d. All the above, with the MCO defining each entity’s role and orchestrating the sequence of events.

24. Which is true about dosing?
   a. Alpha2 agonists are taken once daily.
   b. Prostaglandins are taken once daily.
   c. Beta blockers are taken once daily.
   d. Carbonic anhydrase inhibitors are taken once daily.
Through its Pharmscope.com Web site, MediMedia USA solicited information from pharmacy and therapeutics committee members about monitoring utilization of newer glaucoma drugs. The results are suggestive of what Sharad Mansukani, MD, indicates in the introductory article of this publication: Managed care organizations are only now beginning to understand the financial implications of effective new treatments for glaucoma, and as a result, their interest in managing use of these products is growing.

Nearly 8 of 10 organizations represented in the survey do not actively monitor utilization of alpha2 agonists, prostaglandins, or topical carbonic anhydrase inhibitors. Similarly, 84 percent have not established guidelines for utilization of these products. However, by a 2 to 1 ratio, plans expect to do so in the near future. Though this survey was non-scientific, a reasonable inference can be drawn that P&T committee members will seek greater information about the clinical and financial outcomes associated with these medications as the popularity of these drugs increases.

**Profile of respondents**

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<td>Formulary chair</td>
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<td>Pharmacy director/assistant director</td>
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**MONITORING AND UTILIZATION ACTIVITIES**

Do you monitor utilization of prescription drugs within the newer pharmacotherapeutic classes available to treat glaucoma (e.g., alpha2 agonists, prostaglandins and prosta-mides, topical CAIs)?

- Yes: 21%
- No: 79%

If you answered yes, which classes do you monitor?

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How do you structure your formulary options for newer glaucoma products?

- Don't monitor/not specified: 26%
- Single tier: 11%
- 2-tier: 21%
- 3-tier: 21%
- 4-tier: 0%
- Covered with other restrictions: 11%
- Not covered: 0%
- Other: 5%
- Don't know: 5%

Have you established guidelines for appropriate utilization of newer glaucoma drugs?

- Yes: 16%
- No: 84%

If you answered no to the previous question, does your organization plan to do this in the near future?

- Yes: 27%
- No: 13%
- Don't know: 60%

FAMILIARITY WITH GLAUCOMA TREATMENT

Do you have an ophthalmologist on your P&T committee?

- Yes: 79%
- No: 21%

Do you have an ophthalmology consultant on your P&T committee?

- Yes: 14%
- No: 72%
- Don't know: 14%

If you answered no to the previous two questions, does your organization either plan to add an ophthalmology consultant or is it considering doing so?

- Don't know: 14%
- Yes: 14%
- No: 72%
MARKET RESEARCH

PHARmacoeconomic Issues

Does your organization share, or is it willing to share, actual claims data with pharmaceutical companies or a third-party vendor to develop pharmacoeconomic models for various disease states?

- Yes: 16%
- No: 63%
- Don't know: 21%

CLINICAL ISSUES

Does your organization offer a disease management program for glaucoma?

- Yes: 32%
- No: 68%
- Don't know: 5%

Does your organization engage in any specific programs to encourage patient adherence to glaucoma medications?

- Yes: 32%
- No: 63%
- Don't know: 5%

OUTSIDE INTEREST IN MANAGEMENT GUIDELINES

Have eye care professionals been in contact with your organization regarding your formulary options and limitations for newer glaucoma agents?

- Yes: 16%
- No: 58%
- Don't know: 26%

Have you seen any pharmacoeconomic data on glaucoma therapies?

- Yes: 32%
- No: 68%

SOURCE: PHARMSCOPE.COM SURVEY
“PHARMACOTHERAPEUTIC OPTIONS FOR GLAUCOMA TREATMENT,” MEDIMEDIA USA, YARDLEY, PA, OCTOBER 2002