Introduction

Open-angle glaucoma (OAG) is the second largest single cause of blindness in the elderly, afflicting an estimated 2 to 3 percent of this age group at any time. Approximately 4,600 elderly people will go blind from some form of glaucoma this year, many from OAG (84).[1] Many other elderly people have substantial visual disability short of blindness as a consequence of the disease.

There are many different forms of glaucoma, all characterized by progressive loss of vision associated with increased intraocular pressure (IOP) and subsequent deterioration of the optic nerve. OAG, the most common type of glaucoma and the only one currently targeted by mass screening programs, is the subject of this paper.

Despite considerable study, the exact cause of OAG remains elusive. It is a disease strongly associated with old age; OAG is very rare in people under age 40, but it is common among the elderly. Although the exact incidence of OAG is not known, a "best guess" based on prevalence data is that at least 2 in every 1,000 elderly people develop the disease each year.

The single most important predictor of future OAG is the existence of elevated IOP, commonly defined as pressure within the eye of 21 mm Hg or greater. Between one-tenth and one-fourth of the elderly have this characteristic. Of those in whom the elevation is modest (2 1 to 30 mm Hg), about one-third will go on to develop OAG over the next 20 years. For those with very high IOPs (greater than 30 mm Hg) the risk is much greater; it will take only about 5 years for OAG to become manifest in about one-third of this population.

In classic OAG, the next sign of disease, after elevated IOP, is abnormality of the optic disc (the area where the optic nerve enters the eye). This abnormality is a result of damage to the optic nerve. As nerve damage becomes more extensive, defects--dim or blind areas--develop in the field of vision. These visual field defects initially go unnoticed by an individual but eventually become extensive enough to cause visual impairment, including blindness.

Not all people with OAG follow this classic model, and diagnosis of early OAG is often not a simple matter. First, elevated IOP and OAG are not always related. Many people with elevated IOPs will not develop any other signs of OAG. In addition, some people develop OAG despite having apparently normal IOPs. It appears that some people have eyes that can cope well with modest elevations in IOP, while other people have eyes that are particularly susceptible to damage at seemingly normal IOP levels.

Second, an optic disc that appears somewhat abnormal is not necessarily indicative of OAG. The disc may in fact be normal for that individual, or the abnormality may be related to some other eye disorder. There are certain characteristics that are especially strongly linked to OAG--for example, a disc whose central area occupies an abnormally large proportion of the disc as a whole. But since the assessment of these features is subjective, the accuracy of an examiner in diagnosing OAG based on them depends heavily on the examiner's skill and experience.

Third, not all people in whom visual field defects are detected have OAG. Their fields of vision may be deteriorating due to some other cause.

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1 This number is based on rates reported by the National Society to Prevent Blindness but is updated based on an estimated 1988 elderly population of 30,263,000.

Thus, when a person has all the classic signs of manifest OAG, *and* when other possible causes of these signs (e.g., another form of glaucoma) have been ruled out, the examiner can be reasonably confident of a diagnosis of OAG. A diagnosis inconsiderably more difficult when only one or two signs are present--for example, when a person has elevated IOP and apparent abnormalities of the optic disc, but no visual field defects. Such a person may be termed an *OAG suspect,* with a definitive diagnosis held in abeyance until visual field defects develop, making it clear to the examiner that the eye is truly suffering from manifest disease.

The larger group of people who have elevated IOPs but no other signs of disease are often said to have *ocular hypertension* (OH), to distinguish them from people with more specific signs of OAG. This group includes some people for whom a moderately elevated IOP is normal (or at least well-tolerated by the eye); some in whom OAG is beginning to develop; and some for whom the elevated IOP is a sign of abnormality or disease, but not of OAG.

The complexities of establishing that OAG is present are reflected in the definitions of the disease used in various studies in the literature. Some studies define a patient as having manifest OAG only if both an abnormal optic disc and visual field defects are present (13). Others, however, consider subjects to have OAG not only if they have these features but also if they have less conclusive signs--for example, subjects who have an IOP of greater than 30 mm Hg, but no other signs of disease (24). These differing definitions are a partial explanation for the varying results among studies discussed in this paper. Greater weight has been given in this analysis to studies in which visual field defects were measured and used as a criterion for a diagnosis of OAG. This was done on two grounds: first, that the development of visual field defects where none previously existed is unequivocal evidence that disease exists; and, second, that this criterion is less subjective than the assessment that an optic disc is abnormal and thus is more comparable among studies.

Summary of Findings

Screening is the detection of disease in asymptomatic people. To be an appropriate disease for screening, OAG must meet three minimum criteria:[2]

1. OAG must have a recognizable latent or early stage, during which persons with the disease can be identified before symptoms develop. If there is no such early stage, screening is useless, since patients will appear when they develop the symptoms in any case.
2. There must be an accepted and effective treatment for patients with OAG. Furthermore, the treatment must be more effective at preventing visual impairment and disability when initiated in the early (symptomatic) stage than when begun in the later, symptomatic stages of the disease.
3. There must be an appropriate, acceptable, and reasonably accurate screening test.

These three criteria are discussed below.

Early-Stage OAG

OAG does have an early stage at which the disease can be diagnosed but the patient has no outward signs. Once both optic disc changes and visual field defects have developed, a diagnosis of OAG can be made with reasonable confidence, even though the patient does not usually notice a change in visual ability until the defects have become fairly extensive.

Although they precede actual visual impairment, visual field defects do not develop until the disease is well established and has already caused injury to the eye. Consequently, there has been great interest in identifying people with OAG at earlier stages--when abnormalities of the optic disc first appear, or even when the disc still ap-

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Z These three criteria are derived from the basic principles of screening first set out by Wilson and Junger twenty years ago (125).

pears normal but elevated IOP is present. The difficulties with these criteria for identifying people with OAG were mentioned earlier. People with OH are at higher risk for OAG than are others in the population, but they are not all destined to develop manifest OAG within their lifetimes. People with abnormalities of the optic disc are often designated OAG "suspects, " but not all of them have that particular disease. Still, if treatment is safe and sufficiently effective in preventing impairment in those who have OAG, people may wish to be treated upon the finding of signs associated with the earliest stages of the disease, even if some of those people do not, in fact, have OAG and are therefore treated unnecessarily. Thus we are led to the next question: effective is treatment?

Treatment

Treating people with OAG has been established medical practice since the nineteenth century. Standard treatment consists of medication to lower IOP. If medication alone is insufficient in achieving this, a physician may perform surgery to create an artificial opening through which fluid can flow out of the eye, lowering IOP. New drugs (with fewer side effects) and laser surgery[3] (with fewer complications) have been added to the array of therapeutic alternatives over the past decade, but the basic treatment framework remains.

Many eye care practitioners treat people they consider to be at high risk of OAG as well as those with manifest disease (i. e., visual field defects). A patient might be considered "high risk" in the opinion of that particular practitioner if the patient has a high IOP, suspicious abnormalities! of the optic disc, a family history of OAG, or any combination of these and other factors.

Just as the assessment of who is sufficiently "high risk" to be treated is considered a matter of individual judgment, treatment policies and preferences vary considerably among physicians and optometrists.[4] For example, one physician might prescribe medical treatment for a patient with an IOP of 24 mm Hg and a family history of OAG, even if no more definitive signs of OAG are present. Another might treat only patients in whom highly abnormal optic discs and/or visual field defects are detectable. Both would be within the range of currently accepted medical practice.

The difficulty of deciding who should be treated is compounded by the uncertainties of treatment effectiveness. On the one hand, treatment is inconvenient, costly, and uncomfortable; for a few patients, treatment is itself a risk to health. It has distinct drawbacks even for those with manifest OAG. On the other hand, if treatment is very effective at preventing visual impairment from OAG, *and* if it is more effective if initiated earlier in the course of the disease, it may be desirable to treat some or all people with OH, even at the expense of treating many of them unnecessarily y.

That treatment of both OH and manifest OAG is effective is an accepted tenet of the medical profession,[5] but it has not been documented in the literature to date. The relationship between IOP and OAG is well-established; it has been shown that higher IOP is associated with higher risk of OAG, and that a rapid rise in IOP to very high levels induces glaucoma (5,38,95). What is absent is sufficiently convincing evidence that the reverse is true: that lowering IOP by conventional means also lowers the risk of OAG in those with OH, and that lowering IOP slows or prevents visual impairment in those who have manifest OAG.

3 The most promising form of laser surgery, argon laser trabeculoplasty (ALT), is not quite analogous to traditional surgery to lower IOP. Rather than creating new openings to enhance fluid flow from the eye, it scars the tissue around the existing natural openings, stretching the openings and enabling better out flow.

4 Thirteen States permit optometrists to treat glaucoma patients with medications. In 11 of those States , the opt omet r i s t need not consu l t a physician before initiating treatment (122).

5 One medical researcher has recently questioned the effectiveness of OAG treatment (32).

No adequate studies comparing treated with untreated patients with manifest OAG exist, because physicians have considered it unnecessary and unethical to mount such a study. Consequently, one must turn to the results of studies of treatment for patients with OH (i.e., elevated IOP only) and infer the results to treatment for manifest OAG.

A few studies comparing treated and untreated patients with OH have been conducted; their findings are mixed, ranging from effective to no effect to harmful. All have deficiencies in design that either make it difficult for the study to find an effect (for example, small sample sizes or short study duration), render the conclusions suspect, or make the findings inapplicable to the larger population.

Two very recent clinical trials, whose final results are still unpublished, may establish the effectiveness of treatment in preventing OAG in persons with OH. Preliminary results from these studies suggest that if an effect exists, it may be substantial. It remains to be seen whether the final study results will reach statistical significance. (It is possible for even a substantial difference in outcomes between groups to be due to chance; if the results of these studies reach statistical significance, this explanation is unlikely and a true effect of treatment probably exists). Both studies are nearing completion (68,71).

If treatment of OH is shown effective in preventing or delaying the onset of manifest OAG, and if treatment of manifest OAG is therefore presumed effective in preventing or delaying visual impairment resulting from the disease, the *degree* of effectiveness may still depend heavily on the criteria used to decide when the current level of treatment is sufficient. Under the treatment practices of the past, most patients with manifest OAG still suffered gradual visual deterioration. These treatment practices included acceptance of the idea that if an elevated IOP could be lowered to the high end of normal--e. g., from 30 mm Hg to 21 mm Hg--treatment was adequate. In the past decade, as evidence has accumulated that people suffered visual deterioration despite this level of treatment, many ophthalmologists have emphasized more aggressive treatment, striving for even lower IOPs if any signs of deterioration occur. They believe that current treatment practice is thus more effective than in the past. This difference has not been documented; it is an important hypothesis to investigate, both in order to assess the potential gains and in order to determine whether more aggressive treatment leads to an increase in the severity or frequency of side-effects.

Screening Technologies

Three technologies have been used in OAG screening:

- *tonometry,* which measures IOP by calculating the resistance of the eye to a force;
- *ophthalmoscopy*, a tool enabling an examiner to scrutinize the optic disc of a patient and detect abnormalities characteristic of OAG, and
- *Perimetry, which* detects defects in the visual field through a patient's responses to dots of light introduced at various points in the field.

Each of these three technologies is designed to identify a somewhat different group of people. Tonometry is designed to detect people with elevated IOPs who are thus at risk of OAG, and it is effective at doing so. It is much less effective at identifying people who already have manifest OAG (since some people have the disease without having elevated IOP). Thus, when tonometry is used to screen for elevated IOP, it has a relatively small false positive rate (it is not zero, because some people whose IOPs were slightly high at the screening are normal upon reexamination). When tonometry is used to screen for manifest OAG, however, it has a high false positive rate, because most people with elevated TOPS do not have manifest OAG.

Both ophthalmoscopy and perimetry also may produce false positive tests for manifest OAG, because people may have apparently abnormal optic discs or visual field defects for reasons other than OAG. However, the rate of false positives under ideal conditions

is much lower for both of these tests than for tonometry.

Still, despite the potentially greater accuracy of these two technologies in detecting manifest OAG, neither is without drawbacks. Ophthalmoscopy can detect the first visible signs of deterioration due to OAG--i.e., degeneration of the optic nerve. But since evaluations of the optic disc are subjective, it has a high inherent variation that depends on the experience of the examiner. Perimetry is designed to detect defects in the visual field, the most definitive outward sign of manifest OAG. Its most significant inherent limitation is that it cannot identify patients with OAG before visual field defects occur (although it can identify them before visual *impairment* occurs).

In practice, the relative accuracies of these three technologies, alone or in combination, in correctly identifying people with manifest OAG are very poorly documented. Only one study was found that compared the effectiveness of all three technologies in detecting manifest OAG in the same population. The study has not been published (although an abstract of results is available), and because the setting of the study was mass screening performed in community facilities (e.g., churches), its findings may not be applicable to screening performed in the offices of physicians and other eye care practitioners. A few other studies exist of the accuracy of specific technologies alone, but the study designs and the results vary widely. Consequently, it is possible to make some reasonable guesses about the relative accuracy of the three technologies and the factors that affect their accuracy, but major questions remain about average effectiveness in practice.

Implications for Medicare

The prevalence of OAG is sufficiently high to warrant considering the disease a substantial health problem. In an ongoing screening program, however, it is not the total number of existing cases but the number of new cases that the program will detect. Because new cases of manifest OAG are relatively rare, even among the elderly --a few cases per 1,000 elderly per year- -any screening program will incur considerable costs to detect those cases.

To gain a sense of the magnitude of potential costs that might be incurred by Medicare if an OAG screening benefit were offered, the average costs of identifying and confirming a case of manifest OAG in an every-other-year screening program were estimated. Under the assumptions of the model, and assuming that Medicare paid 80 percent of all allowed charges associated with the screening and follow up/confirmatory visits, it is estimated that Medicare costs for an OAG screening program would range from approximately $160 million to $800 million per year. These costs do not include the costs of treating the glaucoma cases detected by the program. The costs of a screening program to identify those with elevated IOP (most of whom would have only OH, but some of whom would also be found to have manifest OAG) would be similar. Again, however, the costs cited here do not include either the costs of treating OH patients or the costs of long-term followup of untreated OH patients.

The potential number of OAG cases diagnosed as a result of a screening program for manifest OAG is highly uncertain. Such a program might detect anywhere from 10,000 to 90,000 cases of manifest OAG per year in an ongoing program, depending on factors such as the accuracy of the screening tests and the true incidence of OAG in the elderly. (In the initial years of such a program, when a backlog of undiagnosed OAG cases exist, anywhere from 50,000 to 340,000 cases might be detected.) If the goal of the program was to identify all individuals with high IOP, the program would ultimately detect between 30,000 and 350,000 cases per year (with between 300,000 and 3 million per year detected in initial years).

The accuracy of the screening tests has a particularly important impact on costs. The costs of a screening program depend heavily on the number of people with positive tests who are referred for a followup visit, and whether a substantial proportion of those are false positives. If many people test positive, and thus many undergo a comprehensive fol-

lowup visit, total costs will be high. If most of these are true positives, however, the cost per case found will be relatively low; if most of them are false positives, the cost per case found will be high.

These screening costs should be compared to the costs of treatment and the economic and net health benefits resulting from treatment. OTA has not attempted such a comparison because of the major uncertainties associated with treatment effectiveness. The higher the screening costs, the greater the benefits of treatment must be to justify screening. Potential benefits include improved visual function, improved quality of life, lessened dependency on others, and lower expenditures for public programs that provide financial and personal assistance to the disabled.

Apart from the potential benefits of screening itself, the potential benefits of *Medicare coverage* for OAG screening depend heavily on how many people would be encouraged to undergo screening if the service were covered. Over 50 percent of the elderly already undergo frequent OAG screening; for these people, Medicare coverage will bring some relief from out-of-pocket costs but no additional benefits in preventing visual impairment. (A small benefit is possible if, as a result of Medicare coverage, these people were screened in settings where test accuracy was higher than wherever they receive the service at present.)

Elderly people who would not have undergone screening without Medicare coverage, on the other hand, could potentially improve their health. OTA assumed that total utilization of a Medicare biannual screening program would be 75 percent-- i.e., one-third of those screened would not have undergone screening without Medicare coverage. If this assumption is correct, then between 3,000 and 30,000 people per year would have manifest OAG diagnosed earlier (i. e., before they would otherwise be screened or developed symptoms), and between 10,000 and 100,000 people per year might have high IOP identified (if tonometry were the screening test used), if Medicare covered screening for OAG.

This analysis examined only the costs and yield of glaucoma screening as a single service. It did not examine the benefits of detecting disorders other than OAG as a result of the glaucoma screening visit. Nor did it examine the effectiveness and cost of a comprehensive eye visit in its entirely.

Conclusions

An OAG screening program for the elderly, whether aimed at detecting only those with manifest disease or also those at risk due to high IOPs, is likely to be fairly expensive.[6] The potential benefits of such a program are substantial, but whether those benefits can actually be realized is still highly uncertain. It depends heavily on two unknown factors: first, on the true accuracy of the various screening tests in the settings in which they would be used; and, second, on the effectiveness of treatment in preventing, halting, or delaying the progression of visual impairment due to OAG.

Most critical to the question of whether screening for OAG is useful is whether treatment of people with OH (if screening for high IOP) or OAG (if screening only for manifest disease) alters the course of the disease. The evidence in the literature to date leads neither to the conclusion that treatment is effective nor that it is ineffective; by and large, the few relevant studies are too small to detect an effect even if one exists. A consensus panel of eye care professionals would undoubtedly conclude that treatment is effective, although such a panel would likely also acknowledge that support for this belief has been inadequately documented. The opinions and personal experiences of eye care experts are compelling, but they are also subjective.

In light of the preliminary results reported from unpublished research, it is likely that treatment does reduce the incidence of OAG among those at high risk

6 As a rough measure of comparison, the annual total cost of screening for OAG would be approximate 1 y one- tenth to one- third of the $3 bi 11 ion annual cost of the Medicare End-Stage Rena 1 Disease program (116).

and, probably, delays visual impairment among those in whom OAG is already man if est. If this expectation is borne out, screening would be effective in reducing visual impairment due to OAG. That said, certain reservations regarding glaucoma screening deserve reiteration:

- The amount of impairment that might be prevented through a screening program is unknown. The degree of effectiveness of such a program depends on the unknown degree of effectiveness of treatment in preventing or delaying the development of OAG (in those with OH) or the development of visual impairment due to OAG (in those with manifest disease). It also depends on the accuracy of the various potential screening tests in the settings in which they might be performed, which is unknown except within a very broad range.
- Consequently, both the benefits of screening -- i.e., visual impairment prevented -- and the costs of screening and resultant treatment are highly uncertain. OTA's estimates, which include only costs to Medicare for the screening episode and confirmatory visit, cover a five-fold range (from about $160 million to $800 million). Treatment costs for those who are detected with the disease prior to onset of symptoms would add to the total cost of screening.
- The field of OAG screening and treatment is one that deserves more self-examination and critique than it has received. The potential research agenda for this field is large, and some important areas are outlined below.

Research Needs

Sustained investment in clinical research on OAG treatment is crucial to evaluating the effectiveness of current treatment technologies and protocols and to developing better ones. For example, a clinical trial currently sponsored by the National Eye Institute comparing standard medical treatment with a new treatment-- early argon laser trabeculoplasty (ALT)--may give some insight into treatment effectiveness. Although "no treatment" is not an option in this trial, the trial does include rigorous documentation of the outcomes of two different types of treatments. Since ALT is a relatively new technology but appears to be widely used, documenting its effects is critically important.

The theory that outcomes will be improved if treatment is more aggressive also deserves in-depth examination. Current expert opinion supports the idea of increasing the intensity of treatment whenever visual deterioration is suspected, regardless of the absolute level of IOP. This more aggressive treatment practice has merit considering the history of deterioration of many treated patients in the past. Its incremental effectiveness over more conservative drug therapy should be studied to determine whether very low IOPs can be sustained for long periods of time, and whether such a consequence reduces vision loss. An examination of this practice could also illuminate any increase in side-effects that might result from it. If the effectiveness of this practice is demonstrated, the information should be disseminated so that treatment practices of eye care practitioners can be changed.

The natural history of OAG is still perplexing. It is still unknown which people with OH will develop OAG and how to identify people without OH who nevertheless will develop the disease. Researchers have tackled these questions with some energy over the past decades, but they are still far from the answers.

Useful information could be obtained on one important aspect of the natural history of OAG without a major investment of resources. The natural course of untreated OAG is unclear and subject to a great deal of individual interpretation. Documented case studies of patients who were untreated for personal reasons would help establish a baseline against which treatment outcomes could be assessed.

The tradeoff between immediate inconvenience and discomfort and long-term prevention of impairment is one faced by every eye care practitioner and every patient

with elevated IOPs contemplating the initiation of treatment to decrease the risk of developing OAG. A more precise estimate of the magnitude of the costs and benefits of that tradeoff- -for example, a quantified compilation of the frequency and intensity with which different side-effects of the various medications occur--can be greatly aided by research. Such an information base would help physicians predict which patients are most likely to be aided by treatment. But the essential dilemma of how to balance the benefits and drawbacks of treatment for a particular individual is likely to remain for a very long time.