Description

Patients may be treated for potential or confirmed open-angle glaucoma (OAG) at any of four stages:

1) after the intraocular pressure (IOP) has reached a level suspected to be intolerable to that individual's optic nerve, but before any other characteristics of glaucoma appear;
2) after changes in the optic disc have appeared, but before any visual field defects have occurred;
3) after defects are apparent to the physician but before the patient is visually impaired in any way; or
4) after some visual impairment occurs, to prevent further impairment.

Treatment cannot reverse impairment; it is prescribed on the assumption that it can prevent visual deterioration by lowering the pressure in the eye and preventing further damage to the optic nerve. Eye care professionals believe that the earlier treatment is begun, the greater the likelihood that visual impairment can be prevented. This belief has been bolstered by evidence that a substantial proportion of the optic nerve dies before a patient becomes visually impaired (98).

Treatment for OAG follows a well-established pattern (34,67). Initial treatment nearly always consists of topical application of one of three drugs: epinephrine, pilocarpine, or timolol. Although these drugs act in different ways, the goal of each is to lower the IOP (either by decreasing formation of fluid or by enhancing outflow), thus presumably preventing further damage to the optic nerve. If one of these drugs is inadequate in lowering pressure, they may be combined, given at higher dosage, and/or substituted with similar, alternative drugs. If pressure still remains high, a stronger, systemic drug with more side effects (e. g., acetazolamide) may be added. Finally, if even maximum tolerable medication is inadequate, an ophthalmologist will perform laser or filtering surgery to enhance outflow of the ocular fluid.

The medications used to lower IOP must be taken for life, and all have numerous common side effects (e. g., blurred vision, headache, nausea, and increased blood pressure and heartbeat (33)). Some medications also increase the risk of cataract formation (8,101). These side effects and sequelae, plus the cost of the medications and the inconvenience of applying them up to 4 times per day, have resulted in noncompliance rates of up to 58 percent in various studies (6,61). Timolol, one of the only two new medications to be approved for glaucoma treatment in recent years,[1] has become a popular first medication because it is better tolerated by patients than epinephrine or pilocarpine. (Unfortunately, an initial lack of understanding of timolol's full effects led to several deaths in glaucoma patients with respiratory and cardiovascular diseases exacerbated by the drug (86)). Other topically-applied drugs that are chemically similar to timolol are under investigation in the hope that they may be more effective or have more limited systemic effects (2, 15,17,22,121).

Despite the disadvantages of glaucoma medications, they are still usually considered preferable to surgery. Traditional filtering surgery--the creation of an artificial opening through which fluid can flow out of the eye--is reported to be successful in lowering IOP in 60 to 90 percent of patients, depending on patient characteristics (57). However, filtering surgery also carries the risks of permanent damage to the eye from infection, excessive drainage (causing soft, shrunken eyes), and hemorrhage (57). OAG patients who have undergone filtering surgery are much more likely than other OAG patients to

1 The second relatively new medication for glaucoma is dipivalyl epinephrine, a form of epinephrine that becomes active only after interaction with the eye and thus causes fewer side effects (119).

develop cataracts (110).[2] Furthermore, eventual return to medication and/or additional future surgery may be necessary in some patients for continued control of IOP (37).

In recent years, argon laser trabeculoplasty (ALT) has become a frequent intermediate step for patients whose IOP is uncontrolled by medication (57). ALT consists of making tiny laser burns within the trabecular network. It is unclear why this laser scarring facilitates fluid outflow, but ALT has been shown to decrease IOP (1 14,1 17). Among the benefits of ALT are an avoidance of some of the risks of filtering surgery (e. g., infection), but unlike surgery, most patients must continue taking medication even after undergoing the procedure (37). The long-term effects of ALT scarring are unknown. The National Eye Institute is currently conducting two clinical trials of the procedure: one of ALT (instead of medication) as primary treatment in patients with early evidence of OAG, and one comparing ALT with filtering surgery in patients with advanced OAG (120).

Treatment Outcomes

A number of studies have reported the proportion of OAG patients whose visual field deteriorated while under treatment (2,25,43,45,46,69,82,83,87,97,109). The reported outcomes vary considerably, with anywhere from 11 to 82 percent of patients in these studies suffering further deterioration while under long-term treatment. Patients with advanced OAG suffer deterioration **more rapidly than patients with only minor visual field defects (69),** perhaps because the loss of additional optic nerve fibers in people with advanced disease leads to proportionately greater impairment (98). In general in these studies, longer followup results in more patients deteriorating.[3] It appears that about one-fourth of all patients with existing defects suffer deterioration within 4 years (87, 109). However, another one-fourth of patients suffer no deterioration even after many years (83).

Surprisingly little information exists on the rate at which people with OAG, treated or untreated, actually become visually impaired. Table 5 summarizes the results of three studies that reported on rates of visual deterioration in treated OAG patients. Of these reports, the one that can be interpreted most directly found that 75 percent of patients with manifest OAG went blind in the affected eye within 20 years, even when treatment was begun soon after the detection of visual field defects (43). (Of patients who

2 Cataract development is especially common in those glaucoma surgery patients in whom surgery-related complications arise (110).

3 Followup in these studies ranged from 1.4 to 42 years.

Table 5.--Three Estimates of Rate of Visual Impairment for Eyes of Patients with Treated Open-Angle Glaucoma

Source	Time period	Initial condition of eyes	Percent of eyes that deteriorated	Condition at end of measured time period
Kronfeld and McGarry, 1948	5 years	"early" OAG	16%	"advanced" OAG
	5 years	"moderate" OAG	50%	"advanced" OAG
	5 years	"moderate" OAG	20%	blindness
Hart and Becker, 1982	10 years	82% of all eyes with OAG suffered Insignificant visual loss" (not necessarily synonymous with further impairment)		
Grant and Burke, 1982	5 years	"early" OAG	25%	blindness
	10 years	"early" OAG	38%	blindness
	20 years	"early" OAG	75%	blindness

SOURCES : See references.

began treatment after changes in the optic disc but before the onset of visual field defects, 50 percent went blind in the affected eye within 20 years.)[4] The incidence of blindness was fairly constant across time in this study.

By their very nature, even recent reports of very-long-term outcomes of treated patients with OAG reflect the treatment patterns of many years ago. Some ophthalmologists believe that outcomes are better now than under treatment practices of the past. In the past, they argue, ophthalmologists were content to maintain treatment without change when a patient's IOP had been lowered to a certain level, even if the patient's visual field continued to deteriorate at that level (105). Now, they maintain, patients are treated more aggressively if their visual condition is not stable under the current treatment regimen, and patients deteriorate less rapidly. Continuing documentation of long-term outcomes could both support this contention, assuming it is true, and improve the dissemination of knowledge regarding the most appropriate treatment practices.

Treatment Effectiveness

A necessary condition for OAG screening to be effective is that treatment is effective. One might choose to screen for an OAG risk factor (i.e., high IOP), for probable early OAG (i.e., suspected optic nerve damage), for fully developed OAG as manifested through visual field defects, or not to screen for OAG or its risk factors at all. Which screening policies should be considered depends heavily on whether and at what stage treatment is effective in preventing visual deterioration.

The assumption that early treatment can prevent visual field defects pervades the literature. Studies of patients with ocular hypertension (OH) have tended to reinforce the assumption by emphasizing how few patients who were treated early suffered visual deterioration. (In fact, only a small proportion of such patients would be expected to suffer measurable deterioration even without treatment.) The belief in the importance of early detection and treatment has continued almost unabated despite the fact that a few eminent researchers pointed out the inconsistencies between documented evidence and clinical practice as early as the 1960s (23). Their conclusion, that the efficacy of treatment for OH and OAG was undocumented, has been reiterated by others in recent years (3 1). The Canadian Periodic Health Examination Task Force likewise concluded that the evidence for effectiveness of treatment for OAG consisted of the opinions of respected authorities (2 1,39).

What exactly is the evidence regarding 1) the effectiveness of treating OH to prevent OAG, and 2) the effectiveness of treating manifest OAG to prevent or delay functional visual impairment? Not surprisingly, there is no direct evidence regarding the effectiveness of treating manifest OAG. There have been no studies of comparable groups of treated and untreated patients with visual field defects, because the standard of care is to treat all such patients. However, it is possible to review the evidence for the effectiveness of treating OH and assume that if treatment of OH is effective in preventing or delaying the development of visual field defects, then treatment of manifest OAG is likewise effective. It is also possible to examine other indirect evidence of the effectiveness of OAG treatment.

Evidence of the effectiveness of treating OH to prevent OAG

To be considered direct evidence of the effectiveness of treatment of OH for preventing OAG, a study must, at a minimum, meet three criteria:

4 The lower incidence of bl indness in those treated before onset of vi sual field defects could ref lect one or both of two poss i bi l i t i es: 1) that i t nat - ura l ly takes a longer time for those with only optic disc changes to reach blindness, since they are identified at an earlier stage in the disease than are those with visual field defects; or 2) that treatment of those with abnormal optic discs was more effective because it was initiated earlier in the stage of the disease.

1. Long-term followup of the study population (at least 1 year, and preferably much longer if differences are to be detectable),
2. Monitoring of visual field changes in the study population, and
3. Existence of well-defined treated and untreated groups of patients (or eyes of patients). Ideally, these patients (or eyes) should be randomized prospectively into the two groups, although studies in which patients are matched for salient characteristics also provide useful evidence. *The study must control in some way for differences in the level of IOP among treated and untreated patients* or must be reported in such a way that the evaluator can control retrospectively for this factor, because people with high IOPs are more likely to get OAG than those with low IOPs irrespective of treatment.[5]

Although study size per se is not one of the criteria, the number of subjects studied is crucial to the ability to detect differences and attribute them to treatment. For example, if the incidence of OAG among all people with OH were *2* percent per year, and treatment reduced this by 50 percent --i.e., to an incidence of 1 percent per year--a 1 -year study would require hundreds of subjects to show this result with a probability of less than 5 percent that the result is due to chance (even assuming full compliance of all subjects).

Despite the large published literature relating to OAG, OTA could identify only seven studies of OH treatment (two published only in abstract form) that meet these three basic criteria. The results of these studies are summarized in table 6. The studies are of two types: those that compared treated with untreated patients, and those in which one eye of each patient was treated, while the other eye was left untreated.

Of the three studies that compared treated with untreated patients, the one finding the most positive effect of treatment is also the most recent. Preliminary results of this study (still ongoing), which employs a prospective, randomized design, suggest that a statistically significant positive effect of treatment may be found (70). A less recent study, in which matched patients were prospectively assigned to treatment or placebo, found a positive but not statistically significant effect (only 12 placebo and 15 treated patients completed the study) (64). Finally, the oldest study, which neither randomized nor matched patients, found that treated patients were actually more likely to develop OAG (27). When patients in this last study are grouped by IOP, it appears that treated patients with the lowest IOPs (21-25 mm Hg) were significantly more likely to develop OAG than untreated patients; the differences in development of OAG between treated and untreated patients with initial IOPs of 26-30 mm Hg and over 31 mm Hg are not significant.

Studies that use eyes rather than patients as the unit to be treated pose some problems in interpretation, because treatment of one eye could affect the outcome of the untreated eye. Of the four studies that compared treated with untreated eyes, three found a significant positive effect of treatment (see table 6). The fourth study found a negative effect, but the difference between the treated and untreated groups was not statistically significant (77). In the study showing the greatest positive effect, the patients selected for the study were thought to be the subgroup most likely to benefit from the particular treatment (because the patients had previously demonstrated an IOP response to the medication chosen for the study) (102). In this same study, however, the untreated eyes did particularly poorly (i.e., a higher propor-

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5 As a case in point, two commonly cited reports of a Danish epidemiological glaucoma study (87, 104) reported the number of OH patients who went on to develop visual field defects. In both reports, treated patients were more likely than untreated patients to develop visual field defects. The average IOP levels in the two groups (treated and untreated) were not stated in either report. The authors simply reported on the outcome of patients under standard medical care, and it is extremely likely that certain patients were treated because their higher IOPs or other factors placed them at an especially high risk of disease. Thus, these studies cannot be used to evaluate the effectiveness of treatment.

Table 6.--Summary of Evidence Regarding the Effectiveness of Treatment for Ocular Hypertension in Preventing Open-Angle Glaucoma

Source	Study size (no. of patients/eyes) Beginning	End	Study design	Treatment	Length of study	Number percent developing OAG	Effect of treatment	Statistically significant?
Patient-level studies								
Krug et al 1987	54 untreated 53 treated	(ongoing) (ongoing)	randomized	timolol	7 yrs.	13 (24%) untreated 6 (11.3%) ever-treated (as of 1987)	+	(study incomplete)
Kitazawa et al., 1981	26 placebo 26 treated	12 placebo 15 treated	matched prospectively	timolol	1 yr.	2 (7.6%) placebo 1 (3.8%) treated	+	no
David et al., 1977 (IOP 22-25)	(not applicable)	48 untreated 27 treated	retrospective, unmatched	pilocarpine, adrenoline, acetazolamide	1-11 yrs. (average 41 mo.)	0 (0%) untreated 2 (7.4%) treated	-	yes
IOP 26-30	(not applicable)	16 untreated 8 treated	(same as above)	(same as above)	(same as above)	2 (2.5%) untreated 1 (1.1%) treated	+	no
31+	(not applicable	3 untreated 14 treated	(same as above)	(same as above)	(same as above)	1 (33.3%) untreated 6 (48.2%) treated	-	no
Eye-level studies								
Hoff et al 1988	64 patients (128 eyes)	35 patients (as of 1988)	eyes randomized, double-masked	timolol	5 yrs	8 (22.8%) placebo 5 (14.2%) treated	+	(study incomplete)
Levene, 1975	72 patients (144 eyes)	59 patients	eyes randomized	pilocarpine, echothiophate iodide	ave. 55 mo. (min. 6 mo.	2 (3.3%) untreated 4 (6.6%) treated	-	no
Becker and Morton, 1966	50 patients (100 eyes)	(10 patients full 4-5 yrs)	eyes randomized	epinephrine	6 mo.-5 yrs.	7 (14% untreated 2 (4%) treated	+	not reported
Shin et al, 1976	19 patients (38 eyes)	19 patients	eyes randomized; patients were selected for expected response to medication	epinephrine	1-5 yrs.	6 (31.5%) untreated 0 (0%) treated	+	yes

SOURCES: See references.

tion developed OAG than did the eyes of untreated OH patients in the studies discussed earlier).

In addition to the above studies, several investigators have reported the outcomes of treating patients who had either OH or changes in the optic disc (but no visual field defects). These studies had no clear control groups. Relevant results of the studies are summarized in table 7; they are useful primarily as contextual information for assessing the outcomes of treatments in the comparative studies.

Indirect evidence of the efficacy of treatment for manifest OAG

A number of other studies and observations provide indirect evidence of the efficacy of treatment for manifest OAG in delaying or preventing further visual field defects. For example:

- Studies in animals in which IOP was artificially raised have been able to induce glaucomatous changes in the eye (38), implying that the level of IOP is causally related to damage to the eye.
- Several studies have found improvement in the appearance of the optic disc after treatment (44,62,91).
- Some researchers have observed, in retrospect, that patients whose IOPs were maintained at relatively low levels while under treatment (e.g., under 20 mm Hg) suffered less loss of vision over time than patients whose IOPs remained relatively high despite treatment (66). It may be that a drastic lowering of IOP is necessary in some patients before treatment is effective (62); it is possible that some studies have not detected an effect of lower IOP because the treatment was inadequate.

Table 7--- Studies Relating Long-term Outcomes of Treatment to Lower Intraocular Pressure in Patients Without Visual Field Defects

Source	Treatment duration	Percent of treated patients developing OAG	Selected characteristics and limitations
Schappert-Kimmijser, 1971	5 years	16%	OH patients only
Airaksenen et al., 1982	2 years	0	OH patients only; timolol treatment
Nielsen, 1982	4 years	0	OH patients only; timolol treatment
Graham, 1968	2 years	--	study of OH patients comparing treatment to placebo, halted after 2 years when no differences in IOP were found. Fields were not measured when study was halted.
Hildreth and Becker, 1956	0.5-1.5 years	5%	differences in IOPs and followup times between treated and untreated patients unstated
Sorensen et al., 1978	15 years	42%	patients were ocular hypertensives considered to be at especially high risk
Markowitz and Morin, 1983	4 years	16%	not all patients may have been free of visual field defects at beginning of study
Neilsen, 1982	4 years	12.1%	patients were "glaucoma suspects" without field defects
Cockburn, 1983	1.4-19.8 years	10.5%	patients were "glaucoma suspects" without field defects
Grant and Burke, 1982	20 years	52%	patients had changes in the optic disc but no visual field defects at the time treatment was begun

SOURCES: See references.

Most convincing to ophthalmologists, however, is their own experience with glaucoma patients, in whom visual deterioration is proceeding rapidly until the patients are successfully treated (36, 106). Although dramatic treatment effects are most common with closed-angle glaucoma patients, ophthalmologists' experience with these patients leads them to believe that lowering IOP is very beneficial in OAG patients as well.

Compliance as a factor in the effectiveness of treatment

One possible explanation for the lack of documentation of treatment effectiveness is inadequate patient compliance with the long-term treatment regimens prescribed in the studies. In one early study, for example, only 20 percent of patients on treatment at the beginning the study remained on treatment for the full 4 to 5 years; the remainder dropped out of treatment, primarily due to side effects (10). Researchers have noted that patients with established OAG are more compliant (i.e., keep appointments and take medications as scheduled) than patients with OH but no visual field defects (18, 107). Patient noncompliance with treatment regimens means that treatment effectiveness (in actual practice) may differ substantially from treatment efficacy (in research or ideal situations).

Conclusions

Considering both the inadequacies and contradictions in the literature and the experience and opinions of practicing eye care professionals, the following conclusions regarding treatment effectiveness seem warranted:

1. Most people with modestly elevated IOP but no visual field defects upon initial screening will not develop OAG in the near future, even if left untreated (see chapter 2).

2. Justification for the current mode of treatment for OH and OAG is based on theory, personal experience, and the postulates shared among physicians rather than on direct evidence documented in the literature.

3. The evidence regarding the efficacy of medical treatment to prevent OAG by lowering IOP is sparse, conflicting, and largely of poor quality. Two very recent studies, yet to be published, are likely to provide more convincing evidence than currently exists in the literature. It is likely, based on preliminary results, that both will show treatment of OH patients to be efficacious in preventing or delaying the onset of manifest OAG.

4. If treatment of OH is shown to be efficacious, further research will still be needed to clarify which groups of OH patients are most likely to benefit from treatment, which are likely to suffer as much harm as good if treated, and what the most effective treatment regimen is.

5. Patient compliance with medical treatment is highly variable and can be very poor, leading to potentially poor real-world effectiveness of treatment even if treatment is shown to be efficacious.

6. If treatment of OH is shown to be effective in preventing visual field defects associated with OAG, then treating manifest OAG is probably effective in preventing or delaying visual impairment. The extent of effectiveness is unknown and cannot be inferred directly from the effectiveness of OH treatment, since the degree of effectiveness may depend on when treatment is begun.

7. Even with more aggressive medical treatment than in the past, and even with early treatment of patients, it is unlikely that treatment will prevent eventual visual impairment in all patients. However, to the extent that treatment delays blindness, it is valuable in enabling many elderly people to live out their lives with sight.

8. The knowledge base for treatment of manifest OAG would be improved with research on comparative long-term effectiveness of different treatment modalities, establishing the most effec-

tive overall strategy (including criteria for when current treatment of a patient is insufficient), and delineating more clearly the best treatment at different stages of the disease and in different types of patients. Documenting the course of the disease when patients with OAG are not treated (e. g., when the patient's religious beliefs prohibit treatment) would also be extremely useful in describing the natural course of untreated OAG.