tvst

DOI: 10.1167/tvst.4.2.1

Perspective

# Why Do People (Still) Go Blind from Glaucoma?

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**Received:** 13 August 2014
**Accepted:** 18 January 2015
**Published:** 9 March 2015

**Keywords:** glaucoma; blindness; intraocular pressure; visual fields; adherence

**Citation:** Susanna Jr R, De Moraes CG, Cioffi GA, Ritch R. Why do people (still) go blind from glaucoma? Trans Vis Sci Tech. 2015;4(2): 1, http://tvstjournal.org/doi/full/10.1167/tvst.4.2.1, doi:10.1167/tvst.4.2.1

Glaucoma is a progressive optic neuropathy and is the leading cause of irreversible blindness worldwide. Over 60 million people were estimated to be affected with open-angle glaucoma (OAG) in 2010, and bilateral blindness from the disease was estimated to be present in 4.5 million people with OAG in 2010, rising to 5.9 million people in 2020.[1]

In 1982, Grant and Burke[2] published an article with a title similar to the present article suggesting three potential reasons why people go blind from glaucoma: one-third were undiagnosed; one-third had not been treated properly; and one-third were noncompliant with therapy. They also noted that, when abnormalities ranging from early glaucomatous cupping to advanced visual field defects were present at initial evaluation, progressive visual field loss continued to occur even with lowered intraocular pressure (IOP).

In the consensus of Medical Treatment of Glaucoma by the World Glaucoma Association, the definition of target IOP includes the need to adjust therapy based on numerous factors, among them the initial level of damage, rate of progression, and life expectancy.[3] It appears that eyes with more severe damage at presentation require lower IOP to prevent further functional loss or blindness. Forchheimer et al.[4] investigated the relationship between baseline visual field damage, IOP, and rate of progression and found that among eyes with more severe functional damage (mean deviation [MD] worse than −12 dB), those with mean follow-up IOP < 14 mmHg progressed more slowly than those with higher pressures. Kotecha et al.[5] found that following trabeculectomy, eyes showing changes in both optic nerve and visual field sensitivity had less IOP reduction from baseline compared with eyes showing no progression. Lee et al.[6] reported that patients with more severe glaucomatous damage, as measured by both visual field and optic disc cupping, are at highest risk for rapid worsening of the disease and that more aggressive treatment of such patients should be considered to prevent visual disability. Heijl et al.[7] showed that treatment is more effective in patients with MD better than −4.5 dB compared to patients with MD worse than −4.5 dB.

Thirty years later, despite meaningful improvements in technology, therapeutic tools, and knowledge of the disease, patients continue to go blind from glaucoma. In a retrospective chart review by Peters et al.[8] in Sweden, at the time of the last visit 42.2% and 16.4% of patients had at least one eye blind or bilateral blindness from glaucoma, respectively. Overall, the cumulative incidences of blindness in at least one eye and bilateral blindness from glaucoma were 26.5% and 5.5%, respectively, after 10 years, and 38.1% and 13.5% at 20 years.[8] A recent report of the population-based study of all residents of Olmsted County, Minnesota,[9] showed that the 20-year probability and the population incidence of blindness due to OAG in at least one eye decreased over the 45 years from 1965 to 2009. They also suggested that "… a subset of patients with glaucoma may have more aggressive disease and may be particularly susceptible to progression, possibly because of non-IOP-related factors that contribute to retinal ganglion cell (RGC) death and vision loss."[4]



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Although there is compelling evidence that "non-IOP-related factors" may indeed have a significant role in glaucoma pathogenesis,[10–12] IOP is the major component associated with fast progression rate.[13] In a recent review on the pathophysiology of glaucoma, Weinreb et al.[14] stated that although the loss of ganglion cells is related to the level of IOP, other factors may also play a role. To date, there is no high-level evidence that non-IOP lowering medications can alter the progression of glaucoma. Yet, it is possible that other treatments may be needed to supplement IOP lowering or to make a given amount of IOP lowering more effective.

Our working hypothesis is that even after 30 years of substantial advances in the field, the challenges faced by patients and eye care providers to prevent blindness due to glaucoma have not changed as substantially.

## Glaucoma Is (Still) Undiagnosed

Population-based studies suggest that over half of all glaucoma cases in the United States remain undiagnosed. In the Baltimore Eye Survey,[15] 56% of patients with glaucoma were not diagnosed, and in Proyecto VER,[16] 62% screened were unaware they had glaucoma. Shaikh et al.,[17] investigating the prevalence and burden of undiagnosed glaucoma in the United States among noninstitutionalized subjects $\geq$ age 40 between 2005 and 2008, found the prevalence of undiagnosed glaucoma to be 2.9%, increasing with age to 6.6% of the population older than age 70. Among those subsequently diagnosed with glaucoma, 78% were previously undiagnosed and untreated. In the Thessaloniki Eye Study,[18] the prevalence of undiagnosed primary OAG was 57%. These numbers go up to 87% in South Africa.[19]

In addition to these numbers, many individuals suffer severe visual field loss by the time they are diagnosed.[20] Due to inherent methodological difficulties, there is no study to date testing the hypothesis that this phenomenon is due to inability to recognize glaucomatous discs or fields as opposed to failure of surveillance or referral. The data available provide suggestions, not certainty, regarding this hypothesis. In the Thessaloniki Eye Study,[18] the main risk factor associated with undiagnosed OAG was lack of regular visits to an ophthalmologist. Weih et al.[21] also reported that increased time since last visit to an eye care provider was associated with elevated risk of undiagnosed glaucoma. In the Los Angeles Latino Eye Study,[22] lack of health insurance reduced access to eye care and increased the burden of OAG by reducing the likelihood of early detection and treatment. These studies, therefore, suggest that failure of surveillance or referral may be more important. Supporting the alternative hypothesis, in the Glaucoma Optic Neuropathy Evaluation Project,[23] ophthalmology trainees and comprehensive ophthalmologists underestimated glaucoma likelihood in approximately one in five disc photographs and were twice as likely to underestimate as overestimate glaucoma likelihood. Underestimating the vertical cup-disc ratio and cup shape and missing retinal nerve fiber layer (RNFL) defects and disc hemorrhage were the key errors that led to underestimation. In the European Structure and Function Assessment Trial,[24] ophthalmologists correctly matched stereoscopic optic disc photographs to their corresponding visual field in only 59% of cases and those with more recent training in glaucoma were less likely to miss cases with the disease. We believe these results are not conflicting but rather complementary and that a combination of the two factors (i.e., inability to recognize glaucomatous damage versus failure of surveillance or referral) is the main reason for glaucoma underdiagnosis, though which factor plays a stronger role warrants an objective investigation.

The inability to recognize glaucomatous optic disc and RNFL damage is one common reason glaucoma is not diagnosed early. Often, ophthalmologists rely primarily on IOP and visual fields and not on the appearance of the optic disc. However, IOP alone has its limitations for a variety of reasons, including variations among patients in corneal thickness and biomechanics (name hysteresis). The IOP is underestimated in patients with thin corneas and low hysteresis and overestimated in those with thicker corneas and high hysteresis. Moreover, IOP fluctuates within and between days, and the threshold for IOP-induced damage varies within patients, as disease progresses, and between patients, likely related to stress and strain in the pathophysiology of glaucomatous optic nerve damage.

In the past decades, imaging diagnostic technologies, such as optical coherence tomography (OCT), scanning laser ophthalmoscopy (SLO), and confocal scanning laser ophthalmoscopy (CSLO), have helped improve the ability to diagnose and monitor glaucoma by providing objective measures and how these measures relate to normative databases. These technologies perform well against the gold standard of expert judgment.[25,26] Considering that the newest modalities of OCT have an average sensitivity of around 70% to 80% at a fixed specificity of 80%,[27] the





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diagnostic ability of these devices for glaucoma diagnosis on a population basis warrants further investigation regarding their utility for glaucoma screening. In a simulation model testing its potential usefulness as a screening tool, Blumberg et al.[28] found that the use of spectral domain OCT as a screening tool could decrease the prevalence of undiagnosed glaucoma from 75% to 38%. They also found that the cost of one quality-adjusted life year (QALY) gained by screening, including management and treatment, in comparison with opportunistic case finding, ranged from $46,416 to $67,813. Nevertheless, there is still no evidence that the information obtained from imaging devices may be used in isolation in clinical practice or as a basis for tailoring glaucoma therapy. In fact, digital imaging devices improve general ophthalmologists' ability to diagnose glaucoma,[26] as well as their level of agreement.[29] Bae et al.[29] found that the interobserver agreement to diagnose glaucoma increased from 0.54 to 0.63 when OCT was added to disc photographs. The Consensus of the World Glaucoma Association on Glaucoma Screening[30] and Glaucoma Diagnosis[31] recommends that patients with or suspected glaucoma should be examined with a combination of structural and functional tests and that imaging technologies play a complementary role and should not be used alone. Future research aiming to make screening (or targeted screening) more effective is needed.

## Glaucoma Is (Still) Improperly Treated

### The Severity of Damage Is Underestimated

There are several reasons a given glaucoma patient may not be treated properly. One reason is the severity of damage is underestimated, resulting in higher target IOP, less aggressive therapeutic interventions, and less frequent follow-up visits.

Although loss of visual function is associated with progressive structural damage,[32,33] both clinical and preclinical studies have demonstrated that clinical detection of structural alterations often precedes visual function deterioration as measured by standard automated perimetry. First, in a study of enucleated human eyes by Quigley et al.,[34] definite loss of axons occurred prior to reproducible visual field defects in some patients suspected of having glaucoma. The eye with the mildest degree of visual field loss (defined with Goldmann perimetry) that led to a glaucoma diagnosis was found to have half the normal number of axons.

Subsequently, Harwerth et al.[35] evaluated the relationship between RGC loss and visual field defects using an experimental model of glaucoma in rhesus monkeys. Histologic data demonstrated reduced numbers of cells in the RGC layer while visual field loss measured by behavioral perimetry was not proportional to RGC loss. Mild visual defects were noted only after reductions of approximately 50% of RGCs, but these increased significantly with progressively greater reductions in RGC counts. A similar quantitative relationship between structure and function was also established by Harwerth and Quigley[36] using comparative histologic data from humans with documented glaucoma and rhesus monkeys with experimental glaucoma. Therefore, clinically, once there is a visual field defect, there is also a significant loss of neurons, and the disease in general should not be classified as being in the early stages. Notably, moderate or severe RNFL defects at baseline were found to be associated with a seven to eight times greater risk of future visual field loss in a study of 647 individuals with ocular hypertension.[37]

Johnson et al.,[38] in a prospective longitudinal study in patients with elevated IOP but normal visual fields at baseline, demonstrated a relationship between glaucomatous optic disc damage and subsequent development of visual field defects. The lack of or mild relationship between structural and functional change may reflect the limitations of current exams used to measure each. Two proposed explanations for the detection of RGC death before detectable visual field loss include the redundancy of RGC and the substantial variability inherent in perimetric methods to assess visual field. Perimetry is a subjective psychophysical test with limitations regarding accuracy and repeatability.[39] Variability is inherent in both the testing method and patient response, which therefore requires a high number of tests to be repeated in order to produce a true estimation of an underlying defect.[40–42]

Another possible reason the severity of damage is underestimated is that some clinicians rely their judgment of presence and severity of visual field loss solely based on global indices (e.g., MD and visual field index [VFI]) and automated summary measures (Glaucoma Hemifield Test [GHT] and Guided Progression Analysis [GPA]), rather than clinical clues to glaucoma progression. Artes et al.[43] found that although the VFI provides a simple and understandable metric of visual field damage, its estimates of remaining visual field were more optimistic than those of the experts. Tanna et al.[44] found that the level of agreement between majority



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expert consensus of subjective determination of visual field progression and GPA is fair and that in cases of disagreement with GPA, the expert consensus classification was usually progression.

Changes in the visual field ought to be defined in combination with structural tests, such as stereophotography and OCT. The development of a rim notch or a new disc hemorrhage, for example, may provide the basis for more aggressive treatment even in the absence of statistically significant visual field abnormalities.[45,46]

In a recent analysis of rates of visual field change and why glaucoma patients go blind from glaucoma in the United Kingdom, Saunders et al.[47] found that only 3.0% of patient eyes progressed faster than −1.5 dB/year, conventionally considered a fast rate of MD deterioration. Nevertheless, more than 90% of patients predicted to progress to legal blindness had a MD worse than −6 dB in at least one eye at presentation.

## Insufficient IOP Reduction

Reducing the IOP may not completely prevent disease progression. The Early Manifest Glaucoma Trial (EMGT)[48] reported that despite an average 25% decrease in IOP, which translated to 5.1 mmHg in that trial, 59% of patients still progressed on visual fields over a 4-year period. However, in the Collaborative Initial Glaucoma Treatment Study (CIGTS),[49] IOP reductions ranging from 35% to 48% (target IOP) resulted in no net glaucoma progression. In the Advanced Glaucoma Intervention Study (AGIS),[50] a mean IOP of 12.3 mmHg and intervisit IOP measurements consistently below 18 mmHg staved off glaucoma progression. The Collaborative Normal-Tension Glaucoma Study (CNTGS)[51] reported that with a 30% decrease in IOP, the progression rate decreased from 60% to 20%. It is clear from these clinical trials that it is important not only to reduce IOP, but also to do it effectively.

Insufficient IOP lowering could be the cause of progression in some patients, although it is possible that even maximal IOP lowering may not be enough for some patients given the role of IOP-independent risk factors. Although the results of the major clinical trials provide compelling evidence that IOP lowering decreases the rate of glaucoma onset and progression, none of them have specifically addressed what the ideal pressure should be for individual patients or groups of patients. The AGIS posthoc analysis, for example, should be interpreted with caution, as the results described above refer to pooled patient data and are based on specific AGIS progression criteria, which cannot be directly compared to criteria employed in other trials.

Therefore, the idea of "one-size-fits-all" should not be applied to glaucoma treatment. Rather, clinicians should make their decision based on known risk factors, for which there is a vast literature, in addition to patient-specific characteristics, such as age, baseline level of damage, the IOP at which damaged occurred, life expectancy, systemic comorbidities, and tolerability to different types of medication. Future studies should investigate more objective methods to determine patient-specific IOP lowering targets based on these variables.

## IOP Peaks and Mean Are Not Adequately Assessed

IOP is a dynamic parameter that is subject to circadian fluctuation (short-term fluctuation) as well as variations over time (long-term fluctuation). As clinicians follow their patients over time, they are frequently challenged by these forms of variation and how they could affect treatment and progression. It is important to notice that IOP peaks detected between office visits are significantly lower than those detected during diurnal curves, as shown by Barkana et al.[52]

IOP peaks are potentially an important cause of glaucoma progression[53–55] and most of the time are not detected during office hours.[52,56] Twenty-four-hour pressure monitoring may be the best way to assess the IOP profile and detect peaks; however, this is a time- and resource-consuming test rarely feasible in routine practice. As an alternative, a modified diurnal tension curve is more frequently performed and consists of four to five IOP measurements during office hours (e.g., from 8 AM to 6 PM). Also, IOP measurements at different times of the day between different days can also be used to assess IOP peaks. Limitations to these approaches are that more than 50% of IOP peaks occur outside office hours.[52] In addition to this between-visit IOP variability, there is an "ultra-short-term" IOP fluctuation that we are unable to measure in vivo in humans and thus we know little about its importance. This variability corresponds to a "second-to-second" fluctuation that relates to IOP changes from squeezing the eyes, eye movements, and even blinks, for instance. Semicontinuous IOP monitoring using a contact lens sensor has been evaluated in humans,[57] although there is currently no study testing whether these transient IOP spikes play a significant role in glaucoma progression. Another issue is that



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these contact lens sensors do not provide direct estimation of the IOP in millimeters of mercury. Rather, this technology provides values corresponding to the relative variation of the electrical signal from spontaneous circumferential changes at the corneoscleral area. Although these measures correlate with fluctuations in IOP,[57] they can be influenced by intersubject differences in corneal curvature, thickness, and hysteresis. It also remains unclear how these transient IOP changes are counter-balanced by the eye's auto regulatory mechanisms, such as changes in blood flow and cerebrospinal fluid pressure, and how these mechanisms differ between healthy and glaucomatous eyes. In this context, the water-drinking test (WDT) has been proposed as a practical alternative method to evaluate IOP profile of glaucomatous patients.[58–61] The WDT has been shown to be superior to detecting IOP peaks compared with the modified diurnal tension curve.[62]

High mean IOP has also been consistently associated with glaucoma progression.[63,64] While peak IOP detection is based on measurements at office visits, the mean IOP requires longitudinal IOP data collection and may be affected by the interval between visits. Establishing a target peak IOP is clinically easier than establishing a target mean IOP in many patients.[54] Despite this advantage and some evidence in the literature that peak IOP may play a greater role on progression than mean IOP, comparative studies investigating whether treatment interventions based on peak or mean IOP targets lead to slower rates of progression are not yet available.

The importance of IOP fluctuation as a factor for glaucoma progression is debatable in the literature. Some authors suggest that it is important.[65–67] Other authors considered that IOP fluctuation is not an independent risk factor for glaucoma onset or progression.[63,64,68] This discrepancy may be due to the use of different hypotensive medications, different populations and study designs, as well as the lack of a standard definition and reproducibility of IOP fluctuation.[69,70] The true role of IOP fluctuation, including both short- and long-term variability, has not yet been adequately addressed in clinical trials given the difficulty in performing diurnal curves in all patients on a regular basis.

Excessive IOP lowering regimens to slow progression (based either on mean or peak IOP) need to be weighed against patient-specific characteristics and side-effects. For instance, it has been shown that the impact of dry eyes secondary to glaucoma medications on quality-of-life is similar to a 10 dB loss in the visual field MD.[71] For some patients, certain types of medical therapy or surgery are contraindicated despite detected IOP peaks considered hazardous. Recent new drugs and surgical modalities are promising options and may enhance the repertoire of treatment options in these patients.

## Difficulties in Evaluating the Rate of Progression

Rate of disease progression is one of the most important factors determining the risk of visual disability or blindness in glaucoma, and the assessment of rate of progression in routine care is often recommended for glaucoma management.[72,73]

Even when progression is detected, clinicians often do not assess the rate of progression due to lack of expertise, lack of sufficient data, or a busy schedule. There are eyes with very rapid deterioration, which deserve maximum therapy or even surgical procedures as the first choice of treatment. This can happen because it may not be possible to calculate the velocity of progression when very few visual field tests are available when patients are initially followed. Treatment at that point is largely based on risk factors, mainly IOP. After more tests are done, a more accurate estimate of the velocity of progression becomes possible, and the initial therapy may prove insufficient hence requiring maximum medical therapy or surgery. For instance, in the CIGTS, initial surgery led to less visual field progression than initial medicine in subjects with advanced loss at baseline.[49]

There is a great discrepancy between what the best practice guidelines recommend and what is in reality done. For instance, Malik et al.[74] investigated the attitudes of glaucoma specialists to the frequency of visual field testing in the United Kingdom using the National Institute of Clinical Excellence (NICE) recommendations as a standard for ideal practice. They found that intervals for testing were inconsistent with the guidelines from NICE in over 70% of respondents. In another analysis in England, most newly diagnosed OAG patients received less than three visual fields in the first 2 years following diagnosis and an average of 0.7 tests per year over the duration of follow-up.[75] In an analysis of a sample of Medicare beneficiaries in the United States, Coleman et al.[76] found that the use of visual field testing before surgery was suboptimal relative to the recommended standard of care. In a chart review from private, community-based ophthalmologists, Hertzog et al.[77] found that while patients are generally likely to



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be scheduled for follow-up within American Academy of Ophthalmology's Preferred Practice Pattern (PPP)-recommended intervals, patients with unstable glaucoma are the least likely to be so scheduled. Remarkably, only 39.4% had a pupil examination; gonioscopy was performed in 51.3%; and only 23.3% of patients had an optic nerve head drawing or photograph within 15 months of the most recent visit. In addition, the authors found that 37.8% of patient charts had neither an optic nerve head drawing nor a photograph documented after the initial visit. Freemont et al.[78] obtained data on working-age patients with OAG enrolled in managed care plans between 1997 and 1999. They found that 53% of patients had an optic nerve head photograph or drawing and only 1% had a target IOP level documented. Using specific criteria for control, IOP was controlled in 66% of follow-up visits for patients with mild glaucoma and 52% of visits for patients with moderate to severe glaucoma. IOP adjustments occurred in only half of visits where the IOP was 30 mmHg or higher. Their conclusion was that OAG is undertreated relative to standards for IOP control established in recent clinical trials. Quigley et al.[79] performed a chart review to measure the validity of large claims databases in estimating patient cooperation with eye drop therapy and assessed physician adherence with guidelines for a PPP. They found that disc evaluations and imaging, and visual field tests were performed on 90% of OAG patients, although gonioscopy, central corneal thickness measurement, and setting of target IOP was done on half of patients.

Glaucoma is frequently considered a slowly progressive disease. Although this is true in general, it is advisable to exercise caution in individual cases. In the Ocular Hypertension Treatment Study (OHTS),[80] of 1636 participants with ocular hypertension (24–32 mmHg) only 9.5% of untreated patients converted to glaucoma at 60 months. In the EMGT,[7] the mean rate of progression was 6 dB/10 years in nontreated patients. That means that it would take a mean time of 40 years to reach a 24-dB loss, which may be considered blindness depending on the definition adopted.

Based on data from the St. Lucia study[81] and OHTS,[80] the number needed to treat (NNT) to prevent blindness in one patient for 15 years is 83.[33] However, one should be reminded that this NNT is applicable to a 15-year follow-up and that a large proportion of OHT patients are diagnosed at a young age (the mean age at baseline in the OHTS was 55 years) and thus have a longer life expectancy.

Based on numbers from pooled population data described above, some authors have advocated that glaucoma does not need to be treated in the early stages.[82] Nonetheless, the EMGT showed that in patients with newly diagnosed glaucoma IOP-lowering therapy leads to better visual field outcomes after 10 years than no treatment.[48] Also, based on the OHTS data, Kymes et al.[83] suggested that delay of treatment for all people with ocular hypertension until glaucoma-related symptoms are present appears to be unnecessarily conservative. Kass et al.[84] proposed that OHT individuals at high risk of developing OAG may benefit from more frequent examinations and early preventive treatment. By looking at the observation group of the OHTS, De Moraes et al.[85] found that IOP-lowering when patients do not yet have visual field loss leads to grater reduction in the rate of visual field change than treatment after conversion to OAG.

Even with treatment ,15% to 20% of patients become blind in at least one eye in 15 to 20 years of follow-up.[86–88] In a recent study, Peters et al.[3] found that at the last visit before death, 42.2% of treated patients were blind unilaterally and 16.4% bilaterally. In this study, the median time from a glaucoma diagnosis to death was only 12 years. These figures are very similar to the data presented by Hattenhauer et al.[89] who found a 54% risk of unilateral blindness and a 22% risk of bilateral blindness after 20 years among treated glaucoma patients.

One reason for the disagreement regarding rates of blindness between well-designed clinical trials and real-world observation reports may be that the relative risk of progressive visual field loss is greater in the real world. The risk of progression was on average 368% (range, 209%–673%) higher among eyes not enrolled in longitudinal studies according to a study.[90] Some of the reasons are that patients willing to enroll in longitudinal studies are generally more attentive to their disease, possibly more compliant with therapy, are examined more frequently, and are better evaluated than nonstudy patients.[90] De Moraes et al.[91] suggested that decisions to treat or not to treat should be based on reliable pragmatic data derived from real-world patients and not only randomized clinical trials. Added to that, in many patients progression is not linear and the interpatient variability is large.[13,92]

## (Still) Lack of Compliance

In a review of the association between dose regimens and compliance with medication that includ-



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ed 76 studies,[93] the authors showed that as the need for more frequent dosing during the day increased, compliance with taking the medication and the timing of the dose decreased. With everyday dosing, 79% and 74% of patients complied with the dose, respectively, and the timing of the dose. In contrast, with patients who needed dosing four times daily, the respective percentages were only 51% and 40%. When patients were questioned about barriers to adherence, reasons included are forgetfulness (30%), other priorities (11%), lack of information (9%), emotional factors (7%), and 27% did not provide a reason.[94] Compliance with dosing regimens is also affected by side-effect profiles, the cost of therapy, patient education, and the doctor–patient relationship.

Although it is reasonable to assume that poor adherence could increase the risk of glaucoma progression and blindness, no randomized clinical trial to date has tested this hypothesis. There are many different forms of intervention to improve adherence to glaucoma therapy, including patient and physician education, phone call reminders, and dosing aid devices. For instance, Hahn et al.[95] showed that a 3-hour educational program can significantly improve physician's communication strategies and ability to detect and address nonadherence to glaucoma therapy. In a randomized clinical trial testing whether interventions can improve rates of adherence (as determined by an electronic dosing aid device), investigators found no significant difference in IOP between the intervention and observation groups, although adherence increased by 20%.[96] On the other hand, Rossi et al.[97] retrospectively investigated the relationship between visual field progression and adherence rate in patients with glaucoma using an electronic dosing aid device. Seventy-one percent of patients with stable visual fields had a median adherence rate of 85%, whereas patients who progressed (29%) recorded a median adherence of 21%.

The Glaucoma Adherence and Persistency Study (GAPS)[98] is the largest study to date on adherence in glaucoma patients and identified the main factors associated with poor adherence. The following factors were independently associated with a lower adherence (based on their definitions): (1) hearing all of what you know about glaucoma from your doctor (compared with some or nothing); (2) not believing that reduced vision is a risk of not taking medication as recommended; (3) having a problem paying for medications; (4) difficulty while traveling or away from home; (5) not acknowledging stinging and burning; (6) being nonwhite; (7) receiving samples; and (8) not receiving a phone call visit reminder. About 21% of the variance in poor adherence was explained by this set of variables.[98]

As discussed above, IOP peaks and fluctuation have been associated with glaucoma progression. The occurrence of large variations and peaks (detected and undetected) is at least in part due to adherence to medical therapy. In the CIGTS,[49] patients randomly assigned to medical therapy with higher IOP variability during follow-up had increased rates of visual field decay compared to those who underwent surgery. Given its minor dependence on adherence, filtering surgery should be considered earlier among patients with poor adherence to medical therapy—defined either based on self-report or risk factors.

Recent innovations in glaucoma surgery may also circumvent issues related with adherence. Minimally invasive glaucoma surgery techniques have shown promising results,[99] although their superiority to trabeculectomy has not been proven. Also, trabeculectomy techniques have changed in many centers aiming to increase success rates and minimize complications. Khaw et al.[100] reported that one such technique, named "Moorfields Safer Surgery System," considerably reduced the incidence of major complications including hypotony, cystic blebs, and endophthalmitis in practices around the world.

In addition, new drug delivery systems have been described for glaucoma medical therapy and may potentially help decrease the burdens of nonadherence.[101] In animal models, researchers have been able to safely deliver prostaglandins and alpha-agonist agents to the supraciliary space leading to significant IOP lowering and allowing multiple-dose sparing (up to 100-fold).[102] In another study, prostaglandin-loaded inserts were administered into the conjunctival sac of rats and resulted in significant IOP lowering with decreased RGC loss compared to controls.[103] There are ongoing clinical trials testing the safety and efficacy of these new drug delivery systems in humans and we expect these alternatives to better control IOP variability and slow progression in the near future.[101]

## Conclusions (and a Possible Fourth Reason)

Since the article by Grant and Burke[2] in 1982, the field of glaucoma has underdone considerable changes that ranged from a better understanding of



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glaucoma pathogenesis to advances in diagnosis and treatment. The majority of the large randomized clinical trials in glaucoma were conducted in that period and provided invaluable information on the benefit of IOP reduction along the glaucoma continuum as an effective means to slow progression and, by reasoning, to reduce rates of blindness from the disease. Perhaps these trials made the strongest contribution to the observed decrease in the trends of glaucoma-related blindness reported in the past 20 years.[9] Indirectly, these trials stimulated extensive research on the development of new and more objective methods to detect glaucoma and monitor progression, as well as new forms of therapy. All these direct and indirect contributions possibly explain the observed reduction in rates of blindness observed recently.[9]

Nonetheless, the incidence and prevalence of glaucoma-related blindness remains high. Future studies focused on the unanswered questions from the main clinical trials are warranted to further help decrease these rates. Since glaucoma is often a slowly progressing disease, prospective studies assessing rates of blindness as the main outcome would be extremely lengthy and require very large populations enrolled, which limit their feasibility. Consequently, translational researchers may still depend on surrogate measures of functional impairment to address these unanswered questions and to test new interventions.

In each section above, we discussed the three causes proposed by Grant and Burke[2] and cited some of the questions that ought to be addressed in future studies. In brief, these questions are: What kind of interventions could massively improve clinicians' ability to detect early glaucoma? How could we better monitor IOP short- and long-term variability in an inexpensive and safe fashion to determine treatment efficacy? Could IOP-independent risk factors be modified to slow progression? Could improvements in adherence to therapy lead to better functional outcomes?

Similarly to the measures that helped eradicate or mitigate the burdens of many diseases in the past centuries, the key solutions to glaucoma-related blindness may lie on basic public health interventions, such as better medical training and patient education. Also, increased accessibility to technological advances by eye care providers may play an important role to reduce glaucoma morbidity in the next decades.

## Acknowledgments

Disclosure: **R. Susanna Jr**, None; **C.G. De Moraes**, None; **G.A. Cioffi**, None; **R. Ritch**, None

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