Expert Review of Ophthalmology >
Volume 19, 2024 - Issue 5

Open access

Perspective

Interventional glaucoma and the patient perspective

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Pages 311-318 | Received 22 Apr 2024, Accepted 16 Jul 2024, Published online: 23 Jul 2024

Cite this article https://doi.org/10.1080/17469899.2024.2382149 Check for updates

ABSTRACT

Introduction

The glaucoma treatment paradigm is beginning to undergo a reevaluation – one that promotes a proactive approach with minimally invasive intervention(s) instead of the traditional reactive strategy that leaves patients on topical eyedrops and allows for progressive decline in ocular health before intervening further. Earlier low-risk interventions may include laser, minimally invasive glaucoma surgery (MIGS), and/or

Areas covered

Earlier intervention has been shown to benefit patients, clinicians, society, and the disease trajectory itself. The present article specifically discusses the patient-centric benefits of an interventional treatment paradigm. These can include physical benefits, such as decreased ocular surface disease with lower medication usage; practical or occupational benefits, such as alleviated medication-instillation difficulties, lower costs, and better treatment adherence; and emotional benefits and improved quality of life.

Expert opinion

For the best care of our patients, it is ophthalmologists' responsibility to understand and employ the treatments that produce the highest quality of care and patient quality of life. In light of the breadth of treatment modalities and an abundance of scientific literature now afforded to us, it behooves us – and our patients – to adopt a more proactive, interventional, and ultimately patient-centric approach to the glaucoma treatment paradigm.

KEYWORDS: MIGS patient intervention interventional drug-delivery glaucoma

1. Introduction

Glaucoma is a chronic optic neuropathy and one of the leading causes of irreversible blindness worldwide [1]. Glaucoma treatments to-date have usually centered around reducing intraocular pressure (IOP), one of the most consistently proven methods of preventing or reducing glaucoma incidence and progression. IOP reduction can be achieved by increasing conventional (AKA physiologic) outflow, increasing uveoscleral or suprachoroidal outflow, decreasing aqueous production, or creating a fistula between the anterior chamber (AC) and the subconjunctival space. Among those four methods, the conventional outflow system facilitates up to 80–90% of normal aqueous outflow

glaucoma (POAG) [2,3]. Thus, it may be thought to provide the greatest opportunity for procedural treatments, especially in the setting of earlier interventions [2]. Many of the more proactive minimally invasive glaucoma treatments indeed target this physiologic outflow pathway, in contrast to traditional filtering surgeries such as trabeculectomies and tube shunts that create a higher-risk AC-subconjunctival fistula. Different classes of medications can act upon different pathways, but their patient-centric drawbacks and limitations (as will be discussed in this article) can often make them unfit as a first-line solution for a chronic progressive disease such as glaucoma.

The glaucoma treatment paradigm is beginning to undergo a reevaluation – one that promotes a proactive approach with minimally invasive intervention(s) (possibly using medications as an adjunctive or bridge therapy) instead of the traditional reactive strategy that leaves patients on topical eyedrops as first-line and allows for progressive decline in ocular health before intervening further. The traditional approach was fundamentally reactive, typically starting with topical medications followed by selective laser trabeculoplasty, minimally invasive glaucoma surgery, and eventually filtering surgery. Each stepwise acceleration of care was preceded by a decrease in visual function, making gradual decline almost inevitable. In the meantime, patients were experiencing the negative physical and emotional impacts of the treatments employed. In this traditional model, as long as IOP was at target and VF was stable, the case was a 'success,' even if patients were suffering as a result. This model has often used topical medications to stabilize key disease parameters such as intraocular pressure and visual fields, but it may have overlooked the toll these medications take upon patients and their families.

Over the past one to two decades, glaucoma treatments have evolved considerably, most notably with the introduction of increasing numbers and diversity of minimally invasive interventions. Treatments that allow earlier more proactive intervention now may include laser trabeculoplasty, as supported by the findings of the LiGHT (LiGHT) trial [4]; micro-invasive glaucoma surgery (MIGS); and/or intracameral procedural

the most conservative and most invasive ends of the treatment spectrum, as represented by topical medications (conservative) and filtering surgery or cilioablative procedures (invasive), respectively. MIGS now comprises the majority of glaucoma surgeries in the United States. A study from the American Academy of Ophthalmology (AAO) Intelligent Research in Sight (IRIS) Registry showed that U.S. MIGS procedures rose from 31.9% (7586/23801) of annual glaucoma procedures in 2013 to 74.3% (39677/53378) of annual glaucoma procedures in 2018 [5,6]. This dramatic rise in MIGS has been accompanied by a concomitant decline in traditional filtering surgeries [7].

The favorable benefit-to-risk profile of these minimally invasive procedures has led them to be considered earlier in the treatment cascade: alongside or in place of topical medications and/or laser trabeculoplasty, and performed in standalone settings or combined with cataract surgery. Such earlier proactive intervention, termed *interventional glaucoma* [8,9], has many advantages over the former conservative 'wait and see' reactive approach. These benefits have been shown to pertain to patients, clinicians, society, and the disease trajectory itself [8–10].

Although this article will contrast the interventional and traditional paradigms, it is important to note that they are not necessarily mutually exclusive, but rather they are differing approaches to achieving the same goal of preserving patients' vision. Adopting an interventional mind-set does not eliminate topical medications, for example, but rather it simply moves away from assuming topical medications to be the automatic reflexive first-line remedy in glaucoma treatment. Likewise, it does not eliminate filtering surgery for appropriate patients, but rather it advocates earlier minimally invasive interventions to hopefully prevent filtering surgery altogether. Different treatments are appropriate at different stages of disease (progressive vs non-progressive, controlled vs uncontrolled), and treatment is not a 'one size fits all' solution. Leveraging minimally invasive procedures to attain earlier IOP reduction can be advantageous in many stages of glaucoma; and it may be especially beneficial for patients with advanced disc damage and visual field loss, which is known to require even lower pressures to slow disease

centric benefits of such a proactive approach: that is, interventional glaucoma and the patient perspective. This interventional paradigm is an evolution from the topical-medications-first model, which no longer meets our current therapeutic goals of both maintaining vision and improving quality of life. We can do better. We *must* do better. We can no longer treat a chart; we must approach our patients in a more humanistic way.

Benefits to the patient of an interventional glaucoma treatment paradigm can be broadly categorized into three areas, to be described herein: physical, practical/occupational, and emotional.

2. Physical

Physically, the unwanted side effects of topical glaucoma medications pose a significant deterrent for patients. Some of the most common effects can include ocular surface disease (discussed below); hyperemia [13]; damage to the corneal and conjunctival surface; periorbital fat atrophy [14–16]; hyperpigmentation of the eyelids and iris [17]; and systemic reactions that can include fatalities [18–20]. These physical issues can negatively affect patients' quality of life, as will be discussed later in this article.

In addition to the side effects above, topical medications are closely associated with ocular surface disease (OSD) [21–25], contributing to the higher prevalence of the disorder in glaucoma patients than in the general population [26–29]. The causes of glaucoma-associated OSD are multifactorial and involve a self-perpetuating cycle of inflammatory cytokines and proteins [26]. These effects are known to increase with higher medication loads [28,30,31]. For example, a study by Erb et al. reported a higher prevalence of dry eye disease with each eyedrop used (1 eye drop 50.9%, 5 eye drops 66.7%) [31]. Rossi et al. also showed the prevalence of dry eye symptoms to be correlated with the number of active glaucoma medications a patient is using: 5% with no medications, 11% with one medication, and 20% with two medications, and 40% with

another medication-related risk factor for OSD [32]. The tear film instability caused by OSD in turn is associated with a significant decline in contrast sensitivity [33].

The preservatives in topical medications, most commonly benzalkonium chloride (BAK), are widely known to cause pathologic cellular changes [25,29,32,34,35]. Various studies have specifically characterized the effects of this association. For example, Leung et al. showed that each additional BAK-containing eye drop was associated with an approximately 2 times higher odds of showing abnormal lissamine green staining [28]. Jaenen et al. showed that each recorded ocular sign (such as anterior/posterior blepharitis, conjunctival hyperemia, and staining) was significantly more prevalent in the preservative group vs preservative-free group [36]. Further, exposure to topical medications increases the risk of failure of future filtering surgery [37–39], should it be needed. This is thought to be due to chronic subclinical conjunctival inflammation induced by topical medication and its preservatives, which can decrease the total effective filtration area of the conventional outflow system during future surgery [34,37,38,40–44]. In an effort to avoid these physical effects of medications, preservative-free formulations have been developed. These can be valuable options for patients who cannot tolerate or who wish to avoid the side effects of traditional topical eyedrops. However, they are often more expensive, and they still carry the other limitations of topical medications discussed in this article, such as nonadherence, IOP variability, and potential VF progression.

Given the ocular issues associated with topical medications, it is not surprising that the reduction of medication burden through surgical intervention can lead to an improvement in the objective physical signs and subjective symptoms of dry eye [45–47]. For example, a study by Schweitzer et al. showed that the medication reduction following iStent implantation was associated with a significant decrease in the percentage of eyes with moderate to severe ocular surface disease index (OSDI) score (a subjective patient-reported measurement), accompanied by similar improvements in

objective examination findings (e.g. conjunctival hyperemia, tear film breakup time, and corneal and conjunctival staining) [45].

3. Practical or occupational

Practical or occupational health issues also stand to benefit from a more proactive interventional mind-set. Glaucoma is associated with greater use of inpatient and home health aid services; and patients' perception of vision loss may be associated with depression, falls, and difficulty walking [48,49]. Glaucoma patients typically have other comorbidities and medication regimens, which can heighten the risk of forgetfulness or mis-dosing [50,51]. Adherence is particularly difficult with increasing numbers of medications, as shown by a study by Robin et al. of multiple vs single eyedrop regimens [52]. This is consequential considering that approximately half of glaucoma patients are on more than one medication [53]. And drop instillation itself is known to be difficult in glaucoma patients due to factors such as older age, arthritis or other limitation of manual dexterity, and cognitive difficulties [51,54–56].

Medication adherence is well-known to be low. Studies have shown that approximately 60–90% of patients are non-adherent with topical medications, and approximately 50% purposely discontinue their topical medication(s) within 6 months [54]. Even in the presence of free medication and assistive technologies, the majority of patients do not use their medications properly [50,51,54,57–59]. So although medications are effective and reasonably safe, the fact they must be used correctly and consistently poses a significant challenge. Medication noncompliance, in turn, is associated with higher rates of glaucoma progression and worse visual field outcomes [50,51,60–63]. Thus, nonadherence with topical glaucoma medication should no longer be overlooked and must be acknowledged as a common problem associated with irreversible glaucoma progression.

Additionally, medications are known to reach a plateau-like effect in both single and

agents, efficacy may decrease over time [64]; for combination therapy, increasing numbers of medications have been shown to have less incremental benefit to overall IOP lowering [65]. Moreover, each additional medication is associated with lower medication adherence [53,65], higher incremental cost, and shorter time to further accelerations of care, in comparison to the first medication(s) [65]. This has led some to question whether heightening the medication load, such as with a third or fourth agent, is worthwhile in the overall treatment paradigm for glaucoma [66].

The costs of medications must also be considered as an important patient-centric consequence of medication use [67–69], even if patients do not frequently bring this up to their health providers [70]. A nationally representative sample of the U.S. population showed that glaucoma patients reported cost-related medication nonadherence more frequently than patients without glaucoma [71]. In turn, this nonadherence can contribute to glaucoma progression, as highlighted previously. In comparison to medications, procedural interventions may be more cost-effective in treating glaucoma over the long term. For example, the aforementioned LiGHT trial showed that initial treatment of ocular hypertension or open-angle glaucoma with SLT was more cost-effective than initial treatment with medication after 3 years [4]. In addition, over 20 health economics studies have examined the cost-effectiveness and cost-utility of MIGS interventions, including data from countries around the world with both national-healthcare and private-payer networks. One U.S. example is a cost-utility analysis by Sood et al. of cataract surgery with either Hydrus or iStent *inject* compared to cataract surgery alone; the study found that the device arms dominated or were cost-effective compared with cataract surgery alone within 5 years, with surgery being cost-effective in approximately 94–95% of cases. Another example is a cost-utility analysis from Italy, which showed iStent inject + cataract surgery to be a cost-effective option for the treatment of patients affected by mild-to-moderate POAG, compared with cataract surgery alone [72]. A third study was a Canadian Health Technology Assessment, which showed iStent implantation to be more cost-effective than topical medication(s) [73]. These findings are not entirely surprising, as increasing glaucoma severity has been

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prevalence and severity of glaucoma may result in improvements in non-glaucomatous medical conditions and resultant health care costs [49]. Thus, it behooves the cost-sensitive healthcare system to stabilize the disease as early as possible, since a proactive, patient-centric approach may benefit national payers in addition to patients themselves.

4. Emotional

Emotionally, there are myriad benefits to preserving visual function via earlier procedural intervention. Patients' perception of glaucomatous vision loss may be associated with depression [49] and also may result in loss of confidence in performing routine daily tasks [75]. Feeling out of control of their disease may lead glaucoma patients to have higher levels of anxiety, lower self-image, and reduced confidence in health care [76].

Studies evaluating quality of life have consistently shown an association between eyedrop usage and significantly diminished quality of life [30,77,78], and/or general patient dissatisfaction [79]. For example, a study by Nordmann et al. of approximately 600 glaucoma patients showed that nearly two-thirds had local side effect(s) of glaucoma medications. These side effects in turn were associated with poor vision-related quality of life and poor treatment satisfaction [78] and led to increased visits of patients to their ophthalmologists. The existence of physical or mental comorbidities alongside the glaucoma diagnosis can further reduce the health-related quality of life reported by glaucoma patients in the current treatment paradigm [80].

Given these limitations, a procedural intervention with a favorable safety profile may be an appropriate and desirable treatment alternative, especially when a reduction in medication burden is sought. Consistent with this thinking, a study by Al Habash et al. showed a clear improvement in quality of life after various types of MIGS surgery, with 70% of patients reporting that their overall quality of life improved after the procedure [

and better Glaucoma Symptom Scale scores (GSS) after phacoemulsification with XEN Gel Stent implantation, with improved patient satisfaction observed specifically when the procedure led to a reduction in glaucoma medication [81]. The LiGHT study reported better GSS scores in the SLT arm than the medications arm [82], while the other markers of quality of life were similar between groups. Among MIGS pivotal trials, one trial [46] evaluated quality of life outcomes after surgery. The study found that vision-related quality of life parameters significantly improved following iStent inject implantation with phacoemulsification, in comparison to phacoemulsification alone. This improvement was largely attributed to reduction in topical medications.

A less-frequently characterized but no less important aspect of medication administration may be the burden it places upon patients' relatives and caregivers, in addition to patients themselves. A study by Stagg et al. showed that ongoing glaucoma treatment (including medications and appointments) can constitute a substantial burden, often even more than the disease itself [83]. The burden of glaucoma and glaucoma treatment can include patients' difficulties with reading, driving, mobility, and facial recognition; and financial and psychological implications for patients' caregivers and family members [84]. This may be particularly problematic for patients with mild glaucoma who may not be motivated to use medications for a far-off consequence like glaucoma progression. Indeed, patients' understanding of glaucoma progression to irreversible visual impairment is a critical determinant of their benefit: risk evaluation of both medical and surgical glaucoma interventions. In a study by Jampel et al., patients were asked what portion of their life they would give up to retain their sight for their lifetime; those without visual impairment stated 10%, while visually disabled patients stated 33% [85]. Not surprisingly, then, patients with mild glaucoma may have greater difficulties with adherence to medication and appointments, which in turn can have vision-impacting consequences [83].

The "fear factor" of undergoing a procedure must also not be overlooked, as there may be understandable hesitation around going to the operating room rather than self-

landscape of minimally invasive glaucoma interventions. First, glaucoma procedures are often completed in conjunction with cataract surgery, thereby addressing two ocular issues in a single trip to the operating room. And second, if cataract surgery is not needed or indicated, the high safety profile of minimally invasive laser, MIGS, and procedural pharmaceutical interventions can be reassuring to patients, especially when compared to the well-known side effects of topical glaucoma medications.

5. Conclusion

It is clear that the glaucoma treatment paradigm has evolved considerably over the past few decades. Minimally invasive surgical options with favorable safety profiles have allowed clinicians and patients to reconsider laser, surgical, and procedural pharmaceutical interventions earlier in the treatment cascade, rather than waiting for advancing glaucomatous damage to warrant an intervention. This interventional glaucoma mind-set provides several avenues to improve the lives of patients. As reviewed in this paper, these can include physical benefits, such as decreased ocular surface disease with lower medication usage; practical or occupational benefits, such as alleviated medication-instillation difficulties, lower costs, and better treatment adherence; and emotional benefits and improved quality of life. The ultimate goal of glaucoma treatment is to benefit the patient by maintaining their sight and quality of life, and we must embrace any available modality for doing so. We stand now at an inflection point in glaucoma care. In light of the breadth of treatment modalities and an abundance of scientific literature now afforded to us, it behooves us – and our patients – to adopt a more proactive, interventional, and ultimately patient-centric approach to the glaucoma treatment paradigm. The adoption of a caring, updated approach to glaucoma management will solidify the advocacy role that strengthens the physician-patient bond and promotes better healthcare.

As discussed in this article, there are clear benefits – physically, practically/occupationally, and emotionally – of an interventional glaucoma paradigm to patients; these are in addition to the benefits to clinicians, society, and the disease trajectory itself. Despite these advantages, we would be naïve to overlook the very real hurdles that prevent the paradigm's more widespread adoption. For example, clinics must balance patient care with reimbursement difficulties and limitations by insurance plans; some providers may have inertia in transitioning to earlier intervention due to the need to learn and incorporate newer techniques into their routines; newer techniques can be seen as a threat that might slow the pace of the clinic or operating room; staff may need to be trained to use new diagnostic and therapeutic technologies; and patients themselves may distrust the medical establishment and see a surgical procedure as something potentially more harmful than drops.

Certainly, these hurdles can be limitations, but they also can be viewed as opportunities for research and forward-thinking progress. For example, research could further investigate the patient-level impacts of switching to an interventional glaucoma treatment approach; new diagnostic modalities could be further studied and developed to detect glaucoma earlier and monitor for progression more closely; physician education could be undertaken to facilitate surgeon training and implementation of newer techniques; and patient education could be completed to mitigate misconceptions about different treatment options. In addition, possible new areas of study might include time-motion studies of clinic flow, which could validate that interventional approaches can be time- and space-efficient; health economics studies to assess the cost-utility of an interventional glaucoma approach from a health systems perspective; and/or patient–feedback studies to evaluate quality of life before and after a minimally invasive intervention.

Perhaps it is time for us to consider rebranding our field as an interventional field. Following the example of other specialties such as cardiology, which have both cardiologists and interventional cardiologists, we could be at the forefront of a new wave

of care should have evolved from simply watching a patient suffer from the side effects of maximum medical treatment until they progress before we perform an intervention. We will diagnose earlier, monitor for progression earlier, and intervene earlier. We will employ lower-risk interventions such as laser, MIGS procedures, and/or procedural pharmaceuticals rather than reflexively reaching for a topical medication. As a result, patients will be better off physically, practically, and emotionally. Their disease will be treated proactively, at a stage when interventions can have greater positive impact and actually change the disease trajectory itself. Physicians will feel more confident that they are addressing both the patient and his/her disease. And society and health systems as a whole will bear a lower overall treatment burden. Just as we no longer question coronary stents because the alternative is simply not acceptable, we should approach glaucoma treatment similarly. The time is now and our patients need us to take action.

Article highlights

- The approach to glaucoma treatment is evolving to become more proactive and interventional, instead of the traditional reactive heavy reliance on topical medications.
- This article summarizes the physical, practical, and emotional benefits to the patient of an interventional treatment approach.
- Physical benefits can include fewer unwanted side effects of topical medications (e.g. ocular surface disease, hyperemia, periorbital fat atrophy, eyelid and iris hyperpigmentation, systemic reactions); improvement in patient-reported symptoms of ocular surface disease; and avoidance or lessening of corneal and conjunctival inflammation.
- Practical or occupational benefits can include fewer medication-instillation difficulties, lower overall cost, and better treatment adherence.

- Emotional benefits can include reduction in patient depression and anxiety, increase in patient confidence, lower burden on patients' relatives and caregivers, and improved quality of life.
- For the best care of our patients, we need to consider a more proactive, interventional, and patient-focused treatment approach for glaucoma.

Declaration of interest

M Gallardo has acted as a speaker, consultant, and investigator for Glaukos, Alcon, AbbVie, Nova Eye, and Sight Science, and as a consultant and investigator for ELIOS, and as a consultant for Zeiss. M Gallardo has also received royalties from Glaukos, and grant support from AbbVie. O Smith has acted as a consultant and lecturer for Allergan and Bausch and Lomb, and as a consultant for Alcon, Belkin Vision, Glaukos, Iris Vision, New World Medical, and Sanoculis, and as a researcher for Ocular Therapeutix, and owns stock in Nova Eye and Ollyes. V Trubnik has acted as a consultant for Glaukos, and a speaker for Alcon. G Reiss has received research support from Allergan, ELIOS, Glaukos, iStar, and Sanoculis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

All authors contributed to the manuscript's conception, literature review, drafting, revising, and decision to submit for publication.

Financial support

No financial support was supplied for the work in this manuscript. Editorial assistance (Dana M. Hornbeak, MD, MPH) and article processing fees were provided by Glaukos Corporation (Aliso Viejo, CA).

Disclosures

MG:Glaukos (speaker, consultant, investigator, royalties) Alcon (speaker, consultant, investigator), AbbVie (speaker, consultant, investigator, grant support), Nova Eye (speaker, consultant, investigator), ELIOS (consultant and investigator), Sight Sciences (Consultant, investigator, speaker), Zeiss (consultant)

OS: Alcon, C; Allergan, C, L; Bausch and Lomb, C, L; Belkin Vision, C; Elios Vision, C; Glaukos, C; Iris vision, C; New world medical, C; Nova Eye, O; Ocular Therapeutix, R; Olleyes, O; Sanoculis, C

VT: Glaukos (consultant); Alcon (speaker)

GR: Allergan (research support); Elios (research support); Glaukos (research support); iStar (research support); Sanoculis (research support)

Additional information

Funding

This paper was not funded. Editorial assistance was provided by Dana M. Hornbeak, MD, MPH of Glaukos Corporation.

References

1. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. Lancet Glob Health. 2017 Dec;5(12):e1221–e1234. doi: 10.1016/S2214-109X(17)30393-5
PubMed | Web of Science ® | Google Scholar

2. Francis BA, Akil H, Bert BB. Ab interno Schlemm's canal surgery. Dev Ophthalmol. 2017;59:127–146.
PubMed | Google Scholar

3. Qin M, Yu-Wai-Man C. Glaucoma: novel antifibrotic therapeutics for the trabecular meshwork. Eur J Pharmacol. 2023 Sep 5;954:175882. doi: 10.1016/j.ejphar.2023.175882
PubMed | Web of Science ® | Google Scholar

4. Gazzard G, Konstantakopoulou E, Garway-Heath D, et al. Selective laser trabeculoplasty versus drops for newly diagnosed ocular hypertension and glaucoma: the LiGHT RCT. Health Technol Assess. 2019 Jun;23(31):1–102. doi: 10.3310/hta23310
PubMed | Web of Science ® | Google Scholar

5. Yang SA, Mitchell W, Hall N, et al. Trends and usage patterns of minimally invasive glaucoma surgery in the United States: IRIS(R) registry analysis 2013-2018. Ophthalmol Glaucoma. 2021 Nov;4(6):558–568. doi: 10.1016/j.ogla.2021.03.012

6. Yang SA, Mitchell WG, Hall N, et al. Usage patterns of minimally invasive glaucoma surgery (MIGS) differ by glaucoma type: IRIS registry analysis 2013-2018. Ophthalmic Epidemiol. 2022 Aug;29(4):443–451. doi: 10.1080/09286586.2021.1955391
PubMed | Web of Science ® | Google Scholar

7. Ma AK, Lee JH, Warren JL, et al. GlaucoMap - distribution of glaucoma surgical procedures in the United States. Clin Ophthalmol. 2020;14:2551–2560. doi: 10.2147/OPTH.S257361
PubMed | Web of Science ® | Google Scholar

8. Radcliffe NM, Shah M, Samuelson TW. Challenging the “topical medications-first” approach to glaucoma: a treatment paradigm in evolution. Ophthalmol Ther. 2023 Dec;12(6):2823–2839. doi: 10.1007/s40123-023-00831-9
PubMed | Web of Science ® | Google Scholar

9. Bedrood S, Berdahl J, Sheybani A, et al. Alternatives to topical glaucoma medication for glaucoma management. Clin Ophthalmol. 2023;17:3899–3913.
PubMed | Web of Science ® | Google Scholar

10. Caprioli J. The importance of rates in glaucoma. Am J Ophthalmol. 2008 Feb;145(2):191–192. doi: 10.1016/j.ajo.2007.12.003
PubMed | Web of Science ® | Google Scholar

11. Shin YI, Jeong Y, Huh MG, et al. Longitudinal evaluation of advanced glaucoma: ten year follow-up cohort study. Sci Rep. 2024 Jan 4;14(1):476. doi: 10.1038/s41598-023-50512-7
PubMed | Web of Science ® | Google Scholar

12. Kastner A, King AJ. Advanced glaucoma at diagnosis: current perspectives. Eye (Lond).

PubMed | Web of Science ® | Google Scholar

13. Honrubia F, Garcia-Sanchez J, Polo V, et al. Conjunctival hyperaemia with the use of latanoprost versus other prostaglandin analogues in patients with ocular hypertension or glaucoma: a meta-analysis of randomised clinical trials. Br J Ophthalmol. 2009 Mar;93(3):316–321. doi: 10.1136/bjo.2007.135111
PubMed | Web of Science ® | Google Scholar

14. Servat JJ, Bernardino CR. Effects of common topical antiglaucoma medications on the ocular surface, eyelids and periorbital tissue. Drugs Aging. 2011 Apr 1;28(4):267–282. doi: 10.2165/11588830-000000000-00000
PubMed | Web of Science ® | Google Scholar

15. Ishida A, Miki T, Naito T, et al. Surgical results of trabeculectomy among groups stratified by prostaglandin-associated periorbitopathy severity. Ophthalmology. 2023 Mar;130(3):297–303. doi: 10.1016/j.ophtha.2022.10.024
PubMed | Web of Science ® | Google Scholar

16. Kucukevcilioglu M, Bayer A, Uysal Y, et al. Prostaglandin associated periorbitopathy in patients using bimatoprost, latanoprost and travoprost. Clin Exp Ophthalmol. 2014 Mar;42(2):126–131. doi: 10.1111/ceo.12163
PubMed | Web of Science ® | Google Scholar

17. Inoue K. Managing adverse effects of glaucoma medications. Clin Ophthalmol. 2014;8:903–913. doi: 10.2147/OPTH.S44708
PubMed | Google Scholar

18. Ergin A, Ornek K, Gullu R, et al. Effects of timolol and latanoprost on respiratory and cardiovascular status in elderly patients with glaucoma. J Ocul Pharmacol Ther. 2009

Oct;25(5):463–466. doi: 10.1089/jop.2008.0137

PubMed | Web of Science ® | Google Scholar

19. Nelson WL, Fraunfelder FT, Sills JM, et al. Adverse respiratory and cardiovascular events attributed to timolol ophthalmic solution, 1978-1985. Am J Ophthalmol. 1986 Nov 15;102(5):606–611. doi: 10.1016/0002-9394(86)90532-5

PubMed | Web of Science ® | Google Scholar

20. Han JA, Frishman WH, Wu Sun S, et al. Cardiovascular and respiratory considerations with pharmacotherapy of glaucoma and ocular hypertension. Cardiol Rev. 2008 Mar;16(2):95–108. doi: 10.1097/CRD.0b013e318156ec64

PubMed | Web of Science ® | Google Scholar

21. Zhang X, Vadoothker S, Munir WM, et al. Ocular surface disease and glaucoma medications: a clinical approach. Eye Contact Lens. 2019 Jan;45(1):11–18. doi: 10.1097/ICL.0000000000000544

PubMed | Web of Science ® | Google Scholar

22. Anwar Z, Wellik SR, Galor A. Glaucoma therapy and ocular surface disease: current literature and recommendations. Curr Opin Ophthalmol. 2013 Mar;24(2):136–143. doi: 10.1097/ICU.0b013e32835c8aba

PubMed | Web of Science ® | Google Scholar

23. Fechtner RD, Godfrey DG, Budenz D, et al. Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. Cornea. 2010 Jun;29(6):618–621. doi: 10.1097/ICO.0b013e3181c325b2

PubMed | Web of Science ® | Google Scholar

24. Arici MK, Arici DS, Topalkara A, et al. Adverse effects of topical antiglaucoma drugs on

9071.2000.00237.x

PubMed | Web of Science ® | Google Scholar

25. Aptel F, Labbe A, Baudouin C, et al. Glaucoma medications, preservatives and the ocular surface. J Fr Ophtalmol. 2014 Nov;37(9):728–736. doi: 10.1016/j.jfo.2014.06.005

PubMed | Web of Science ® | Google Scholar

26. Nijm LM, De Benito-Llopis L, Rossi GC, et al. Understanding the dual dilemma of dry eye and glaucoma: an international review. Asia Pac J Ophthalmol (Phila). 2020 Dec;9(6):481–490. doi: 10.1097/APO.0000000000000327

PubMed | Web of Science ® | Google Scholar

27. Nijm LM, Schweitzer J, Gould Blackmore J. Glaucoma and dry eye disease: opportunity to assess and treat. Clin Ophthalmol. 2023;17:3063–3076. doi: 10.2147/OPTH.S420932

PubMed | Web of Science ® | Google Scholar

28. Leung EW, Medeiros FA, Weinreb RN. Prevalence of ocular surface disease in glaucoma patients. J Glaucoma. 2008 Aug;17(5):350–355. doi: 10.1097/IJG.0b013e31815c5f4f

PubMed | Web of Science ® | Google Scholar

29. Gomes JAP, Azar DT, Baudouin C, et al. TFOS DEWS II iatrogenic report. Ocul Surf. 2017 Jul;15(3):511–538. doi: 10.1016/j.jtos.2017.05.004

PubMed | Web of Science ® | Google Scholar

30. Rossi GC, Tinelli C, Pasinetti GM, et al. Dry eye syndrome-related quality of life in glaucoma patients. Eur J Ophthalmol. 2009 Jul;19(4):572–579. doi: 10.1177/112067210901900409

PubMed | Web of Science ® | Google Scholar

31. Erb C, Gast U, Schremmer D. German register for glaucoma patients with dry eye. I. Basic outcome with respect to dry eye. Graefes Arch Clin Exp Ophthalmol. 2008 Nov;246(11):1593–1601. doi: 10.1007/s00417-008-0881-9
PubMed | Web of Science ® | Google Scholar

32. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. Br J Ophthalmol. 2002 Apr;86(4):418–423. doi: 10.1136/bjo.86.4.418
PubMed | Web of Science ® | Google Scholar

33. Szczotka-Flynn LB, Maguire MG, Ying GS, et al. Impact of dry eye on visual acuity and contrast sensitivity: dry eye assessment and management study. Optom Vis Sci. 2019 Jun;96(6):387–396. doi: 10.1097/OPX.0000000000001387
PubMed | Web of Science ® | Google Scholar

34. Baudouin C, Labbe A, Liang H, et al. Preservatives in eyedrops: the good, the bad and the ugly. Prog Retin Eye Res. 2010 Jul;29(4):312–334. doi: 10.1016/j.preteyeres.2010.03.001
PubMed | Web of Science ® | Google Scholar

35. Moon J, Ko JH, Yoon CH, et al. Effects of 20% human serum on corneal epithelial toxicity induced by benzalkonium chloride: in vitro and clinical studies. Cornea. 2018 May;37(5):617–623. doi: 10.1097/ICO.0000000000001475
PubMed | Web of Science ® | Google Scholar

36. Jaenen N, Baudouin C, Pouliquen P, et al. Ocular symptoms and signs with preserved and preservative-free glaucoma medications. Eur J Ophthalmol. 2007 May;17(3):341–349. doi: 10.1177/112067210701700311
PubMed | Web of Science ® | Google Scholar

37. Broadway D, Hitchings R, Grierson I. Topical antiglaucomatous therapy: adverse effects on the conjunctiva and implications for filtration surgery. J Glaucoma. 1995 Apr;4(2):136. doi: 10.1097/00061198-199504000-00012
PubMed | Google Scholar

38. Broadway DC, Grierson I, O'Brien C, et al. Adverse effects of topical antiglaucoma medication. II. The outcome of filtration surgery. Arch Ophthalmol. 1994 Nov;112(11):1446–1454. doi: 10.1001/archopht.1994.01090230060021
PubMed | Google Scholar

39. Kolko M, Gazzard G, Baudouin C, et al. Impact of glaucoma medications on the ocular surface and how ocular surface disease can influence glaucoma treatment. Ocul Surf. 2023 Jul;29:456–468. doi: 10.1016/j.jtos.2023.05.012
PubMed | Web of Science ® | Google Scholar

40. Broadway D, Grierson I, Hitchings R. Adverse effects of topical antiglaucomatous medications on the conjunctiva. Br J Ophthalmol. 1993 Sep;77(9):590–596. doi: 10.1136/bjo.77.9.590
PubMed | Web of Science ® | Google Scholar

41. Broadway DC, Grierson I, O'Brien C, et al. Adverse effects of topical antiglaucoma medication. I. The conjunctival cell profile. Arch Ophthalmol. 1994 Nov;112(11):1437–1445. doi: 10.1001/archopht.1994.01090230051020
PubMed | Google Scholar

42. Brandt JD, Wittpenn JR, Katz LJ, et al. Conjunctival impression cytology in patients with glaucoma using long-term topical medication. Am J Ophthalmol. 1991 Sep 15;112(3):297–301. doi: 10.1016/S0002-9394(14)76730-3
PubMed | Web of Science ® | Google Scholar

43. Johnson DH, Yoshikawa K, Brubaker RF, et al. The effect of long-term medical therapy on the outcome of filtration surgery. Am J Ophthalmol. 1994 Feb 15;117(2):139–148. doi: 10.1016/S0002-9394(14)73068-5

PubMed | Web of Science ® | Google Scholar

44. Noecker RJ, Herrygers LA, Anwaruddin R. Corneal and conjunctival changes caused by commonly used glaucoma medications. Cornea. 2004 Jul;23(5):490–496. doi: 10.1097/01.ico.0000116526.57227.82

PubMed | Web of Science ® | Google Scholar

45. Schweitzer JA, Hauser WH, Ibach M, et al. Prospective interventional cohort study of ocular surface disease changes in eyes after trabecular micro-bypass stent(s) implantation (iStent or iStent inject) with phacoemulsification. Ophthalmol Ther. 2020 Dec;9(4):941–953. doi: 10.1007/s40123-020-00290-6

PubMed | Web of Science ® | Google Scholar

46. Samuelson TW, Singh IP, Williamson BK, et al. Quality of life in primary open-angle glaucoma and cataract: an analysis of VFQ-25 and OSDI from the iStent inject(R) pivotal trial. Am J Ophthalmol. 2021 Sep;229:220–229. doi: 10.1016/j.ajo.2021.03.007

PubMed | Web of Science ® | Google Scholar

47. Al Habash A, Nagshbandi AA. Quality of life after combined cataract and minimally invasive glaucoma surgery in glaucoma patients. Clin Ophthalmol. 2020;14:3049–3056. doi: 10.2147/OPTH.S276124

PubMed | Web of Science ® | Google Scholar

48. Gomes HA, Moreira BS, Sampaio RF, et al. Gait parameters, functional mobility and fall risk in individuals with early to moderate primary open angle glaucoma: a cross-sectional study. Braz J Phys Ther. 2018 Sep;22(5):376–382. doi:

10.1016/j.bjpt.2018.03.004

PubMed | Web of Science ® | Google Scholar

49. Prager AJ, Liebmann JM, Cioffi GA, et al. Self-reported function, health resource use, and total health care costs among medicare beneficiaries with glaucoma. JAMA Ophthalmol. 2016 Apr;134(4):357–365. doi: 10.1001/jamaophthalmol.2015.5479

PubMed | Web of Science ® | Google Scholar

50. Newman-Casey PA, Blachley T, Lee PP, et al. Patterns of glaucoma medication adherence over four years of follow-up. Ophthalmology. 2015 Oct;122(10):2010–2021. doi: 10.1016/j.ophtha.2015.06.039

PubMed | Web of Science ® | Google Scholar

51. Newman-Casey PA, Robin AL, Blachley T, et al. The most common barriers to glaucoma medication adherence: a cross-sectional survey. Ophthalmology. 2015 Jul;122(7):1308–1316. doi: 10.1016/j.ophtha.2015.03.026

PubMed | Web of Science ® | Google Scholar

52. Robin AL, Covert D. Does adjunctive glaucoma therapy affect adherence to the initial primary therapy? Ophthalmology. 2005 May;112(5):863–868. doi: 10.1016/j.ophtha.2004.12.026

PubMed | Web of Science ® | Google Scholar

53. Saini SD, Schoenfeld P, Kaulback K, et al. Effect of medication dosing frequency on adherence in chronic diseases. Am J Manag Care. 2009 Jun 1;15(6):e22–33.

PubMed | Web of Science ® | Google Scholar

54. Nordstrom BL, Friedman DS, Mozaffari E, et al. Persistence and adherence with topical glaucoma therapy. Am J Ophthalmol. 2005 Oct;140(4):598–606. doi:

10.1016/j.ajo.2005.04.051

PubMed | Web of Science ® | Google Scholar

55. Lanzl IM, Poimenidou M, Spaeth GL. Possibilities and limitations of eye drops for glaucoma therapy. Ophthalmologe. 2016 Oct;113(10):824–832. doi: 10.1007/s00347-016-0332-7

PubMed | Web of Science ® | Google Scholar

56. Gomes BF, Paredes AF, Madeira N, et al. Assessment of eye drop instillation technique in glaucoma patients. Arq Bras Oftalmol. 2017 Jul;80(4):238–241. doi: 10.5935/0004-2749.20170058

PubMed | Web of Science ® | Google Scholar

57. Olthoff CM, Schouten JS, van de Borne BW, et al. Noncompliance with ocular hypotensive treatment in patients with glaucoma or ocular hypertension an evidence-based review. Ophthalmology. 2005 Jun;112(6):953–961. doi: 10.1016/j.ophtha.2004.12.035

PubMed | Web of Science ® | Google Scholar

58. Schwartz GF, Quigley HA. Adherence and persistence with glaucoma therapy. Surv Ophthalmol. 2008 Nov;53(Suppl 6):S57–68. doi: 10.1016/j.survophthal.2008.08.002

PubMed | Google Scholar

59. Tsai JC. A comprehensive perspective on patient adherence to topical glaucoma therapy. Ophthalmology. 2009 Nov;116(11 Suppl):S30–6. doi: 10.1016/j.ophtha.2009.06.024

PubMed | Web of Science ® | Google Scholar

60. Rossi GC, Pasinetti GM, Scudeller L, et al. Do adherence rates and glaucomatous visual

10.5301/EJO.2010.6112

PubMed | Web of Science ® | Google Scholar

61. Stewart WC, Konstas AG, Nelson LA, et al. Meta-analysis of 24-hour intraocular pressure studies evaluating the efficacy of glaucoma medicines. Ophthalmology. 2008 Jul;115(7):1117–1122.e1. doi: 10.1016/j.ophtha.2007.10.004

PubMed | Web of Science ® | Google Scholar

62. Sleath B, Blalock S, Covert D, et al. The relationship between glaucoma medication adherence, eye drop technique, and visual field defect severity. Ophthalmology. 2011 Dec;118(12):2398–2402. doi: 10.1016/j.ophtha.2011.05.013

PubMed | Web of Science ® | Google Scholar

63. Paula JS, Furtado JM, Santos AS, et al. Risk factors for blindness in patients with open-angle glaucoma followed-up for at least 15 years. Arq Bras Oftalmol. 2012 Jul;75(4):243–246. doi: 10.1590/S0004-27492012000400004

PubMed | Web of Science ® | Google Scholar

64. Boger WP. 3rd. Shortterm “escape” and longterm “drift”. the dissipation effects of the beta adrenergic blocking agents. Surv Ophthalmol. 1983 Dec;28(Suppl):235–242.

PubMed | Google Scholar

65. Patel AR, Schwartz GF, Campbell JH, et al. Economic and clinical burden associated with intensification of glaucoma topical therapy: a us claims-based analysis. J Glaucoma. 2021 Mar 1;30(3):242–250. doi: 10.1097/IJG.0000000000001730

PubMed | Web of Science ® | Google Scholar

66. Neelakantan A, Vaishnav HD, Iyer SA, et al. Is addition of a third or fourth antiglaucoma medication effective? J Glaucoma. 2004 Apr;13(2):130–136. doi:

10.1097/00061198-200404000-00008

PubMed | Web of Science ® | Google Scholar

67. Bhosle MJ, Reardon G, Camacho FT, et al. Medication adherence and health care costs with the introduction of latanoprost therapy for glaucoma in a medicare managed care population. Am J Geriatr Pharmacother. 2007 Jun;5(2):100–111. doi: 10.1016/j.amjopharm.2007.05.004

PubMed | Google Scholar

68. Ngan K, Fraser E, Buller S, et al. A cost minimisation analysis comparing iStent accompanying cataract surgery and selective laser trabeculoplasty versus topical glaucoma medications in a public healthcare setting in New Zealand. Graefes Arch Clin Exp Ophthalmol. 2018 Nov;256(11):2181–2189. doi: 10.1007/s00417-018-4104-8

PubMed | Web of Science ® | Google Scholar

69. Buys YM, Kagan D, Jin YP, et al. Cost-related nonadherence with glaucoma medications in Ontario. Can J Ophthalmol. 2021 Dec;56(6):379–384. doi: 10.1016/j.jcjo.2021.01.008

PubMed | Web of Science ® | Google Scholar

70. Slota C, Davis SA, Blalock SJ, et al. Patient-physician communication on medication cost during glaucoma visits. Optom Vis Sci. 2017 Dec;94(12):1095–1101. doi: 10.1097/OPX.0000000000001139

PubMed | Web of Science ® | Google Scholar

71. Gupta D, Ehrlich JR, Newman-Casey PA, et al. Cost-related medication nonadherence in a nationally representative US population with self-reported glaucoma. Ophthalmol Glaucoma. 2021 Mar;4(2):126–130. doi: 10.1016/j.ogla.2020.08.010

PubMed | Google Scholar

72. Fea AM, Cattel F, Gandolfi S, et al. Cost-utility analysis of trabecular micro-bypass stents (TBS) in patients with mild-to-moderate open-angle glaucoma in Italy. BMC Health Serv Res. 2021 Aug 17;21(1):824. doi: 10.1186/s12913-021-06862-x

PubMed | Web of Science ® | Google Scholar

73. Iordanous Y, Kent JS, Hutnik CM, et al. Projected cost comparison of Trabectome, iStent, and endoscopic cyclophotocoagulation versus glaucoma medication in the Ontario health insurance plan. J Glaucoma. 2014 Feb;23(2):e112–8. doi: 10.1097/IJG.0b013e31829d9bc7

PubMed | Web of Science ® | Google Scholar

74. Lee PP, Walt JG, Doyle JJ, et al. A multicenter, retrospective pilot study of resource use and costs associated with severity of disease in glaucoma. Arch Ophthalmol. 2006 Jan;124(1):12–19. doi: 10.1001/archopht.124.1.12

PubMed | Web of Science ® | Google Scholar

75. Nelson P, Aspinall P, O'Brien C. Patients' perception of visual impairment in glaucoma: a pilot study. Br J Ophthalmol. 1999 May;83(5):546–552. doi: 10.1136/bjo.83.5.546

PubMed | Web of Science ® | Google Scholar

76. Chan EW, Chiang PP, Liao J, et al. Glaucoma and associated visual acuity and field loss significantly affect glaucoma-specific psychosocial functioning. Ophthalmology. 2015 Mar;122(3):494–501. doi: 10.1016/j.ophtha.2014.09.030

PubMed | Web of Science ® | Google Scholar

77. Skalicky SE, Goldberg I, McCluskey P. Ocular surface disease and quality of life in patients with glaucoma. Am J Ophthalmol. 2012 Jan;153(1):1–9 e2. doi: 10.1016/j.ajo.2011.05.033

PubMed | Web of Science ® | Google Scholar

78. Nordmann JP, Auzanneau N, Ricard S, et al. Vision related quality of life and topical glaucoma treatment side effects. Health Qual Life Outcomes. 2003 Dec 10;1(1):75. doi: 10.1186/1477-7525-1-75

PubMed | Google Scholar

79. Stalmans I, Lemij H, Clarke J, et al. Signs and symptoms of ocular surface disease: the reasons for patient dissatisfaction with glaucoma treatments. Clin Ophthalmol. 2020;14:3675–3680. doi: 10.2147/OPTH.S269586

PubMed | Web of Science ® | Google Scholar

80. Serbin M, Devine B, Campbell J, et al. Assessing health care burden in glaucoma patients with and without physical or mental comorbidities. J Manag Care Spec Pharm. 2020 Mar;26(3):325–331. doi: 10.18553/jmcp.2020.26.3.325

PubMed | Web of Science ® | Google Scholar

81. Pahljina C, Sarny S, Hoeflechner L, et al. Glaucoma medication and quality of life after phacoemulsification combined with a xen gel stent. J Clin Med. 2022 Jun 15;11(12):3450. doi: 10.3390/jcm11123450

PubMed | Web of Science ® | Google Scholar

82. Gazzard G, Konstantakopoulou E, Garway-Heath D, et al. Laser in glaucoma and ocular hypertension (LiGHT) trial: six-year results of primary selective laser trabeculoplasty versus eye drops for the treatment of glaucoma and ocular hypertension. Ophthalmology. 2023 Feb;130(2):139–151. doi: 10.1016/j.ophtha.2022.09.009

PubMed | Web of Science ® | Google Scholar

83. Stagg BC, Granger A, Guetterman TC, et al. The burden of caring for and treating glaucoma: the patient perspective. Ophthalmol Glaucoma. 2022 Jan;5(1):32–39. doi: 10.1016/j.ogla.2021.04.011

34. Sotimehin AE, Ramulu PY. Measuring disability in glaucoma. J Glaucoma. 2018 Nov;27(11):939–949. doi: 10.1097/IJG.0000000000001068
PubMed | Web of Science ® | Google Scholar

35. Jampel HD, Schwartz A, Pollack I, et al. Glaucoma patients' assessment of their visual function and quality of life. J Glaucoma. 2002 Apr;11(2):154–163. doi: 10.1097/00061198-200204000-00012
PubMed | Web of Science ® | Google Scholar

Published online: 5 Jul 2024

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