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ORIGINAL ARTICLE

Clinical recommendations for early identification of patients with open-angle glaucoma at higher risk of low adherence to topical treatment: An Italian Delphi consensus

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Abstract

Purpose: It is important for clinicians to identify patients with glaucoma at higher risk of poor adherence to topical therapy at an early stage to prescribe alternative treatments. An expert-based set of statements was developed to assist clinicians in the early identification of patients at high risk of low adherence and subsequent poorer clinical outcomes.

Methods: A two-step strategy was used. First, statements were developed by a panel of experts using data from a literature search as a starting point. Second, we measured agreement with the statements in a representative group of ophthalmologists managing patients affected by glaucoma.

Results: A total of 18 statements and consensus was reached for all. The available evidence and clinical experience have identified some subpopulations at high risk of poor adherence. These include young individuals with competing interests, being frequently away from home, multiple comorbidities and particularly when they affect joint function of the hands or cognitive abilities, being asymptomatic, and being poorly informed about the severity of the disease. The unavailability of caregivers and living alone seems to be relevant factors, particularly in older and more frail patients.

Conclusion: Taken together our results allow us to profile patients with glaucoma who will be more likely to show poor adherence to topical treatments. Moreover, the consensus statements can be used to identify patients who are unsuitable for topical drops and who would benefit more from alternative treatments.

KEYWORDS
adherence, consensus, Delphi, glaucoma, topical therapy

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1 | INTRODUCTION

Glaucoma is a leading cause of irreversible blindness worldwide, significantly affecting both individuals and healthcare systems (Tham et al., 2014). Glaucoma-related blindness has declined slightly over recent decades, mainly due to a better understanding of the disease and greater availability of effective treatments (GBD 2019, 2021), while there is less consensus regarding a parallel decline in disability. However, the total number of affected individuals continues to rise due to population ageing. The global prevalence of glaucoma among individuals aged 40–80 years is estimated to be around 3.54%, affecting ~76 million people in 2020, with projections of increasing to 111.8 million by 2040 (Sun et al., 2022). Glaucoma also causes a significant economic burden stemming from direct medical costs, indirect costs from lost productivity, and non-medical costs. The global costs are difficult to estimate, but with direct costs alone exceeding hundreds of millions of dollars annually (Rouland et al., 2005). In Italy, a real-world analysis of patients with glaucoma under treatment, hypertension (60.2%) and diabetes (17%) were common comorbidities; moreover, the mean annual costs per patient were estimated to be €1725, predominantly due to medications and hospitalisations (Perrone et al., 2023).

Topical medical therapy is the most common approach for the treatment of glaucoma. Standard of care is highly effective in reducing intraocular pressure (IOP) and controlling the progression of the disease (Bengtsson et al., 2022; Radcliffe et al., 2023). Topical therapies have been widely used despite a number of limitations, mainly the scarcity of viable alternatives other than surgery. In recent years, several novel therapeutic approaches have emerged. Less invasive surgical treatments are challenging the role of topical treatments, pushing towards a change in the therapeutic paradigm of the disease. Devices aimed at enhancing outflow have shown early promising results as well as sustained-release drug delivery devices and extraocular devices aimed at lowering IOP via other novel means (Abegao Pinto et al., 2023; Bicket et al., 2021; Chan et al., 2023; Lenzhofer et al., 2019).

This changing landscape poses new challenges to ophthalmologists. In particular, the timely identification of patients who are poorly suitable for topical treatments and thus at higher risk of disease progression is paramount, even if the prescription of topical medications has become a priority in clinical practice. The frequent coexistence of other ocular or extraocular pathological conditions increases the risk of adverse effects or inadequate administration of ocular drops; indeed, several studies have identified factors that can unfavourably influence the response to topical treatments such as side effects and poor adherence to prescribed schedules (Bedrood et al., 2023; Moore et al., 2023; Cordeiro, Denis, et al., 2024; Cordeiro, Gandolfi, et al., 2024). However, limits related to the inherent difficulty of studying an elusive problem like adherence, the poor generalisability of findings, and the use of inadequate methodologies have prevented a clear identification of the clinical profile of patients who may be candidates for alternative treatments, for example, not initiating with a topical IOP lowering treatment.

We produced an expert-based set of statements aiming to assist clinicians in the early identification of patients at high risk of low adherence and subsequent poorer clinical outcomes. To meet this purpose, we chose a two-step strategy. First, we conducted a systematic initiative to develop and measure consent among a panel of experts; second, we obtained agreement among a large and representative group of ophthalmologists routinely involved in the care of patients affected by glaucoma.

2 | MATERIALS AND METHODS

2.1 | Organising committee

This project was prompted and developed by an Organising Committee (OC), composed of MF, RC, and SG. In January 2024, the OC established a group of nine ophthalmologists with recognised experience in the field of research and clinical care for patients with glaucoma. Two methodologists (GP, Alessia Ferrarini) with specific expertise in designing and conducting consensus initiatives were also enrolled for support. For this project, a systematic approach, mainly based on the Delphi technique, was used as recommended by the National Institutes of Health in 2009 (National Institutes of Health, 2009) and by the analogous Italian National System for Guidelines, with specific adaptation to the topic of interest (McMillan et al., 2016).

2.2 | Phase 1: Definition of the problem, questions, literature search, and appraisal

The OC identified three areas of interest: (1) Definition, measure, and clinical impact of low adherence to topical treatment; (2) Identification of the most relevant risk factors for low adherence, to identify adult patients who might not benefit from topical treatment; (3) Identification of factors other than low adherence that would be useful to profile an adult patient who is unsuitable for topical therapy. For each area, the expert panel defined specific clinical and organisational scenarios with related questions. This was carried out through discussion during a structured face-to-face meeting, where the results of a preliminary search of the literature were compared with personal experience and values (EPICOT+ method (Brown et al., 2006)). A final list of 18 questions was produced and approved. Thereafter, an extended search of the literature was carried out in order to assess the current state of evidence on the topic. PubMed was searched using the following search strings: a. ('Medication Adherence'[Mesh]) AND ('Glaucoma/therapy'[Mesh]); b. 'Glaucoma, Open-Angle/therapy'[Mesh] AND 'ocular surface'; c. ('Glaucoma, Open-Angle/therapy'[Mesh]) AND 'Administration, Ophthalmic'[Mesh]; d. ('Glaucoma, Open-Angle/drug therapy'[Mesh]) AND 'Contraindications'[Mesh]; e. ('Corneal Diseases'[Mesh] OR 'ocular surface') AND 'Glaucoma' AND topical.

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No limits were used. The same searches were repeated without using 'Mesh' to overcome limits linked to a still incomplete indexing procedure. Furthermore, a manual search was performed through the references of selected articles. The date of last update was April 30, 2024. Retrieved papers were evaluated for congruity and quality. Studies reporting pertinent clinical outcomes were selected for critical appraisal, data extraction, and level of evidence. Two blind and independent methodologists assessed the level of evidence according to the GRADE method (Balshem et al., 2011) and produced an evidence summary for each question.

2.3 | Phase 2: Statements, consensus development, and measure

Evidence reports and the approved questions were submitted to the expert panel via a dedicated web platform (https://italianglaucomaconsensus.it/). Each participant proposed one statement for each question, together with notes and comments where appropriate. The statements were collected, compared, and harmonised together with the OC, setting up a preliminary list, which was submitted to a first Delphi round to determine the extent of agreement within the panel along with further suggestions. After multiple integrations and modifications, the statements were submitted to two additional Delphi rounds. Voting procedures were managed through a dedicated web platform, providing complete protection of privacy. The GRADE Method was followed to build absentee ballots, count expert votes, and attribute strength to statements.

Specifically, a scale ranging from 1 (no agreement) to 9 (strong agreement) was used. Interquartile ranges (IQR) and medians (M) were calculated to assess the level of agreement. A statement was defined as characterised by:

'Strong agreement' if the median was ≥8 and the lower level of the IQR was >5
'Weak agreement' if the median was 6 or 7 and the lower boundary of the IQR was ≥5
'Disagreement' if the median was <5 and the upper boundary of IQR was ≤5
'Uncertain' in the remaining situations (median = 5; median >5 but lower quartile <5; median <5 but upper quartile >5)

The percentage of 'Strong Agreement' was also calculated. The list of the 18 approved statements was debated in a web meeting (June 2024) through a structured discussion to refine wording and gather any comments.

2.4 | Phase 3: External review and comparison with clinical experience

A group of 26 clinicians, experienced in managing patients with glaucoma and coming from diverse work settings and different geographic areas of Italy, convened in October 2024 at a meeting without the participation of the 11 expert ophthalmologists involved in Phase 1 and Phase 2. After detailed presentations and thorough discussion, each clinician anonymously voted their agreement on each statement using the semi-quantitative 1–9 scale described above. The percentage of agreement, defined as assigning a score of 6 or higher was calculated. A predefined threshold of 75% for sufficient agreement was set. Suggestions, proposals for integration, comments, and criticisms were also collected and are reported herein when relevant. The reviewing clinicians were not aware of the identity of the experts who had participated in the previous phases.

3 | RESULTS

The extensive search of the literature, followed by careful manual screening of 1080 retrieved articles, identified 51 papers pertinent to the 18 questions that were drafted (Table 1). The search algorithm is detailed in Figure S1. Table S1 shows the evidence reports summarising the main characteristics, results, methodological comments, and level of evidence of the studies included. The discussion within the panel of the reviewing clinicians showed some areas of discordance, particularly regarding demographic risk factors. Their observations are integrated in the 'comments' paragraphs below. Substantial agreement was registered for most of the statements as shown by comparing the votes of the expert panel with those of the reviewing clinicians (Figure 1). For each of the topics and similar groups of statements, the evidence background is summarised followed by relevant discussion among the reviewing clinicians.

3.1 | General principles

3.1.1 | Statements 1–4: General principles on adherence

Evidence background

A number of clinical trials have investigated the relationship between adherence to prescribed topical medications and/or insufficient drop instillation technique and visual worsening or disease progression; at least five studies have found some correlation (Newman-Casey et al., 2020; Rajurkar et al., 2018; Rossi et al., 2011; Shu et al., 2021; Sleath et al., 2011). However, most of these studies are affected by the risk of bias, although the magnitude of the effect is uncertain. A reasonable estimate has been provided by Shu et al. (2021), given that a linear dose-effect between poor adherence and disease progression is biologically plausible.

No studies were identified that established a definite threshold to consider a patient 'non-adherent'. Investigations on the impact of low adherence on visual defect and/or disease progression concluded that: (1) missing more than one-third of scheduled instillations correlates with a higher risk of disease progression (Newman-Casey et al., 2020); (2) adherence to treatment >80%–90% predicts disease progression that is similar to fully compliant patients (Rossi et al., 2011; Sleath et al., 2011). However, this group of experts considered

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TABLE 1 Statements and results of expert voting.

#	Statement	Median	IQ25%	%SA	GRADE	LoE
General principles						
1	In patients affected by open-angle glaucoma, scarce adherence to topical therapy increases the risk of disease progression	8	8	83.3	SA	HIGH
2	The expert panel could not establish a definite threshold for low adherence	8	8	83.3	SA	LOW 2-
3	In patients affected by open-angle glaucoma, there is no validated method to assess adherence and compliance to topical treatments in routine practice	8	7.75	75	SA	MODERATE 1-
4	The prevalence of low adherence to topical treatments is hard to estimate due to lack of robust data	8	8	91.7	SA	MODERATE 1-
Factors affecting adherence to medication						
5	In patients affected by open-angle glaucoma, younger age is an independent risk factor for low adherence	8	6.5	58.3	SA	MODERATE
6	In the subset of the more dynamic, younger aged patients affected by open-angle glaucoma, especially with recent diagnosis and non-advanced disease, being away from home and travelling may be considered as risk factors for suboptimal adherence	8	7	66.7	SA	MODERATE 1-
7	In patients affected by open-angle glaucoma, weak evidence suggest that male sex is a risk factor for low adherence to topical treatments	8	6	66.6	SA	MODERATE 2-
8	In patients affected by open-angle glaucoma, a lower level of education is a risk factor for low adherence to topical treatments	8	7	58.3	SA	MODERATE
9	Patients with more severe disease and worse visual acuity tend to be more compliant with topical treatments but may suffer from higher risk of having an inadequate instillation technique	8	8	83.3	SA	MODERATE 2-
10	In patients affected by open-angle glaucoma, asymptomatic may induce the patient to underestimate the progressive nature and the risk of blindness and therefore to be less careful and less adherent to topical treatments	8	8	83.3	SA	LOW 1-
11	Patients affected by open-angle glaucoma and well aware of disease severity have a lower risk of poor adherence to topical treatment	8	7	66.6	SA	MODERATE 1-
12	In patients affected by open-angle glaucoma, upper extremity functional disorders or of any disease impairing hand function/ability/coordination are a risk factor for low adherence, impairing the ability of correctly performing drop instillations	8	8	91.7	SA	MODERATE
13	In patients affected by open-angle glaucoma, cognitive impairment can be considered a risk factor for non-adherence if the patient is not adequately supported by caregivers. Psychiatric disorders such as anxiety or depression may have variable effects on adherence to therapy and should be evaluated at the individual level	8	7.75	75	SA	MODERATE 1-
14	In patients affected by open-angle glaucoma, concomitant systemic morbidities represent a potential risk factor for low adherence. It is difficult to exactly assess the magnitude of multi-morbidity impact on adherence due to inconsistencies in literature data	8	7.75	75	SA	MODERATE 1-
15	In patients affected by open-angle glaucoma receiving topical treatments, multiple doses per day and/or complex medication schemes (e.g. different drugs or different hours of instillation in the two eyes) are strong risk factors for non-adherence	8.5	8	91.7	SA	HIGH
16	The relationship between side effects of topical therapy and low adherence in patients affected by open-angle glaucoma is uncertain, it is influenced by many confounding covariates, and is hard to estimate	8	7.75	75	SA	LOW 2-

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TABLE 1 (Continued)

#	Statement	Median	IQ25%	%SA	GRADE	LoE
17	In patients affected by open-angle glaucoma, emotional support, physical ability to administer treatment, and psychological well-being, which can be influenced by marital status and the presence of caregivers, may play a significant role in medication adherence	8	7.75	75	SA	LOW 2-
Other factors making patients unsuitable for topical treatments						
18	Patients with unfavourable ocular surface disease or experiencing adverse events to drops that have a negative impact on their quality of life should be considered unsuitable for topical treatment	8	8	83.3	SA	MODERATE

Abbreviations: LoE, level of evidence; IQ, interquartile range; SA, strong agreement.

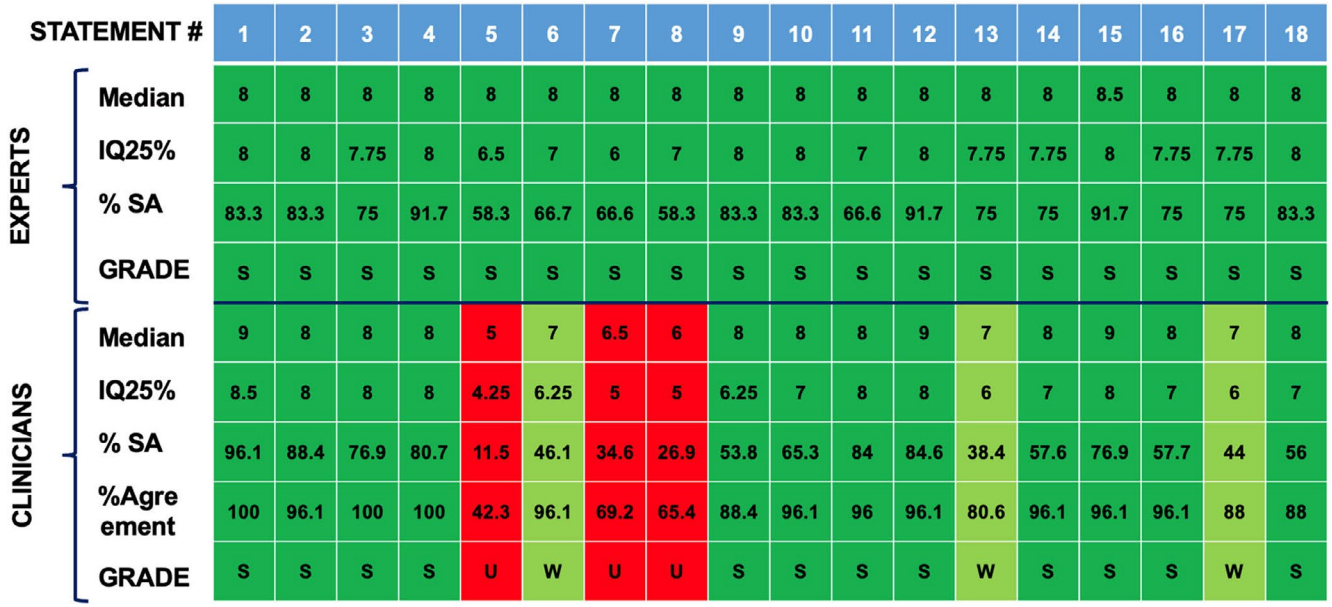

FIGURE 1 Comparison of agreement between experts and clinicians on the 18 statements. IQ, interquartile range; S, strong agreement (dark green); SA, strong agreement; U, uncertain (red); W, weak agreement (green).

'good adherence' as 'at least one drop in the eye' at every scheduled dose.

Statements 3 and 4 utilise data from a recent systematic review analysing 62 clinical studies (Bott et al., 2024). Regarding statement 3, the following items were highlighted: (1) methods to assess adherence have been generally borrowed from other diseases; (2) lack of a gold standard prevents the establishment of accurate measures for the methods adopted; (3) subjective tools (i.e. self-administered questionnaires) are more appropriate for routine practice as they are more straightforward and inexpensive. However, such questionnaires are affected by higher variability in comparison to objective methods. Whether subjective methods lean more towards under- or overestimating low adherence is unclear; (3) few studies have directly compared the accuracy of different methods to assess adherence, with conflicting results. Moreover, studies focusing on the reliability of objective methods, such as pharmacy claims, showed specific sources of vulnerability (i.e. sampling) (Friedman et al., 2007). Many obstacles hamper the reliability of global adherence estimates. In particular, the data reported on global adherence are wildly variable (29%–100%) and sensitive to the method used for assessment. In addition, other factors, such as different study designs, different definitions of adherence to medication, and the different thresholds used to quantify adherence contribute to the scarce comparability across studies.

Comments

There was little doubt among the panel of experts regarding the relevance of good adherence in achieving the results expected from topical treatments. Biological plausibility and clinical experience strongly support the statements. On the other hand, solid evidence confirms the effectiveness and considerable impact on prognosis of topical therapy when administered correctly. Thus, any failure in following the scheduled doses of prescribed medications is likely a determinant of an increased risk of accelerated and significant visual loss, with the magnitude of the effect influenced by the level of adherence.

Although some authors suggest that a threshold for defining a patient as 'not adherent' should be set between 20% and 30% of missed ocular drops, the expert

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panel agreed that establishing any arbitrary threshold value could pose more risks than benefits. Patients or physicians, indeed, could interpret this as a sort of 'range of tolerance', while only full adherence must be set as a desirable target. Although it is a shared belief that being able to measure treatment adherence in patients with glaucoma would be of importance, data from literature and experience have not yet identified a specific method that has sufficient reliability and feasibility. However, a suspicion of low adherence should arise whenever the clinician detects a worsening in visual function despite measuring normal IOP.

3.2 | Factors affecting adherence to medication

3.2.1 | Statements 5 and 6: Risk of adherence and younger age

Evidence background

Most of the studies retrieved report that younger patients are more prone to be non-adherent to topical glaucoma medication (Barr et al., 2023; Cohen Castel et al., 2014; Cook et al., 2015; Dreer et al., 2012; Frech et al., 2018; Miller et al., 2022; Newman-Casey, Blachley, et al., 2015; Newman-Casey, Robin, et al., 2015; Oltramari et al., 2024; Rees et al., 2010; Sleath et al., 2011; Slota et al., 2015; Tse et al., 2016; Vandenbroeck et al., 2011; Zhu et al., 2019). However, obstacles in establishing adherence, heterogeneity of thresholds, and inconsistencies in the results limit the strength of the evidence. Few studies have directly addressed the relationship between travelling away from home or other competing activities and adherence to glaucoma treatment (Friedman et al., 2008; Rajurkar et al., 2018; Schwartz et al., 2009). Nonetheless, a fair concordance emerged among the experts.

Comments

Literature data supports the idea that young patients tend to be less compliant with the prescribed schedules of treatment. However, clinical experience leads to a partial disagreement with this view. In fact, factors related to lifestyle and the presence of specific competing activities, such as frequent travel away from home or shift work, appear to have a greater impact than age itself in determining the risk of poor adherence. Moreover, specific subpopulations of young patients, such as those affected by familial, more severe forms of disease, or adolescents under strict parental supervision, are often more concerned about the disease and thus adherence to prescribed treatments may be better.

3.2.2 | Statement 7: Male sex as a risk factor

Evidence background

Weak evidence supports the claim that male patients are less adherent than females. Studies on this topic, even if characterised by a prospective design, suffer from several flaws that are mainly linked to inaccurate measures of adherence, presence of multiple confounding factors, inadequate statistical analysis, and small sample size. Most studies failed to find any significant correlation between sex and adherence (Owen et al., 2009; Sleath et al., 2011; Newman-Casey, Blachley, et al., 2015; Newman-Casey, Robin, et al., 2015; Frech et al., 2018; Miller et al., 2022; Oltramari et al., 2024), while some seem to suggest a higher risk in males (Barr et al., 2023; Vandenbroeck et al., 2011; Zhu et al., 2019).

Comments

Conflicting evidence and inhomogeneity in clinical experiences led to a high level of uncertainty among the expert panel and clinicians. However, the final statement reflects the low grade of confidence on the relevance of sex as a significant risk factor.

3.2.3 | Statement 8: Lower level of education as a risk factor

Evidence background

Studies have consistently found a tendency towards better adherence to topical medications in patients with a higher educational level (Cook et al., 2015; Oltramari et al., 2024; Salman et al., 2020; Slota et al., 2015). Self-assessed adherence did not differ between high or low levels of education in only one report (Newman-Casey, Blachley, et al., 2015; Newman-Casey, Robin, et al., 2015). However, the lack of control over possible confounders and the heterogeneity in the definition of low adherence weaken the reliability of the results.

Comments

Most of the experts agreed that patients with a higher level of education are more proactive in discussing the aims and practical aspects of prescribed therapies and they are, in general, willing to adhere closely to prescribed regimens. However, some panellists pointed out that high levels of education frequently correlate with high socio-economic status. This can act as a confounding factor, especially in observational research conducted within healthcare systems that do not allow cost-free access to drugs. On the other hand, clinical experience favours the opinion that cultural and/or linguistic barriers are more relevant than educational status. It is likely that the level of education may play a different role in different settings. Persons with higher educational status may place greater trust in highly specialised centres for a second opinion.

3.2.4 | Statements 9, 10, 11: Compliance and severity of severe disease and visual function, being asymptomatic, and awareness of disease severity

Evidence background

A number of studies investigating the relationship between low visual function at baseline and/or glaucoma severity and both low adherence and poor instillation

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techniques have been conducted, but with somewhat conflicting results. Shu et al. (2021) conducted a large prospective study in a strictly controlled healthcare system, allowing a more precise estimation of drug adherence at the individual level. In that study, good adherence to treatment, between 80 and 100% of scheduled doses, was low in general, but significantly better in patients affected by more severe loss of visual function, ranging from 43.7% in those with mild visual impairment to 59.3% in patients with a very severe form of disease. However, control for covariates was incomplete and differences in societal structure and the healthcare system raise concerns about the transferability of the results. Notwithstanding, studies with smaller sample sizes have confirmed those results (Sleath et al., 2011; Ung et al., 2013). Additionally, lower visual function predicts an inappropriate instillation technique (Hennessy et al., 2011; Newman-Casey et al., 2020; Tanito et al., 2023; Windham et al., 2005).

Very few studies have directly shown a relationship between adherence and asymptomatic status, although studies have consistently highlighted a relationship between disease awareness or fear and adherence to medication (Stringham et al., 2018). Three studies (Mansouri et al., 2011; Rees et al., 2010; Salman et al., 2020) showed that the willingness to be compliant with prescribed schedules increases proportionally to knowledge and/or fear of the disease, similarly to that reported for other diseases (Lim et al., 2013). However, intentional compliance is only one component of adherence, which could also be affected by the use of inappropriate instillation techniques or drug unavailability.

Comments

The expert panel agreed that poor visual function up to a certain level may prompt higher adherence. However, more compromised visual function may become a limitation and result in poorer adherence. Clinical experience highlights the fundamental role played by effective caregivers, who can limit the adverse effects of poor visual function on the instillation technique. Furthermore, it is worth underlining the relevance of a good relationship between ophthalmologists and patients. Constant communication can increase patient awareness and knowledge. As clearly highlighted by the group of clinicians, subjective perception of the amount of visual loss, especially if it is associated with the perception of worsening visual function over time, seems to carry much more weight than the loss of visual function measured objectively. However, it is a common belief that the frequent asymptomatic nature of some forms of mild, initial glaucoma, together with individual psychological characteristics, is a factor that increases the risk of scarce adherence to topical treatments.

3.2.5 | Statement 12: Upper extremity functional disorders and impairment of hand function

Evidence background

While almost all narrative reviews point out the relevance of impaired dexterity due to neurological or musculoskeletal diseases on the use of a correct and effective technique for instillation of ocular drops, few publications have directly addressed this topic. A large observational study reported that people with limb disability had a probability of medication adherence that was 17.60 [95% CI: 8.90–26.30 $p<0.001$] percentage points lower than those without disability (Hou & Pu, 2021). Although further smaller studies confirm this relationship (Hein et al., 2019; Tanito et al., 2023), the limited number of publications prevents reaching definite conclusions regarding a specific correlation between disabling conditions and an incorrect technique of administering ocular drops.

Comments

The expert panel largely agreed that disabilities impairing upper limb function would be an obstacle to correct ocular drop administration and lead to poor adherence to topical treatment. The availability of caregivers can attenuate such a problem which does not seem manageable without adequate help, and improvement of the ergonomic design of eyedrop bottles/dispensers would be desirable.

3.2.6 | Statement 13: Cognitive impairment as a risk factor

Evidence background

A large study showed a clear impact of cognitive dysfunction on adherence to medication in patients with glaucoma (Hou & Pu, 2021). In particular, the probability of adherence using a strict definition decreased by ~1.40 (95% CI: −2.30 to −0.60; $p<0.001$) percentage points compared with those without disability. Other studies (Hollo et al., 2009; Lim et al., 2013; Stringham et al., 2018; Tanito et al., 2023) have confirmed the role played by dementia and psychiatric disorders. The inconsistency noted across studies (e.g. the negative results in the large study by Newman-Casey, Blachley, et al. (2015) and Newman-Casey, Robin, et al. (2015)) is likely due to differences in criteria to define non-adherence, small sample sizes, and confounding factors, as well as variations in the availability of caregivers. It is noteworthy that mental and psychiatric disorders also seem to increase the global burden and expenditures related to glaucoma (Serbin et al., 2020).

Comments

Cognitive deterioration is one of the most prevalent disorders affecting adherence to prescribed treatments that emerged from clinical experience. The presence of valid home support is highly relevant in lessening the consequences of mental disorders. However, the worsening of neurological disease appears to decrease the correct administration of scheduled therapy in most cases. The impact of psychiatric disorders such as depression and anxiety is more unpredictable. Anxious individuals may show strong (or even exaggerated) concern for their own health status, leading to high adherence, while profound depression is more often associated with apathy and unselfishness.

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3.2.7 | Statement 14: Concomitant systemic morbidities as risk factors

Evidence background

Few studies have directly addressed the relationship between the number of comorbidities and adherence to medication in patients with open-angle glaucoma. However, in the largest study, patients who had three or more severe diseases in addition to glaucoma had 6.1% less (OR = 0.94, p-value = 0.03) adherence compared with those without comorbidities (Frech et al., 2018). This prospective study on a European population was well conducted; its main limitation is the use of a restricted definition of adherence, based on the filling of prescriptions for topical drops in pharmacies over 1 year. Similar results emerged from a smaller African cohort (Kyei et al., 2023) as well as in a recent Italian cohort of patients under polypharmacotherapy (Novella et al., 2025), while in a study exploring a large cohort of Australian patients (Zhu et al., 2019), multivariate analysis did not confirm the association seen in univariate analysis. Differences in the methods used to assess adherence and in the numbers and types of covariates included in the analysis may be at the basis of these inconsistencies.

Comments

The expert panel was in agreement with the increased risk of non-adherence characterising multi-morbid patients. Clinical experience seemed to agree with the opinions reported in multiple narrative reviews from different authors. People affected by several chronic diseases and taking many different drugs should be treated for glaucoma with the simplest protocol.

3.2.8 | Statement 15: Multiple doses per day and/or complex medication schemes of topical treatments

Evidence background

The large majority of studies addressing this topic found a clear relationship between the complexity of the administration schedule and poorer adherence to topical medications in patients with glaucoma (Dreer et al., 2012; Jiang et al., 2017; Newman-Casey, Blachley, et al., 2015; Newman-Casey, Robin, et al., 2015; Robin et al., 2007; Santos et al., 2016; Tsai, 2009). Most narrative reviews underline the role played by the number of doses prescribed per day as a risk factor for non-adherence (Cordeiro, Denis, et al., 2024; Cordeiro, Gandolfi, et al., 2024).

Comments

A higher number of daily doses, different times of instillations, or different drugs in the two eyes are elements that mostly contribute to the complexity of prescription schedules of topical drugs for glaucoma. The expert panel agreed that such factors should be avoided if possible, especially in patients at risk of non-adherence.

3.2.9 | Statement 16: Side effects of topical therapy as a barrier to adherence

Evidence background

Occurrence of ocular discomfort or side effects associated with topical treatments may be factors that correlate with low adherence. The large number of potential confounding covariates, rarely controlled by adequate statistical techniques, makes it difficult or impossible to identify a single factor (e.g. onset of side effects) on outcomes in most studies (Al-Nuaimi et al., 2015; Dreer et al., 2012; Gatwood et al., 2022; Munoz-Villegas et al., 2023; Oltramari et al., 2024; Rajurkar et al., 2018; Schwartz et al., 2009).

Comments

It is intuitive that the onset of significant adverse effects can lead to a change in therapeutic strategy or even to a complete cessation of ongoing topical treatments, either spontaneously or following the specialist's advice. Patients experiencing side effects are more likely to report the problem to their ophthalmologist rather than autonomously discontinue the treatment. The prevalence of this problem in clinical practice seems quite low and strongly correlates with other covariates discussed above (age, comorbidities, mood disorders, etc.). The clinicians pointed out the importance of comprehensive patient information about possible adverse effects and their management to prevent poor adherence.

3.2.10 | Statement 17: Marital status as a risk factor

Evidence background

Some studies, mainly small, retrospective or cross-sectional, have directly addressed with conflicting results the relationship between marital status and/or living alone and/or the presence of a caregiver with low adherence to glaucoma treatment. Some showed a correlation (Barker et al., 2015; Newman-Casey et al., 2020), but others did not confirm it (Gurwitz et al., 1993; Oltramari et al., 2024; Rajurkar et al., 2018; Ramesh et al., 2021). However, most assert that while direct evidence linking marital status and caregiver availability to adherence in patients with glaucoma is lacking, many observations imply that emotional support, physical ability to administer treatment, and psychological well-being, which can all be influenced by marital status and the presence of a caregiver, play a significant role in adherence to medications.

Comments

In agreement with the literature, the expert panel concurred that marital status poorly correlates with the risk of non-adherence to topical treatments. As mentioned above, however, the availability of an effective caregiver can attenuate the negative impact of many of the pathological conditions affecting good adherence. Therefore, the influence of living alone on the suitability for a

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long-term topical treatment needs to be evaluated on an individual basis.

3.3 | Other factors making patients unsuitable for topical treatments

3.3.1 | Statement 18: Unfavourable ocular surface disease or adverse events to ocular drops

Evidence background

Presence of ocular surface disease or worsening of related symptoms has been found to strongly correlate with the use of topical treatments for glaucoma (Kahook et al., 2024; Konstas et al., 2021; Parkkari et al., 2022; Woo et al., 2021). The use of drops with preservatives, longer treatment duration, and older age are the most important predictive factors (Perez-Bartolome et al., 2017). The onset or worsening of corneal discomfort or dry eyes can induce disaffection to treatment in patients with glaucoma (Zhu et al., 2019).

Comments

In clinical practice, paying attention to ocular surface status is important. It is straightforward that patients with higher degrees of ocular surface disease will experience problems with topical treatments and will more often have poor adherence to medication. Such behaviour is worsened by the fact that devices containing preservative-free ocular drops are often less user-friendly. Due to the impact of reduced quality of life related to topical therapy in these patients, the claim that different therapeutic strategies should be considered is acceptable.

4 | DISCUSSION

In the evolving landscape of the treatment of open-angle glaucoma, it is important for clinicians to be able to identify patients at higher risk of poor adherence to topical therapy at an early stage. This is particularly relevant given the availability of new alternatives to ocular drops. Insufficient adherence to treatment, related to both poor compliance with a prescribed schedule as well as to ineffective instillation technique along with the presence of ocular surface disease, has been identified as the main factors to consider. Unfortunately, clinical research has not yet provided precise, reliable, and consistent information on risk factors for low adherence. Such inconsistencies seem related to differences in the criteria and tools used to define and measure patient adherence, and to heterogeneities in ethnic and social structure and healthcare organisation of the population investigated. Differences in study design, number, and types of covariates included in statistical models, and other methodological issues are also at the basis of these inconsistencies.

The weakness of the available evidence reinforces the value of consensus-building processes among clinicians. The transparent balancing between the available evidence and the clinical experience of these experts allowed them to reach a strong agreement on a significant number of statements. As supported by published data the experts agreed that suboptimal adherence to topical treatment correlates with an increased risk of disease progression and loss of visual function although in a non-predictable pattern. It was also agreed that a patient whose glaucoma is worsening without any evident clinical cause should suggest the need to accurately investigate factors affecting compliance and effective instillation of ocular drops. The experts considered that in general, setting a quantitative threshold for defining treatment adherence as acceptable would not be applicable nor effective and deemed that the variety of objective and subjective evaluation methods proposed in the literature as not practical in a real-world context.

Both the available evidence and clinical experience have identified some subpopulations at high risk of poor adherence. In particular, young individuals with competing interests, being frequently away from home, multiple comorbidities and particularly when they affect joint function of the hands or cognitive abilities, being asymptomatic, being poorly informed thus underestimating the severity of the disease may be more frequently associated with non-adherence. Moreover, the unavailability of caregivers and living alone seem to be relevant factors, particularly in older and more frail patients. In such cases, adopting the simplest schedule of administration and exploring alternatives to topical therapy appear reasonable.

Few doubts were raised by the panellists about the importance of ocular surface disease in identifying patients who are less suitable for topical therapies. Ocular surface disease is an umbrella term that encompasses dry eye disease, eyelid, and corneal and conjunctival diseases. The prevalence of ocular surface disease is quite high in the general population (up to 30%), but is even more frequent in patients affected by glaucoma receiving topical treatments (Kahook et al., 2024). Pre-existent alterations in the ocular surface strongly correlate with the onset of symptoms related to topical drugs, and often deeply affect the quality of life.

The ability to compare expert opinions with clinical experiences coming from a large group of ophthalmologists is a strong point of the present consensus exercise. Few areas of uncertainty remained about the relevance of demographic variables such as age and sex as independent risk factors. Competing activities and specific work-related issues appear to be more relevant than age per se. Similarly, factors like psychological and emotional status and living alone may play a pivotal role. Cultural and/or linguistic differences and levels of income were also judged to be more relevant barriers.

Taken together our results allow us to profile patients with glaucoma who will be more likely to show poor adherence to topical treatments. Moreover, the consensus statements can be used to identify patients who are unsuitable for topical drops and who would benefit more from alternative treatments. The major strength of this project is the use of a systematic approach to integrate different experiences and to compare consensus with the published evidence. A major weakness of our work

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lies in the choice not to conduct a truly systematic review of the literature for each question, restricting the search only to PubMed. A systematic research approach is undoubtedly essential for systematic reviews, meta-analyses, or evidence-based guidelines. However, for consensus initiatives, such as those from scientific associations, systematic reviews may be included but are not always necessary, especially when general questions concerning definitions, risk factors or prognosis are taken. Indeed, it is unlikely that the addition of one or a few studies published in minor, non-Medline indexed journals, would significantly influence expert opinion. Another limitation arises from the difficulties encountered in summarising and extracting useful data from a heterogeneous body of evidence with frequent contradictory results.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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