Persistence with medical glaucoma therapy in newly diagnosed patients

Joana Menino [1], Pedro Camacho [1, 2, 3] and Andre Coelho [1]

[1] H&TRC- Health and Technology Research Center, ESTeSL- Escola Superior de Tecnologia da Saude, Instituto Politecnico de Lisboa, Lisbon, Portugal
[2] iNOVA4Health, NOVA Medical School, Faculdade de Ciencias Medicas, NMS, FCM, Universidade NOVA de Lisboa; Lisbon, Portugal
[3] Instituto de Oftalmologia Dr. Gama Pinto, Lisbon, Portugal

ABSTRACT

Background: Monotherapy, age, and side effects are significant risk factors for the discontinuation of antiglaucoma therapy. Long-term therapy persistence is crucial for slowing disease progression and preventing irreversible blindness. Therefore, it is essential to identify patients at higher risk of discontinuation. In this study, we aimed to evaluate the real-world persistence of antiglaucoma therapy in patients diagnosed with glaucoma in the primary healthcare units of the Lisbon and Tagus Valley regions.

Methods: We conducted a retrospective longitudinal study by collecting data from the prescription records of new antiglaucoma drug users diagnosed with glaucoma between 2012 and 2013 in the Primary Health Care Units of the Lisbon and Tagus Valley Region. These patients were followed over 3 years. Therapy persistence was measured as the proportion of patients remaining on any antiglaucoma drug, regardless of any modifications or switching of drugs over time. Persistence was assessed at three time points: the end of the first, second, and third years of the observation period.

Results: A total of 2138 patients treated using new antiglaucoma drugs (867 [40.6%] male patients; 1271 [59.4%] female patients) were included in the study. Over the observation period, the overall persistence rate decreased from 91.9% (n = 1965) in the first year to 67.3% (n = 1439) in the third year. Older patients (≥ 65 years) showed higher persistence rates, although there was a decrease over the 3-year follow-up period (from 1481 [92.7%] to 1124 [70.4%]). Additionally, participants initially treated with monotherapy showed higher persistence rates, ranging from 92.4% (n = 1186) in the first year to 70.2% (n = 901) in the third year.

Conclusions: The findings highlight the importance of patient follow-up over time, as almost one in three new antiglaucoma therapy users completely discontinued treatment, potentially risking disease progression. This could be mitigated with proper use of these drugs. Further studies should utilize recent health information systems to explore the impact of medication adherence and persistence on the functional and structural outcomes in patients with glaucoma.

KEYWORDS
glaucoma, anti-glaucoma therapy, drug persistence, therapy persistence, drug discontinuation, medication non-adherence

Correspondence: Joana Menino, H&TRC- Health & Technology Research Center, ESTeSL- Escola Superior de Tecnologia da Saude, Instituto Politecnico de Lisboa, Lisbon 1990-096, Portugal. Email: joanamenino24@gmail.com ORCID iD: https://orcid.org/0000-0001-7685-6735

INTRODUCTION

Recent global estimates suggest that 68.58 million people are affected by primary open-angle glaucoma (POAG), highlighting the urgent need for attention to this health issue [1]. The asymptomatic, progressive, and neurodegenerative characteristics of POAG result in retinal structural loss and typical functional impairments, making it a leading cause of irreversible blindness [2-4]. First-line treatment with eye drops is crucial for controlling intraocular pressure (IOP), a modifiable risk factor that can slow disease progression [5]. Studies have shown that medication adherence is associated with a slower rate of visual field loss [3]. Additionally, educational interventions have improved eye drop instillation techniques [6].

Despite the fundamental importance of consistent use of antiglaucoma drugs to control IOP and prevent disease progression and exacerbations [7], both adherence to and persistence with these medications are low worldwide [8-11]. Adherence refers to the degree to which a patient follows treatment instructions over a specific period, while persistence refers to the duration from treatment initiation to discontinuation [12, 13]. These components of medication-taking behavior are distinct and should be measured separately [13]. In chronic diseases like glaucoma, up to half of the patients discontinue their medications within the first few months of starting therapy. We previously reported that in Portugal, approximately 39.7% of patients either did not initiate glaucoma treatment or discontinued it shortly after diagnosis [8]. In European countries, persistence rates range from 69% to 84%, with an average duration of therapy ranging from 10.8 to 21.8 months [14].

While electronic records for medication adherence evaluation do not fully elucidate why patients discontinue therapy [15], they can be used to identify those who have stopped treatment. Factors such as therapeutic regimen, age, and side effects have been identified as significant risk factors for discontinuation of antiglaucoma therapy [16]. Variability in persistence rates may reflect differences in education, forgetfulness, tolerability, and medication costs [17]. In this study, we aimed to evaluate the real-world persistence of antiglaucoma therapy in patients with glaucoma. Given the tendency for therapy use to decrease over time, we assessed therapy persistence at the end of 1, 2, and 3 years after treatment initiation.

METHODS

We conducted a retrospective longitudinal study involving the data collection and follow-up of participants diagnosed with glaucoma over a past period. This study received approval from the ethics committees of the Lisbon and Tagus Valley Health Administration (CE-ARSLVT-647/CES/2020) and the Lisbon School of Health Technology (CE-ESTeSL-Nº58-2019).

Prescription data were obtained from the Regional Health Administration Information System (SIARS) of Lisbon and the Tagus Valley, which contains electronic prescriptions of antiglaucoma drugs classified according to the Anatomical Therapeutic Chemical (ATC) Classification System. Data were collected over 36 months for each participant. This automated system includes information on diagnoses made according to the International Classification for Primary Care, 2nd version (ICPC-2) [18], recorded within the primary healthcare (PHC) network, along with patient demographics and administrative data. The methodology and types of data retrieved from SIARS have been described previously [8, 9].

The study population consisted of adult patients (aged ≥18 years) who were newly diagnosed with glaucoma (ICPC-2 code F93) in PHC units in the region of Lisbon and Tagus Valley between January 1, 2012, and December 31, 2013. Patients who discontinued therapy early during this period [8] were excluded from the study. We determined therapy persistence, defined as the proportion of patients remaining on any antiglaucoma drug despite any modifications or switches in medication over time [13]. Persistence was evaluated as a dichotomous outcome (yes or no) at the end of the first, second, and third years of the observation period.

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). We compared persistence across various patient characteristics, such as gender and age, and drug characteristics, including whether the drug was generic or brand name, its strength, pharmaceutical form, presentation (package size), and the number of packages prescribed. Comparisons were made using the chi-square test or Fisher's exact test, as appropriate. A P-value of <0.05 was considered statistically significant.

RESULTS

A total of 2138 new patients treated with antiglaucoma drugs (867 [40.6%] male patients; 1271 [59.4%] female patients) were participated in this study. The majority of participants were aged 65 years or older (n = 1597; 74.7%). Monotherapy was the initial treatment for 1283 (60.0%) participants (495 [57.1%] male patients and 788 [62.0%] female patients) ($P < 0.05$). A substantial majority of participants (1258; 98.1%) opted for a brand-name drug, and 1193 (93.0%) used a dropper bottle as their initial medication delivery method (Table 1).

By the end of the first year, 91.9% (1965) of the patients continued their treatment. Persistence rates varied by age group ($P < 0.05$), with older patients showing higher persistence (92.7% [n = 1481]) compared to younger patients (87.7% [n = 64]). While not statistically significant, patients initially treated with one (92.4% [n = 1186]) or two (92.7% [n = 444]) antiglaucoma drugs demonstrated higher persistence rates than those treated with three or more drugs, who had a non-persistence/discontinuation rate of 10.9% (n = 41) (Table 2).

In prescriptions involving a single drug, prostaglandin analogs showed the highest persistence (93.7% [n = 449]), followed by carbonic anhydrase inhibitors (93.4% [n = 71]). Sympathomimetics had the lowest first-year persistence rate (84.8% [n = 28]; $P > 0.05$) (Table 2).

Table 1. Baseline characterization of study participants and first prescription

Variable	Male, n (%)	Female, n (%)	Total, n (%)	P-value
Total	867 (40.6)	1271 (59.4)	2138 (100.0)	-
Age group (years)				0.201
18–44	35 (4.0)	38 (3.0)	73 (3.4)	
45–64	200 (23.1)	268 (21.1)	468 (21.9)	
≥65	632 (72.9)	965 (75.9)	1597 (74.7)	
First prescription, number of drugs				**0.032**
1	495 (57.1)	788 (62.0)	1283 (60.0)	
2	199 (23.0)	280 (22.0)	479 (22.4)	
3 or more	173 (20.0)	203 (16.0)	376 (17.6)	
Initial drug class				0.067
S01EA	8 (0.9)	25 (2.0)	33 (1.5)	
S01EC	28 (3.2)	48 (3.8)	76 (3.6)	
S01ED	278 (32.1)	417 (32.8)	695 (32.5)	
S01EE	181 (20.9)	298 (23.4)	479 (22.4)	
Fixed Combinations	372 (42.9)	483 (38.0)	855 (40.0)	
Drug classification [a]				0.495
Generic	8 (1.6)	17 (2.2)	25 (1.9)	
Brand name	487 (98.4)	771 (97.8)	1258 (98.1)	
Pharmaceutical form [a]				0.736
Dropper bottle	457 (92.3)	736 (93.4)	1193 (93.0)	
Single-dose container	28 (5.7)	37 (4.7)	65 (5.1)	
Per os	10 (2.0)	15 (1.9)	25 (1.9)	

Note: [a] , analysis of only patients who received one drug in the first prescription; *P*-value obtained using the chi-square test; S01EA, sympathomimetics in glaucoma therapy; S01EC, carbonic anhydrase inhibitors; S01ED, beta-blocking agents; S01EE, prostaglandin analogues; *per os,* oral medication.

Table 2. First-year persistence with using anti-glaucoma drugs

Variable	Persistent, n (%)	Non-persistent, n (%)	P-value
Total	1965 (91.9)	173 (8.1)	-
Gender			0.248
Male	804 (92.7)	63 (7.3)	
Female	1161 (91.3)	110 (8.7)	
Age group (years)			**0.045**
18–44	64 (87.7)	9 (12.3)	
45–64	420 (89.7)	48 (10.3)	
≥65	1481 (92.7)	116 (7.3)	
First prescription, number of drugs			0.087
1	1186 (92.4)	97 (7.6)	
2	444 (92.7)	35 (7.3)	
3 or more	335 (89.1)	41 (10.9)	
Initial drug class			0.254
S01EA	28 (84.8)	5 (15.2)	
S01EC	71 (93.4)	5 (6.6)	
S01ED	638 (91.8)	57 (8.2)	
S01EE	449 (93.7)	30 (6.3)	
Fixed Combinations	779 (91.1)	76 (8.9)	
Drug classification [a]			0.292 [b]
Generic	22 (88.0)	3 (12.0)	
Brand name	1164 (92.5)	94 (7.5)	
Pharmaceutical form [a]			0.793 [b]
Dropper bottle	1102 (92.4)	91 (7.6)	
Single-dose container	60 (92.3)	5 (7.7)	
Per os	24 (96.0)	1 (4.0)	

Note: [a] , analysis of only patients who received one drug in the first prescription; [b] , Fisher's exact test; *P*-value obtained using the chi-square test; S01EA, sympathomimetics in glaucoma therapy; S01EC, carbonic anhydrase inhibitors; S01ED, beta-blocking agents; S01EE, prostaglandin analogues; *per os,* oral medication.

Table 3. Second-year persistence with using anti-glaucoma drugs

Variable	Persistent, n (%)	Non-persistent, n (%)	P-value
Total	1740 (81.4)	398 (18.6)	-
Gender			0.416
Male	708 (81.7)	159 (18.3)	
Female	1032 (81.2)	239 (18.8)	
Age group (years)			**< 0.001**
18–44	53 (72.6)	20 (27.4)	
45–64	353 (75.4)	115 (24.6)	
≥65	1334 (83.5)	263 (16.5)	
First prescription, number of drugs			**0.026**
1	1046 (81.5)	237 (18.5)	
2	404 (84.3)	75 (15.7)	
3 or more	290 (77.1)	86 (22.9)	
Initial drug class			0.655
S01EA	24 (72.7)	9 (27.3)	
S01EC	64 (84.2)	12 (15.8)	
S01ED	571 (82.2)	124 (17.8)	
S01EE	387 (80.8)	92 (19.2)	
Fixed Combinations	694 (81.2)	161 (18.8)	
Drug classification [a]			0.503 [b]
Generic	20 (80.0)	5 (20.0)	
Brand name	1026 (81.6)	232 (18.4)	
Pharmaceutical form [a]			0.726
Dropper bottle	975 (81.7)	218 (18.3)	
Single-dose container	52 (80.0)	13 (20.0)	
Per os	19 (76.0)	6 (24.0)	

Note: [a] , analysis of only patients who received one drug in the first prescription; [b] , Fisher's exact test; *P*-value obtained using the chi-square test; S01EA, sympathomimetics in glaucoma therapy; S01EC, carbonic anhydrase inhibitors; S01ED, beta-blocking agents; S01EE, prostaglandin analogues; *per os*, oral medication.

Table 4. Third-year persistence with using anti-glaucoma drugs

Variable	Persistent, n (%)	Non-persistent, n (%)	P-value
Total	1439 (67.3)	699 (32.7)	-
Gender			0.739
Male	580 (66.9)	287 (33.1)	
Female	859 (67.6)	412 (32.4)	
Age group (years)			**< 0.001**
18–44	36 (49.3)	37 (50.7)	
45–64	279 (59.6)	189 (40.4)	
≥65	1124 (70.4)	473 (29.6)	
First prescription, number of drugs			**< 0.001**
1	901 (70.2)	382 (29.8)	
2	331 (69.1)	148 (30.9)	
3 or more	207 (55.1)	169 (44.9)	
Initial drug class			**0.004**
S01EA	19 (57.6)	14 (42.4)	
S01EC	55 (72.4)	21 (27.6)	
S01ED	494 (71.1)	201 (28.9)	
S01EE	333 (69.5)	146 (30.5)	
Fixed Combinations	538 (62.9)	317 (37.1)	
Drug classification [a]			0.478 [b]
Generic	17 (68.0)	8 (32.0)	
Brand name	884 (70.3)	374 (29.7)	
Pharmaceutical form [a]			0.278
Dropper bottle	844 (70.7)	349 (29.3)	
Single-dose container	40 (61.5)	25 (38.5)	
Per os	17 (68.0)	8 (32.0)	

Note: [a] , analysis of only patients who received one drug in the first prescription; [b] , Fisher's exact test; *P*-value obtained using the chi-square test; S01EA, sympathomimetics in glaucoma therapy; S01EC, carbonic anhydrase inhibitors; S01ED, beta-blocking agents; S01EE, prostaglandin analogues; *per os*, oral medication.

During the second year of treatment, the overall persistence rate decreased to 81.4% (n = 1740). This decline was more pronounced among younger patients (individuals aged 18–44 years), with a persistence rate of 72.6% (n = 53) compared to 83.5% (n = 1334) among older patients (individuals aged ≥ 65 years) ($P < 0.001$) (Table 3).

Significant differences were observed among patients who started treatment with two antiglaucoma drugs, maintaining a higher persistence rate (84.3% [n = 404]). Among single-drug prescriptions, sympathomimetics again had the lowest persistence rate (72.7% [n = 24]) ($P > 0.05$) (Table 3). By the end of year three, older patients had the highest persistence rate of 70.4% (n = 1124) ($P < 0.001$). Additionally, patients who started treatment with monotherapy had the highest persistence rate of 70.2% (n = 901) ($P < 0.001$) (Table 4). In terms of pharmacological class, the pattern of low persistence associated with sympathomimetics remained the same (57.6% [n = 19]); however, carbonic anhydrase inhibitors showed the highest persistence (72.4% [n = 55]) ($P < 0.05$) (Table 4).

DISCUSSION

In our study, we observed a decline in persistence with antiglaucoma therapy over time, with approximately one-third of patients with glaucoma discontinuing medication by the end of the third year of follow-up. Older patients and those initiating treatment with monotherapy demonstrated higher persistence rates. These findings underscore the importance of enhancing therapeutic effectiveness to mitigate functional and structural losses that contribute to blindness in patients with glaucoma.

In Portugal, the prevalence of glaucoma among adults aged over 40 years ranges from 2% to 3%, consistent with rates across Europe [19]. The adoption of mainstream treatment practices, guided by Portuguese glaucoma therapy guidelines, is widespread [20]. For the healthcare system, glaucoma represents an ever increasing financial challenge given the chronic condition of the disease and its associated costs for lifelong management and follow-up visit, in an aging population [19]. Therefore, real-world data, such as those presented in this study, are required to define the best approaches for diagnosis and treatment. Antiglaucoma therapy plays a pivotal role in intraocular pressure (IOP) control, proven effective in slowing disease progression [2]. Newman–Casey et al. [21] demonstrated a clear relationship between therapy persistence and preservation of retinal sensitivity by using visual field assessment. Similar to Newman–Casey et al. [21], our study showed that persistence in using antiglaucoma medication decreased over time. However, we did not evaluate the association between the decline in treatment adherence and the rate of glaucomatous structural or functional changes. Future studies are needed to explore negative outcomes of poor patient adherence, as this is currently debated in the literature [3, 22].

Over time, older patients exhibited higher persistence rates compared to younger patients. Shu et al. [3] suggested this may be due to greater functional changes in older individuals with severe glaucoma, leading to more consistent use of antiglaucoma medications. Similarly, Jang et al. [23] concluded that younger patients, often unaware of the gradual progression and asymptomatic nature of early-stage glaucoma, may not fully appreciate the importance of medication adherence, resulting in treatment discontinuation [23].

In Portugal, approximately 72% of patients using IOP-lowering medications are treated with monotherapy [19]. Weinreb et al. [24] recommend achieving the target IOP with minimal drugs and adverse effects. Our study found that patients starting with monotherapy demonstrated the highest persistence rates over time, aligning with the view that complex treatment regimens and frequent dosing increase nonadherence [25]. These findings support European guidelines advocating for simplified treatment approaches [26], consistent with Meier–Gibbons and Toteberg–Harms [27], who linked high persistence to less complex regimens. Among monotherapy prescriptions, the patients who used sympathomimetics showed the lowest persistence in glaucoma therapy, whereas, those who used carbonic anhydrase inhibitors demonstrated the highest persistence. Currently, sympathomimetics are rarely used in glaucoma therapy due to their side effects [28], while carbonic anhydrase inhibitors are among the most commonly used drugs. They effectively reduce IOP during the day but have less effect at night [29, 30]. Persistence in glaucoma therapy is crucial in preventing disease progression [3]. Poor adherence and/or persistence can lead to treatment failure, reducing the clinical benefits of medications, necessitating alternative treatments [3].

The study reveals a troubling trend of decreasing persistence with antiglaucoma therapy over time, with approximately one-third of patients discontinuing medication after 3 years, highlighting significant challenges in maintaining long-term treatment adherence. Age and initial treatment choice emerged as pivotal factors influencing persistence. Particularly noteworthy is the higher persistence rate among older patients and those initially prescribed monotherapies. Utilizing these insights could inform targeted strategies aimed at enhancing treatment adherence. Poor adherence and persistence undermine therapeutic efficacy, thereby diminishing the clinical benefits of treatment [31]. The objective is to bolster patient persistence and ultimately enhance long-term outcomes in glaucoma management [31, 32]. These findings underscore the necessity of implementing diverse strategies that empower individuals with glaucoma to effectively manage their treatment regimen, emphasizing the critical importance of sustained long-term patient follow-up.

Our findings should be interpreted within the context of several limitations. Firstly, medication-taking behavior is highly individualized and influenced by numerous factors [33], which our study did not comprehensively evaluate. Such factors include the quality of physician-patient communication, patient education regarding the disease and treatment options, and patient beliefs and perceptions, often better assessed through questionnaires or interviews [34, 35]. Additionally, our study lacked data on potential confounders such as comorbidities [36] and disease severity [37], which are likely to impact treatment persistence. Secondly, our reliance on prescription records from PHC in the SIARS database may have led to an underestimation of persistence rates, as patients may also obtain prescriptions from specialists and hospital outpatient departments not captured by SIARS. Furthermore, caution is advised when interpreting our results, which should be juxtaposed with recently updated data from the same source over the past three years. Lastly, the use of a single diagnostic code for glaucoma in the ICPC-2 classification [18], used by PHC units in Portugal poses limitations, as distinctions in conditions could influence patient decisions regarding treatment continuation or discontinuation.

Future studies are necessary to elucidate how these findings correlate with clinical aspects of vision, such as functional [21, 38] and structural losses [38], leading to irreversible visual impairment in patients with glaucoma [39, 40]. Future studies should incorporate larger and more diverse patient cohorts, using recent data sourced from Portugal. This enhancement could be achieved by including prescription data from both hospital settings and the private sector. A more detailed exploration of medication persistence, including pharmacological classes and regional disparities, could offer further valuable insights into barriers affecting treatment adherence [14, 41]. Such a comprehensive approach might facilitate targeted interventions tailored to specific geographic regions and drug categories, thereby enhancing our comprehension of glaucoma therapy persistence and optimizing patient outcomes.

CONCLUSIONS

In this study, we observed a concerning trend of decreasing persistence with antiglaucoma therapy over time, as evidenced by approximately one-third of glaucoma patients discontinuing medication by the end of the third year of follow-up. Notably, older patients and those initiated on monotherapy exhibited higher levels of persistence. Our findings offer valuable insights into factors influencing medication persistence in glaucoma, which could inform strategies aimed at enhancing treatment adherence among affected patients.

ETHICAL DECLARATIONS

Ethical approval: This study received approval from the ethics committees of the Lisbon and Tagus Valley Health Administration (CE-ARSLVT-647/CES/2020) and the Lisbon School of Health Technology (CE-ESTeSL-Nº58-2019).
Conflict of interest: None.

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