• Investigation •

Initial medication adherence in newly diagnosed glaucoma patients: three adherence measures

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Abstract

● **AIM:** To determine initial medication adherence in newly diagnosed glaucoma patients treated with anti-glaucoma drugs.

● **METHODS:** This retrospective and observational study included all patients diagnosed with glaucoma in the Primary Health Care units in Portugal during the years 2012 and 2013, which in consequence received a first prescription for anti-glaucoma drugs. Data was collected from electronic prescribing records of the primary care units and from pharmacy claims records. Initiation of glaucoma treatment and early discontinuation were measured, and the combination of (non)-initiation and early discontinuation accounted for initial medication (non)-adherence.

● **RESULTS:** A total of 3548 new glaucoma patients (40.1% male; 59.9% female) were included. The 1133 (31.9%) patients were initially classified as non-users, since there was no pharmacy claim found for their first prescription for glaucoma treatment. Additionally, 277 (11.5%) patients early discontinued their treatment, acquiring only their first prescription. Overall, the initial medication non-adherence rate was 39.7% since 1410 patients either didn't initiate treatment or discontinued it early.

● **CONCLUSION:** This study, reveals a major opportunity to improve glaucoma treatment and its control, since a large proportion of patients fail to engage with their prescribed therapy, which implies that implementation of individual or group strategies that enable patients with glaucoma to correctly perform their treatment is still needed.

● **KEYWORDS:** glaucoma; glaucoma treatment; initiation; early discontinuation; initial medication adherence

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INTRODUCTION

Glaucoma is a chronic, progressive, and neurodegenerative ocular disease described by the death of retinal ganglion cells and the loss of axons[1], which involves long-term treatment[2]. Considered as the main cause of irreversible blindness, and the second most common blindness cause worldwide[3], primary open angle glaucoma (POAG), the most common subtype of glaucoma, is a real public health challenge, whose major risk factors include the level of intraocular pressure (IOP) and advanced age[4-5]. In Portugal, as other European countries, 4% of the population aged 40y or more has POAG[6] and the estimated 68.56 million people with glaucoma in 2020, highlights the need for a quick diagnosis and a careful therapeutic approach[5].

Advanced age, the asymptomatic progression and the chronic condition of this disease requires a life-long treatment which may face a range of challenges[5]. Therefore, it is crucial that the diagnosis occur in an initial phase, with no delays in initiating pharmacological treatment, for correct monitoring and minimize the functional loss of vision that can lead to irreversible blindness[3,7], since lowering IOP is the only proven intervention to slow down disease progression[8]. The benefits of IOP reduction in managing POAG irrespective of the level of untreated IOP as well as reducing the conversion of ocular hypertension to POAG have been well established[4]. Unfortunately, non-adherence to anti-glaucoma therapy can undermine such efforts.

Medication adherence, defined as the process by which patients take their medications as prescribed[9], in glaucoma treatment is of paramount importance to prevent disease progression[3],

since low adherence patients show worse results with bigger visual deficiency and even blindness[10]. Several risk factors for non-adherence including age, gender and ethnicity or geographic locations have been previously described[5]. Others, like the ability to manage eye drops, especially in older patients with glaucoma with visual impairment and physical and mental comorbidities, remain a great challenge[3,11].

Medication adherence consists of three elements: initiation, implementation, and discontinuation[9]. The process starts with initiation of the treatment, which occurs when the patient takes the first dose of a prescribed medication, after its acquisition from a pharmacy and it ends (discontinuation) when the patient stops taking the prescribed medication[12]. Typically, the literature on medication adherence focuses on the implementation of therapy, skipping its first element, initiation[13]. Also, many patients interrupt their treatment after the acquisition in a pharmacy of their first prescription, phenomena called early discontinuation or short persistence[14]. In an aging population, with different comorbidities, knowing the initial medication adherence to glaucoma therapy is essential[15], not just for optimizing patient's patterns of medication-taking behavior, but also the effectiveness of this therapy and the reduction of costs associated with disease progression and its complications.

Thus, this study aims to determine initial medication adherence in newly diagnosed glaucoma patients treated with anti-glaucoma drugs in the Lisbon and Tagus Valley Health Region, during 2012 and 2013, focusing on the initiation rate and early discontinuation of anti-glaucoma therapy and possible risk factors.

SUBJECTS AND METHODS

Ethical Approval All identifiable individual characteristics were removed from the data before transfer to the researchers, which were not evolved in data collection. This study was approved by the ethics committee of ARSLVT (Lisbon and Tagus Valley Regional Health Administration; CE-ARSLVT-647/CES/2020) as well by the ethics committee of Lisbon School of Health Technology (CE-ESTeSL-Nº58-2019).

Data Sources and Study Population Two main data sources were used: 1) electronic prescribing (e-prescribing) records from the Primary Health Care (PHC) units in the Lisbon and Tagus Valley region; 2) pharmacy claims records. The regional health administration of Lisbon and Tagus Valley accounts for about 13% of the Portuguese territory and 34.6% (3.7 million) of its population. Within the PHC units, all prescription information is collected centrally. Pharmacy claims are submitted also electronically to a centralized reimbursement system.

Data were drawn from SIARS–Information System of the Regional Health Administration of Lisbon and Tagus Valley, which is an administrative database, developed to facilitate analysis and monitoring of PHC units' activity and production. This automated system includes information on diagnosis made, according to the International Classification for Primary Care, 2nd version (ICPC-2)[16] and registered within the PHC network, as well as patients demographic and administrative data.

Prescription data includes all e-prescriptions issued within the PHC units, regardless of whether they were eventually filled (*i.e.* dispensed to the patient) or not. As extracted from SIARS, each record includes a unique identification number, patient identification, and prescription date. Drugs are identified by ATC (Anatomical Therapeutic Chemical Classification System) code and national drug code, generic–if classified as such–or brand name, strength, pharmaceutical form, presentation (package size) and number of packages prescribed. Patient identification number allows for linkage within SIARS to collect patient's personal information (age, gender, housing parish code, and diagnosis code).

Pharmacy claims include data on prescriptions that were filled and reimbursed by the National Health System (NHS). The claims data includes the e-prescription identification number, encoded patient identification, and prescription fill date. Dispensed drugs are identified with the same information as prescribed drugs.

Study population consists of all newly diagnosed adult patients (≥18y) with glaucoma (ICPC-2 code F93) in the PHC units of the region of Lisbon and Tagus Valley from January 1st 2012 to December 31st 2013. For these patients, data on all e-prescriptions and pharmacy claims for anti-glaucoma drugs (S01E-antiglaucoma preparations and miotics: S01EA-sympathomimetics in glaucoma therapy; S01EC-carbonic anhydrase inhibitors; S01ED-beta blocking agents, and S01EE-prostaglandin analogues) were collected for a 48-month study period. Additionally, data was collected for the 6mo period prior to the diagnosis date, to account only for new users of anti-glaucoma drugs. All patients diagnosed with glaucoma and with the corresponding first prescription were included.

Linking Pharmacy Claims to E-Prescribing Records Each prescription has its one individual identification number that was used to link pharmacy claims to e-prescribing records. Since each prescription can include up to four different drugs, we've also used the ATC code to match both files. If the prescription has four different drugs, patients may fill only a single drug. Thus, a drug was defined as dispensed if there was a match between both files of the prescription individual identification number and the ATC code at any time prior to the end of our data. This linkage was conducted following the methodology defined by Coelho[17] for the same database.

Table 1 Main characteristics of study participants and first prescription, by gender *n* (%)

Characteristics	Male	Female	Total	[a]*P*
Total	1424 (40.1)	2124 (59.9)	3548 (100)	
Age group				0.426
18-44y	67 (4.7)	81 (3.8)	148 (4.2)	
45-64y	341 (23.9)	510 (24.0)	851 (24.0)	
65y or more	1016 (71.3)	1533 (72.2)	2549 (71.8)	
First prescription number of drugs				0.369
1	740 (52.0)	1155 (54.4)	1895 (53.4)	
2	317 (22.3)	449 (21.1)	766 (21.6)	
3 or more	367 (25.8)	520 (24.5)	887 (25)	
Pharmacological class				0.396
S01EA	15 (1.1)	33 (1.6)	48 (1.4)	
S01EC	42 (2.9)	77 (3.6)	119 (3.4)	
S01ED	413 (29.0)	633 (29.8)	1046 (29.5)	
S01EE	270 (19.0)	412 (19.4)	682 (19.2)	
Fixed combinations	684 (48.0)	969 (45.6)	1653 (46.6)	
Brand/generic classification				0.292
Generic drug	11 (1.5)	25 (2.2)	36 (1.9)	
Brand name drug	729 (98.5)	1130 (97.8)	1859 (98.1)	
Pharmaceutical form of the initial drug				0.722
Dropper bottle	682 (92.2)	1075 (93.1)	1757 (92.7)	
Single dose container	42 (5.7)	56 (4.8)	98 (5.2)	
Orally	16 (2.2)	24 (2.1)	40 (2.1)	

[a]Chi-square test. S01EA: Sympathomimetics in glaucoma therapy; S01EC: Carbonic anhydrase inhibitors; S01ED: Beta blocking agents; S01EE: Prostaglandin analogues.

Analyses Initiation to anti-glaucoma therapy was evaluated as a dichotomous event (patient initiates therapy: yes/no). It was quantified as the proportion of patients filling their first prescription within six months, which is the maximum allowed period for dispensing of a prescribed drug in a community pharmacy in Portugal. Such patients were classified as new users of anti-glaucoma therapy and, consequently, those who didn't fill their first prescription were classified as non-users.

Early discontinuation was also evaluated as a dichotomous event (patient discontinue therapy: yes/no) and it was defined as the failure to ever refill the prescriptions for anti-glaucoma drugs, *i.e.* a patient acquired only his/her first prescription.

The combination of (non)-initiation and early discontinuation accounted for initial medication non-adherence.

We compared all three adherence measures across patients' characteristics, such as gender, age, as well across drug classes and other drug characteristics, such as its classification as generic or brand name drug and pharmaceutical form. Bivariate analysis was conducted to determine which characteristics were related to all three adherence measures. Categorical variables were analyzed using the Chi-square test. All analyses were conducted with the SPSS statistical software package version 26.

RESULTS

A total of 3548 new glaucoma patients (40.1% male, 59.9% female) were included in this study, predominantly older patients (71.8%). Almost half of the patients (46.6%) received a fixed-dose combination of anti-glaucoma drugs as their first prescription, with no differences between male and female patients, which implies that 53.4% of these patients were initially treated with monotherapy, being beta adrenergic blockers, in that case, the most prescribed drug class. Overall, brand name drugs and dropper bottles were the first choice for glaucoma therapy in these patients. All results are shown in Table 1.

Analyzing the initiation rate, 1133 (31.9%) patients were classified as non-users since there was no pharmacy claim found for their first prescription for glaucoma therapy. No differences were found between male and female patients, and between age groups, although a slightly higher initiation rate was found in older patients. Considering the pharmacological classes, 750 (45.4%) of patients who received a prescription of a fixed-dose combination, were classified as non-users and in terms of monotherapy classes, prostaglandin analogues had the highest initiation rate (P<0.001). Also, as the number of drugs in the first prescription increases, the initiation rate decreases (P<0.001). Although not statistically significant, initiation was higher when a generic drug was prescribed (88.9% *vs* 79.6% for brand name drugs). All results are shown in Table 2.

Of the 2415 who initiated glaucoma therapy, 277 (11.5%)

Table 2 Initiation of anti-glaucoma therapy, by patients and first prescription characteristics *n* (%)

Initiation	Yes	No	Total	[a]*P*
Total	2415 (68.1)	1133 (31.9)	3548 (100)	
Gender				0.674
Male	975 (68.5)	449 (31.5)	1424 (40.1)	
Female	1440 (67.8)	684 (32.2)	2124 (59.9)	
Age group				0.131
18-44y	93 (62.8)	55 (37.2)	148 (4.2)	
45-64y	564 (66.3)	287 (33.7)	851 (24.0)	
65y or more	1758 (69.0)	791 (31.0)	2549 (71.8)	
First prescription drug number				<0.001
1	1512 (79.8)	383 (20.2)	1895 (53.4)	
2	523 (68.3)	243 (31.7)	766 (21.6)	
3 or more	380 (42.8)	507 (57.2)	887 (25)	
Pharmacological class				<0.001
S01EA	39 (81.3)	9 (18.8)	48 (1.4)	
S01EC	95 (79.8)	24 (20.2)	119 (3.4)	
S01ED	813 (77.7)	233 (22.3)	1046 (29.5)	
S01EE	565 (82.8)	117 (17.2)	682 (19.2)	
Fixed combinations	903 (54.6)	750 (45.4)	1653 (46.6)	
Brand/generic classification				0.170
Generic drug	32 (88.9)	4 (11.1)	36 (1.9)	
Brand name drug	1480 (79.6)	379 (20.4)	1859 (98.1)	
Pharmaceutical form of the initial drug				0.424
Dropper bottle	1407 (80.1)	350 (19.9)	1757 (92.7)	
Single dose container	76 (77.6)	22 (22.4)	98 (5.2)	
Orally	29 (72.5)	11 (27.5)	40 (2.1)	

[a]Chi-square test. S01EA: Sympathomimetics in glaucoma therapy; S01EC: Carbonic anhydrase inhibitors; S01ED: Beta blocking agents; S01EE: Prostaglandin analogues.

failed to ever refill their prescriptions for anti-glaucoma drugs, meaning that they early on discontinued their treatment. This early discontinuation was more prominent in younger patients, where almost one out five only fill the first prescription. In opposition, only 9.2% of the older patients discontinued their treatment in an early stage (P<0.001). Early discontinuation was higher in patients who received initially a prescription of only one anti-glaucoma drug (84.9% *vs* 98.9% for patients who were initially medicated with three or more drugs, P<0.001). Compared to the other drug classes, early discontinuation was also lower in patients initially prescribed with a fixed-dose combination (Table 3).

Combining the rate of initiation and the proportion of patients who early discontinued glaucoma therapy, initial medication adherence for these patients was 60.3%, which means that 39.7% of the newly diagnosed and treated glaucoma patients failed to initially adhere to their prescribed therapy.

Initial medication adherence was higher in older patients (P<0.001), with a first prescription of just one anti-glaucoma drug (P<0.001), particularly a prostaglandin analogue (P<0.001). Results are shown in Table 4.

DISCUSSION

Glaucoma is the main cause of irreversible blindness, and the second most common blindness cause worldwide[3], being IOP one of its most important risk factors[4-5]. However, and in spite of advances in glaucoma treatment, it continues to be an important public health problem, with low rates of adherence to anti-glaucoma therapy[18] whose prevalence is increasing worldwide, especially in older patients. This means that there is room for improvement in the management of glaucoma, by implementing individual or group strategies that enable patients with glaucoma to correctly perform their treatment. Adherence to anti-glaucoma therapy is an important factor to prevent disease progression. Low adherence is associated with an increased risk of visual impairment and irreversible blindness[18].

Thus, assessing adherence to anti-glaucoma therapy in all its components, and not just for implementation, and the identification of potential risk factors for non-adherence are of major importance in planning preventive strategies aimed at improving IOP control and, therefore, slowing down disease progression. To do so, adherence cannot be seen as a

Table 3 Early discontinuation of anti-glaucoma therapy, by patients and first prescription characteristics *n* (%)

Early discontinuation	No	Yes	Total	[a]*P*
Total	2138 (88.5)	277 (11.5)	2415 (100)	
Gender				0.618
Male	867 (88.9)	108 (11.1)	975 (40.4)	
Female	1271 (88.3)	169 (11.7)	1440 (59.6)	
Age group				<0.001
18-44y	73 (78.5)	20 (21.5)	93 (3.9)	
45-64y	468 (83.0)	96 (17.0)	564 (23.4)	
65y or more	1597 (90.8)	161 (9.2)	1758 (72.8)	
First prescription drug number				<0.001
1	1283 (84.9)	229 (15.1)	1512 (62.6)	
2	479 (91.6)	44 (8.4)	523 (21.7)	
3 or more	376 (98.9)	4 (1.1)	380 (15.7)	
Pharmacological class				<0.001
S01EA	33 (84.6)	6 (15.4)	39 (1.6)	
S01EC	76 (80.0)	19 (20.0)	95 (3.9)	
S01ED	695 (85.5)	118 (14.5)	813 (33.7)	
S01EE	479 (84.8)	86 (15.2)	565 (23.4)	
Fixed combinations	855 (94.7)	48 (5.3)	903 (37.4)	
Brand/generic classification				0.283
Generic drug	25 (78.1)	7 (21.9)	32 (2.1)	
Brand name drug	1258 (85.0)	222 (15.0)	1480 (97.9)	
Pharmaceutical form of the initial drug				0.964
Dropper bottle	1193 (84.8)	214 (15.2)	1407 (93.1)	
Single dose container	65 (85.5)	11 (14.5)	76 (5.0)	
Orally	25 (86.2)	4 (13.8)	29 (1.9)	

[a]Chi-square test. S01EA: Sympathomimetics in glaucoma therapy; S01EC: Carbonic anhydrase inhibitors; S01ED: Beta blocking agents; S01EE: Prostaglandin analogues.

Table 4 Initial medication adherence to anti-glaucoma therapy, by patients and first prescription characteristics *n* (%)

Initial adherence	Yes	No	Total	[a]*P*
Total	2138 (60.3)	1410 (39.7)	3548 (100.0)	
Gender				0.533
Male	867 (60.9)	557 (39.1)	1424 (40.1)	
Female	1271 (59.8)	853 (40.2)	2124 (59.9)	
Age group				0.001
18-44y	73 (49.3)	75 (50.7)	148 (4.2)	
45-64y	468 (55.0)	383 (45.0)	851 (24.0)	
65y or more	1597 (62.7)	952 (37.3)	2549 (71.8)	
First prescription drug number				<0.001
1	1283 (67.7)	612 (32.3)	1895 (53.4)	
2	479 (62.5)	287 (37.5)	766 (21.6)	
3 or more	376 (42.4)	511 (57.6)	887 (25.0)	
Pharmacological class				<0.001
S01EA	33 (68.8)	15 (31.3)	48 (1.4)	
S01EC	76 (63.9)	43 (36.1)	119 (3.4)	
S01ED	695 (66.4)	351 (33.6)	1046 (29.5)	
S01EE	479 (70.2)	203 (29.8)	682 (19.2)	
Fixed combinations	855 (51.7)	798 (48.3)	1653 (46.6)	
Initial drug classification				0.822
Generic drug	25 (69.4)	11 (30.6)	36 (1.9)	
Brand name drug	1258 (67.7)	601 (32.3)	1859 (98.1)	
Pharmaceutical form of the initial drug				0.737
Dropper bottle	1193 (67.9)	564 (32.1)	1757 (92.7)	
Single dose container	65 (66.3)	33 (33.7)	98 (5.2)	
Orally	25 (62.5)	15 (37.5)	40 (2.1)	

[a]Chi-square test. S01EA: Sympathomimetics in glaucoma therapy; S01EC: Carbonic anhydrase inhibitors; S01ED: Beta blocking agents; S01EE: Prostaglandin analogues.

therapeutic parameter that can be described by a single number, as usually reported in the literature, where quantification of adherence and interventions to its improvement have been largely conditional on patients acquiring their initial prescriptions, and have failed to accurately account for the component of initiation.

In this study we found that for the patients diagnosed with glaucoma in 2012 and 2013 in the Lisbon and Tagus Valley Region, almost two out of five failed to engage in anti-glaucoma therapy, by not initiating therapy or by early on discontinuing it. These findings were more relevant for younger patients, those initially treated with three or more anti-glaucoma drugs, including fixed-dose combinations. Based on these results, more attention should be given to this group of glaucoma patients to ensure adequate access to healthcare and medications, adherence to treatment regimes, knowledge of their disease and social support[19].

Possible reasons might have been uncertainty about whether real glaucoma existed (due to the initial asymptomatic nature of this condition) and the appearance of adverse drug effects. During treatment patients may experience no symptom relief and experience more side-effects while taking their medications correctly. Prostaglandin analogues, the most recent drug class in glaucoma therapy, have a superior hypotensive effect to remaining groups, and it is also associated with less adverse drug effects[4], which might explain the higher adherence rates for this drug class when prescribed in monotherapy. Also, and as Wolfram *et al*[20] found, monotherapies, particularly with prostaglandins, and simplified treatment regimens lead to better adherence and persistence. In spite of fixed-combination eye drops may be a convenient treatment option for glaucoma patients according to the patients' medical needs, especially for those who are already at the severe glaucoma stage at the initial glaucoma consultation and need early IOP lowering treatment, for those who are relatively young and for whom it is important to delay blindness, or for those who need personalized medication due to their lifestyle[21], the initial medication adherence for this anti-glaucoma drugs was lower than for the monotherapy drugs.

Our results also show that younger patients were more likely to early discontinue their treatment, after the first dispensing. In fact, almost one out of five patients under 45y interrupted their glaucoma treatment after the first dispensing. Similar results for other components of medication adherence were found by Rosu *et al*[13]. Different factors may play a role in this decision: as we already mentioned, it's well known that the asymptomatic nature of glaucoma reduces patient motivation to take the drugs as prescribed, which might be more relevant for younger patients. Also, younger patients have an active lifestyle and work activity that can relate negatively with the instillation of eye drops, by being more time away from home and forgetting to apply eye drops[22]. Also, the fact that glaucoma is commonly associated with the elderly can represent a lack of literacy in younger patients about this condition and about the importance of adherence to anti-glaucoma therapy[23]. In the opposite end, older patients with more severe forms of glaucoma, as Shu *et al*[7] reported, by having greater functional changes are therefore more likely to adhere to anti-glaucoma therapy.

In spite of the innovative features of this study, our results should weigh against some limitations, most of them related to the method used for estimating adherence to anti-glaucoma therapy.

First of all, medication-taking behavior is extremely complex and individual, and influenced by multiple factors[24]. Unmeasured patient and physician factors, such as the extent of physician–patient communication and education about prescriptions, the absence of data on possible confounding factors, such as co-morbidities and severity of concomitant diseases, are likely to influence adherence, and that was not analyzed in this study. Another limitation refers to the diagnosis of glaucoma, which under ICPC-2 is registered as single code, without specifying the type of glaucoma.

Still, despite the scarcity of information, this study made it possible to characterize for the first time, according to our best knowledge, the early patterns of adherence to anti-glaucoma therapy, by looking at the initiation rate and early discontinuation, considering some patient and drug-related factors.

Second, e-prescriptions data refers only to the PHC network and patients may have received prescriptions from other providers, including specialist and hospital outpatient settings that are not captured by SIARS, which may lead us to underestimate adherence rates. Any other data errors in the prescribing and/or claims records could lead to a drug being falsely labeled as not dispensed; this type of misclassification of the outcome could lead us to overestimate non-adherence.

Also, claims-based research is subject to misclassification because all prescriptions not captured in the claims database are considered not dispensed, yet there are other reasons for not capturing drugs dispensed, such as system failure or malfunction of the prescribing software or still an accidental drug entry prescription by the physician during the consultation.

Nevertheless, prescription and dispensing/claims (refill) databases have been considered the "gold standard" method for initiation measurement if both databases are combined[25], which as we've demonstrated can be done within SIARS, and also for discontinuation. This method would also be important to enhance the usefulness of e-prescribing records in

which future glaucoma centers could monitor and collaborate proactively to reduce therapy discontinuation.

Being a chronic disease, increasing with age, our findings reinforce the need for health promotion strategies related to the disease but also the importance of treatment and correct placement of eye drops[26]. Physician-patient relationship is of paramount importance to enable more information on glaucomatous disease and its outcomes if neglected, in order to clarify a patient's need of therapy. Low medication adherence can reflect the uncertainty of patients about the methods of application and the difficulty in administering the drops[26], and new strategies must be developed such as creating new containers that are easier to handle for the elderly.

Educational strategies must be carried out to get information to the population, brochures should be available on various shelves of health care units so that patients can be informed, also knowing that patients prefer an oral explanation, brochures, videos and exhibits could be held and/or illustrative educational videos could be shown in the waiting rooms to inform patients[27].

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Authors' contributions: Menino J, Coelho A, and Camacho P designed the study, collected, and treated the data. All the team performed the statistical analysis and prepared the manuscript. Coelho A and Camacho P supervised the project. All authors read and approved the final manuscript.

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