Use of Ocular Hypotensive Medications in Portugal: PEM Study: A Cross-sectional Nationwide Analysis

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Purpose: There is scarcity of European data about intraocular pressure (IOP)-lowering prescribing patterns. We aimed to describe and discuss the nationwide prescription of these medications in Portugal.

Materials and Methods: This was a cross-sectional study including all patients who were prescribed at least one IOP-lowering medication in 2015 in Portugal. All ocular hypotensive drug prescriptions were gathered from the common electronic drug prescription system used by all hospitals and clinics in Portugal. Demographic data, medications prescribed (number and formulation), physician specialty, and costs of medications were provided in an encrypted and anonymous form. Statistical analyses were performed using STATA.

Results: A total of 241,552 patients (58% women) were prescribed IOP-lowering medications in 2015, representing 4.3% of the population older than 40 years of age and 2.3% of the Portuguese total population. Mean age was 72 ± 13 years. Topical IOP-lowering medications accounted for a total of 29 million euros (M€) in costs, shared between patients and the national health system. General practitioners (GPs) accounted for 48% of all prescriptions. The most prescribed drugs were latanoprost (27%), timolol/dorzolamide (18%), and brimonidine (13%). Among all, 72% of patients were on monotherapy. Compared with ophthalmologists, GPs presented qualitative differences in their prescription pattern, such as a lower proportion of unit dose prescription.

Conclusion: A significant percentage of the Portuguese population is currently treated with IOP-lowering medications, and the majority of them are on monotherapy. Although GPs are responsible for nearly half the prescriptions, their prescription pattern is different from that of ophthalmologists. This nationwide study revealed prescription patterns and disclosed the burden of the disease in terms of its medical management.

Key Words: glaucoma, intraocular pressure, electronic drug prescription, medical therapy

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Glaucoma is one of the leading causes of irreversible blindness globally, affecting over 60 million people.1,2 By 2040, ~112 million persons worldwide are expected to have glaucoma and many will be bilaterally blind from this condition.3,4 Because of its asymptomatic nature until late stages, glaucoma is sometimes referred as a silent thief of sight, with vision-related consequences for patients’ quality of life.5,7

For the health care system, glaucoma constitutes an increasingly significant financial challenge, given the chronicity of the disease and the associated cost of life-long control visits, tests, and management of an aging population.8–10 The ultimate goal in glaucoma care should be the “Right Services to Right Patients at Right Time in the Right Place.”11 Thus, more reliable and realistic data are required to define best approaches, for both diagnosis and treatment.12,13

On the basis of previous studies,4,14 an estimated glaucoma prevalence between 2% and 3% in the population aged over 40 years of age is expected in Portugal.15 However, there is scarcity of nationwide epidemiological data in the glaucoma field and likewise for antiglaucomatous prescribing patterns.

Since 2014, a common compulsory electronic drug prescription system (PEM) is fully established in our country, which is used by physicians to prescribe all medications in both private and public sectors. This study describes and discusses the nationwide prescription of medications for glaucoma, discloses prescription patterns, and estimates the prevalence and associated burden of the disease.

MATERIALS AND METHODS

Data Collection

Institutional Review Board approval was obtained from Lisbon Academic Medical Center. The nationwide common electronic drug prescription system was used for data extraction. All ocular hypotensive drug prescriptions dated between January 1 and December 31 of 2015 were gathered. In Portugal, the presentation of a prescription at the pharmacy is compulsory to have access to an intraocular pressure (IOP)-lowering drug. Over-the-counter distribution is further discouraged as the 90% price subsidy will apply only to sales under a valid prescription. Demographic data and antiglaucomatous prescriptions were provided in an encrypted form and anonymously extracted for scientific purposes by the government entity responsible for electronic prescription. Records regarding the specialty of the prescribing physician and whether it originated from public or private sector were also anonymously obtained. The inexistence of missing data in the PEM query was confirmed before analysis.

Health care–related costs were calculated based on the information provided by Portuguese National Authority of
Medicines and Health Products I.P. (INFARMED). As details about brand/generic sells were not provided, estimated costs were calculated using the reference price in Portugal for each drug (ie, the price of the generic medicine with the highest price when a generic drug was available), and the brand price in case no generic drug exists. This information was gathered for each drug from the INFARMED website available at http://app7.infarmed.pt/infomed/pesquisa.php (accessed in August 2016). The overall expenditure in ocular hypotensive agents in 2015 was obtained by multiplying the number of prescribed items by the unitary cost, as presented in the Results section. General population data were collected from the population census. In Portugal, the census is conducted every 10 years, 2011 being the most recent.\textsuperscript{15} The prescription rate was calculated by dividing the number of prescriptions by the corresponding population estimate and multiplying by 100,000, to provide the prescription rate per 100,000 population. The number (%) of different participants who were prescribed one or more ocular hypotensive drugs in 2015 was estimated directly from the provided database.

### Study Population

All patients in the 2015 PEM database were included. To account for differences in prescription regarding the type of glaucoma and patients’ age, all analyses were performed separately in 3 age groups: pediatric (aged, 0 to 17 year old), adult (aged, 18 year old and above), and adult-at-risk (aged, 40 year old and above), as the latter is considered to be the main population at risk.\textsuperscript{16} Also, subgroups were created for medical specialty [general practitioner (GP) vs. ophthalmologist vs. other specialties], unit-dosed regimens (ie, preservative-free medications in single unit dose containers), and public versus private environment prescription.

### Statistical Analysis

Subgroup and comparative analyses were performed using STATA Statistical Software: Release 13.1. College Station, TX: StataCorp LP.

Except when specifically designated, all analyses are relative to the number (or percentage) of patients. Correlation between dichotomous variables and categorical or continuous predictors was examined using multivariable logistic regression and was conducted in a set-up manner. Variables fitted in regression models were examined for collinearity using variance inflation factor to indicate the nonredundancy of variables and the consequent stability of the models. A $P < 0.05$ was considered statistically significant.

### Results

#### Overview

The Portuguese population in the 2011 census was 10,562,178. Of these, 5.6 million (53%) were aged 40 year old and above and 1.9 million were aged 0 to 17 years (9%) (Table 1).

A total of 241,552 patients (42% male) were prescribed ocular hypotensive medications in 2015 (Table 1). In this year-long analysis, 54.4% of the patients were prescribed 1 IOP-lowering class. 24.9% were prescribed 2 distinct classes, 15.4% were prescribed 3 different classes, and 3.7% have been prescribed the 4 available classes of IOP-lowering medications (Table 2). The most prescribed drugs in the adult population were latanoprost (27%), timolol/dorzolamide (18%), brimonidine (13%), and timolol (13%). Overall, 58% of the patients were prescribed a prostaglandin analog. The distribution of the population by common drug class associations is depicted in Figure 1.

The Portuguese National Health System (SNS) subsidizes all available ocular hypotensive medication in 90% of their total cost (except for apraclonidine). Overall, in 2015, the total expenditure for IOP-lowering medication was 29.3 M€, equivalent to 2.9 million prescribed items (Table 3). This total amount corresponds to costs for both the SNS (26.4 M€) and patients (2.9 M€, Table 3). Single-agent and fixed-combination therapies accounted for 14.4 M€ and 11.8 M€ in costs for the SNS, respectively (Table 3).

### Age and Gender

The mean age was 72 ± 13 years (Table 1). The total number of prescriptions in 2015 was equivalent to a prescription rate of 15,593 per 100,000 population aged 40 year old and above. By stratifying prescription by age, we found a statistically significantly greater prescription rate of acetazolamide and beta-blockers in the pediatric age group (below 18 y), when compared with both the overall population and patients over 40 years. Interestingly, prostaglandin analogs represent a much smaller proportion of patients in these younger patients than in the older subgroups.

In Portugal, 961,925 people (9%) were aged 75 years or more.\textsuperscript{15} Of these, 105,606 (11%) were prescribed ocular hypotensive medications in 2015.

Of all patients, 7.7% were prescribed an IOP-lowering drug in its unit-dosed formulation. The mean age of patients who were prescribed unit doses (69 ± 13 y) was significantly lower than the ones who were not (72 ± 13 y) ($P < 0.01$, paired t test).

Lastly, considering the totality of participants in our sample, an adjusted logistic regression model suggested that both older age [odds ratio (OR), 1.04; 95% confidence

### Table 1. Demographic Characteristics of the Studied Participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pediatric (0-17 y Old)</th>
<th>Adult (≥ 18 y Old)</th>
<th>Adult-at-Risk (≥ 40 y Old)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population [n (%)]</td>
<td>1,904,938 (18)</td>
<td>8,657,240 (82)</td>
<td>5,588,208 (53)</td>
<td>10,562,178 (100)</td>
</tr>
<tr>
<td>Patients with antiglaucomatous prescriptions (N)</td>
<td>1385</td>
<td>240,167</td>
<td>223,504</td>
<td>241,552</td>
</tr>
<tr>
<td>Subjects under ocular hypotensive therapy (%)</td>
<td>0.07</td>
<td>2.8</td>
<td>4.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>50</td>
<td>43</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Age (mean ± SD) (range) (y)</td>
<td>10 ± 6</td>
<td>72 ± 12</td>
<td>73 ± 11</td>
<td>72 ± 13 (0-108)</td>
</tr>
</tbody>
</table>

Number (%), patients under ocular hypotensive therapy, sex, and age refer to each specific population.
interval (CI), 1.03-1.05; \( P < 0.001 \) and male gender (OR, 1.11; 95% CI, 1.10-1.12; \( P < 0.001 \) were associated with an increasing likelihood of being prescribed a fixed combination.

**Physician Specialty**

Among all prescriptions, 48% were from GPs and 42% from ophthalmologists. Other miscellaneous specialties accounted for the remaining prescriptions. Patients who were prescribed a drug by an ophthalmologist were significantly younger (70 ± 14 y) than the ones who were prescribed by their GP (74 ± 12) (\( P < 0.001 \), paired \( t \) test). Also, the probability of being prescribed a fixed combination was higher if the prescriber was an ophthalmologist (\( P < 0.001 \), \( \chi^2 \) test) (Table 4). When controlling for age and gender, the prescription of both single-dosed regimens (OR, 2.72; 95% CI, 2.66-2.78; \( P < 0.001 \)) and fixed combinations (OR, 1.09; 95% CI, 1.08-1.10; \( P < 0.001 \)) were more likely if the prescribing physician was an ophthalmologist.

**Private Versus Public Environment**

Among all, 596,171 (67%) prescriptions were in the public sector (hospitals or primary care health centers). There were no differences between the 4 most prescribed in private versus public sector. Interestingly, the chances of being prescribed a unit-dosed formulation in a private environment are higher than in public hospitals (OR, 1.81; 95% CI, 1.77-1.85; \( P < 0.001 \)) (Table 4).

**DISCUSSION**

**Prevalence**

The 2015 prevalence of patients treated with IOP-lowering medications in Portugal was 2.3% in the total population and 4.3% in the population 40 years or older (Table 1), compared with the reported glaucoma prevalence of 2.9% in population-based studies for Europe and 3.5% worldwide in 2013 in people aged 40 to 80 years.4

To date, only limited data are available regarding IOP-lowering prescription and glaucoma prevalence in Portugal.17 Our study, although having the inherent limitation of a study based on data originated on a prescription system (undiagnosed glaucoma patients, overtreated non-glaucomatous patients, and glaucoma patients under no therapy due to successful surgery), could provide the backbone data for considering a prospective study on glaucoma prevalence. As electronic prescription systems are becoming increasingly common in Europe, it would be of interest to have similar nationwide studies. As an example, the Social Insurance Institution of Finland has records dating back to 1987 of the usage of medicines in the country. Finland has half of the population of Portugal and the proportion of population over 40 years old was exactly the same as in Portugal in 2015 (53%, Table 1) as well as the percentage of population over 75 years old (9% in both Portugal and Finland). However, the percentage of patients using glaucoma treatment was smaller in Finland considering total population (1.7% in Finland vs. 2.3% in Portugal) and the population over 40 years old (3% in Finland vs.
4.3% in Portugal) in 2015 (http://raportit.kela.fi/ibi_apps/WFServlet?IBIF_ex=NIT084AL&YKIELI=E). Yet, the "right" or optimal level of treatment level is not known. Still, in both countries, the prevalence of treated patients are the same or higher as reported in population-based studies. Overdiagnosis and overtreatment may play a role in this finding in both countries, but the possibility of prescriptions to patients with ocular hypertension and/or glaucoma suspects must also be taken into account. In the latter, the decision to initiate treatment can be challenging because risk factors for progression must be evaluated carefully on an individual basis.18

Prescription Pattern

The prescription pattern of glaucoma therapy in adults roughly depicts the results of a systematic review and meta-analysis of randomized control trials regarding the IOP-lowering effects of each therapeutic class.19

It should be noted that a fixed combination—timolol/dorzolamide—was the second most prescribed drug in Portugal. According to European guidelines and Portuguese recommendations for glaucoma prescription, monotherapy should be favored over fixed combinations as initial therapy.20,21 However, in patients with advanced disease and/or refractory to monotherapy, the introduction of a fixed combination has several recognized advantages: (i) convenience of administration eventually promoting compliance, (ii) reduced exposure to preservatives, and (iii) medication washout effect observed when the time between the application of ≥2 drops is inadequate.22–24 Lack of awareness of these guidelines or simply nonadherence to them by clinicians could be underlying this phenomenon, as already suggested by an English prescription trends study.25

Oral acetazolamide was prescribed to 12% of the patients in the pediatric population, 5.3% of the patients aged above 40 years, and 5.3% of the patients older than 75 years of age. As oral acetazolamide is not recommended as first-line or second-line therapy,21 we may assume that most probably the patients on this drug are the ones with the less controlled IOP values. Childhood glaucoma is a rare entity that poses a true challenge to the ophthalmologists, with acetazolamide commonly used as a bridge therapy before the intervention.21,26

Table 3

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Packs (n)</th>
<th>Unitary Cost (€)</th>
<th>SNS Total Cost (Thousand €)</th>
<th>Patients Total Cost (Thousand €)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>60,255</td>
<td>5</td>
<td>286</td>
<td>15</td>
</tr>
<tr>
<td>Apraclonidine</td>
<td>3790</td>
<td>11</td>
<td>0</td>
<td>43</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>53,371</td>
<td>4.3</td>
<td>205</td>
<td>23</td>
</tr>
<tr>
<td>Bimatoprost</td>
<td>111,878</td>
<td>18</td>
<td>1828</td>
<td>204</td>
</tr>
<tr>
<td>Brimonidine</td>
<td>243,204*</td>
<td>6.4</td>
<td>1411</td>
<td>156</td>
</tr>
<tr>
<td>Brinzolamide</td>
<td>169,534</td>
<td>10</td>
<td>1512</td>
<td>168</td>
</tr>
<tr>
<td>Carteolol</td>
<td>115,687</td>
<td>4.8</td>
<td>502</td>
<td>56</td>
</tr>
<tr>
<td>Clonidina</td>
<td>166</td>
<td>4.9</td>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>Dorzolamida</td>
<td>114,517</td>
<td>5.1</td>
<td>528</td>
<td>58</td>
</tr>
<tr>
<td>Latanoprost</td>
<td>597,504*</td>
<td>5.8</td>
<td>3143*</td>
<td>347*</td>
</tr>
<tr>
<td>Tafluprost</td>
<td>91,611</td>
<td>21</td>
<td>1771</td>
<td>197</td>
</tr>
<tr>
<td>Timolol</td>
<td>247,636*</td>
<td>3.8</td>
<td>842</td>
<td>94</td>
</tr>
<tr>
<td>Brimonidine + timolol</td>
<td>95,982</td>
<td>19*</td>
<td>1708</td>
<td>190</td>
</tr>
<tr>
<td>Brinzolamide + timolol</td>
<td>86,620</td>
<td>16</td>
<td>1253</td>
<td>140</td>
</tr>
<tr>
<td>Dorzolamida + timolol</td>
<td>229,683*</td>
<td>15.8*</td>
<td>3258*</td>
<td>362*</td>
</tr>
<tr>
<td>Latanoprost + timolol</td>
<td>397,720*</td>
<td>7.7</td>
<td>2740*</td>
<td>302*</td>
</tr>
<tr>
<td>Brinzolamide + timolol</td>
<td>189,450</td>
<td>8.7</td>
<td>1483</td>
<td>165</td>
</tr>
<tr>
<td>Travaxoprost</td>
<td>148,419</td>
<td>18*</td>
<td>2345*</td>
<td>260*</td>
</tr>
<tr>
<td>Total cost (thousand €)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>26,364</td>
<td>2929</td>
</tr>
</tbody>
</table>

The 5 highest values per column are marked with an asterisk (*). SNS indicates Portuguese National Health System.

Table 4

<table>
<thead>
<tr>
<th>By Specialty</th>
<th>GP</th>
<th>Ophthalmologist</th>
<th>P</th>
<th>By Setting</th>
<th>Public</th>
<th>Private</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit doses, prescriptions [n (%)]</td>
<td>11.260 (2.5)</td>
<td>23.852 (7.4)</td>
<td>&lt; 0.001</td>
<td>20.046 (3.4)</td>
<td>17.532 (5.9)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Fixed combinations prescriptions [n (%)]</td>
<td>156.172 (34)</td>
<td>125.058 (36)</td>
<td></td>
<td>210.527 (35)</td>
<td>99.066 (33)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

GP indicates general practitioners; IOP, intraocular pressure.
the patients would benefit from preservative-free medications.\(^2^9\),\(^3^0\)

However, in our cohort, this figure was only 8%. Moreover, our analysis revealed that unit doses and fixed associations were more likely to be prescribed by ophthalmologists rather than GPs. Although determining the reason behind this difference is beyond the scope of our study, it could relate in part to ophthalmologists being more alert to any preservative-induced ocular surface problems and thus more prone to use treatment regimens that could decrease the overall burden of preservatives.\(^3^0\) In contrast, GPs may renew the drug in its most economical formulation, which may justify the lower rate of unit doses prescription.

Another interesting finding from our cohort was that older age and male sex were associated with a higher likelihood of being prescribed an IOP-lowering drug in its fixed combination form. As compliance is an important issue in glaucoma, our results could suggest that physicians tend to use easier regimens in these population subgroups that are known to be at risk of low adherence to treatment.\(^3^1\),\(^3^2\)

**GPs in Glaucoma Care**

In this 2015 study, we found that GPs were responsible for the majority of the prescriptions. In a recently published European survey,\(^3^3\) of the 21 countries that had their prescription guidance analyzed, there were 8 (38%) countries in which the ophthalmologist is the only one allowed to prescribe IOP-lowering drugs. In the remaining countries—Portugal included—the initial prescription is initiated by an ophthalmologist, and is usually renewed by the patient’s GP as part of his/her chronic medications.\(^7\),\(^3^1\)

Of note, while this prescription renewal means the same ocular hypotensive active principle, a different brand or formulation of the same drug may be given to the patients by their GP. This fact may further contribute to the prescribing patterns’ qualitative differences between GPs and ophthalmologists.

**Burden of the Disease**

In Portugal, the significant majority of the glaucoma medications are 90% subsidized by the healthcare system (SNS). Thus, even the most expensive drugs have little effect on the patients’ out-of-pocket expenses. As summarized in Table 3, the most expensive drugs for the health care system and the patient do not match the most prescribed medications. For example, despite travoprost, bimatoprost, and travoprost/timolol fixed combination being scarcely prescribed, all rank among the most expensive in the list of total amount paid by the SNS. Whether these investments are cost-effective is unclear.

The total cost of prescription items in 2015 in Portugal was 29 M€, corresponding to a national prescription rate of 15,593 per 100,000 population aged 40 year old and above. A 2013 study in England\(^3^4\) which has about 5 times the Portuguese population, reported a prescription rate of ~25,000 per 100,000 population, equivalent to ~135 M€ spending. In Finland, in 2015, the yearly cost of medication per Finnish glaucoma patient was 247€ in 2015 compared with 121€ in Portugal. Similar to Portugal, in Finland, the Social Insurance Institution also covers 90% of the drug costs, which means there are striking differences in IOP-lowering drugs’ pricing within Europe. In Finland, no differences were found between prescriber physician specialties—ophthalmologists versus GPs (http://raportit.kela.fi/ibi_apps/WFServlet/ IBIF_ex = NIT056AL&YKIELI = E).

As reimbursement of glaucoma medication costs exists in these European countries, it would be interesting to compare these findings with recent data of other health care systems in which this burden is shared with the patient. Of note, while we discussed only the cost with medications, it must be emphasized that there are other costs associated with glaucoma management, such as ancillary test performing, control visits, traveling expenses, and costs of surgery.

**LIMITATIONS AND CONCLUSIONS**

These results should be weighed against some limitations. Whereas the PEM software does provide detailed information about the physicians’ point of view (ie, the medication prescribed), it was not designed to track whether these prescriptions were indeed taken to the pharmacy. Accordingly, it is not possible to crosscheck whether the prescribed drugs were actually bought by the patients and to reliably calculate the frequency at which the drugs were acquired (ie, evaluate adherence) in this year-long study. Moreover, as brand/generic sells were not provided, estimated costs were calculated using the reference pricing of each drug. Also, the population census data were from 2011, that is, a different year than the collected data and drug cost. Lastly, the incomplete overlap between prescriptions and the number of patients is inherently related to the query methodology, which may reflect changes of therapy, patients undergoing surgery, among others. Nevertheless, we consider that this study presents good internal validity as the relative ranking of drugs is similar in both analyses.

This nationwide study revealed prescription trends in Portugal and disclosed the burden of the disease in terms of its medical management. It is thus one of the few available European studies with nationwide recent data on IOP-lowering therapy. Our work should promote an increasingly evidence-based and affordable prescription by every health care stakeholder in glaucoma, which is essential for the whole system sustainability and the best patient care.

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