Original Article

DOI: 10.7860/JCDR/2025/75629.20851

Pharmacology Section

Study of Drug Utilisation and Adverse Drug Reaction Pattern of Anti-glaucoma Drugs in Patients with Primary Open Angle Glaucoma Attending the Glaucoma Clinic at a Tertiary Care Institute in Bihar, India: A Cross-sectional Study

NITU PANDEY[1], SACHIN KUMAR[2], VIDYA BHUSHAN KUMAR[3], RINKY THAKUR[4]

ABSTRACT

Introduction: Primary Open Angle Glaucoma (POAG) is a leading cause of secondary blindness, with pharmacotherapy being the mainstay of treatment. As guidelines and recommendations have evolved, so have prescribing trends. The present study was carried out to assess the utilisation pattern and Adverse Drug Reactions (ADRs) of anti-glaucoma drugs in POAG patients to promote their rational and cost-effective use.

Aim: To evaluate the drug utilisation pattern and ADRs associated with anti-glaucoma drugs in POAG patients.

Materials and Methods: This observational cross-sectional study was conducted at the Department of Pharmacology and the Regional Institute of Ophthalmology (RIO) at IGIMS, Patna, Bihar, India, for a period of six months (December 2023 to May 2024) and included 87 outpatients over 18 years of age diagnosed with POAG. Their prescriptions were analysed for the number and types of drugs, Fixed Dose Combinations (FDCs) and costs {the costs were obtained from Drug Today (April-July 2024); for drugs not available in this source, the online platform (Tata 1 mg) was used). The ADR pattern was observed in 78 participants who were already on anti-glaucoma drugs through inquiry and examination; nine were newly diagnosed and thus their ADRs could not be evaluated. Descriptive statistics were used.

Results: Of the 87 participants, 48 (55.17%) were males and the remaining were females, with a mean age of 53.75±14.83 years. Of the 147 drugs and FDCs prescribed, 145 (98.64%) were topical (eye drops). A single drug was prescribed in 24 (27.59%) instances, while a single FDC was prescribed in 10 (11.5%) of the prescriptions. A total of 50 FDCs were prescribed, with an average of 2.3 drugs per prescription. Prostaglandin (PG) analogues were the most frequently prescribed drugs, followed by beta-blockers (timolol), accounting for 60 (31.09%) and 51 (26.42%) prescriptions, respectively. Carbonic anhydrase inhibitors accounted for 49 (25.39%), α-adrenergic agonists for 29 (15.03%) and Rho-kinase inhibitors for 4 (2.07%) prescriptions. All medications were prescribed as branded generics with complete dosing information regarding dose, dosage form and dose frequency. Out of 78 patients, 23 experienced ADRs, the most common being dryness, burning and grittiness; timolol was the most commonly implicated drug. No significant systemic ADRs were observed except for frequent urination with oral acetazolamide. All data were entered into Microsoft Excel and statistically analysed.

Conclusion: The present study highlights the current prescribing practices in POAG, with a shift from beta-blockers to PG analogues reflecting current guidelines. The increased use of FDCs offers cost-effectiveness and convenience. The choice of branded generics over generic drugs remains a topic for further investigation.

Keywords: Drug monitoring, Eyedrops, Treatment costs

INTRODUCTION

Glaucoma is one of the leading causes of secondary blindness, which is potentially preventable, with around 65 million cases worldwide [1]. India accounts for approximately 12 million cases, with around 1.2 million individuals blind from the disease, underscoring its significance in the current scenario [2].

Glaucoma is a form of progressive optic neuropathy characterised by changes in the optic nerve head, visual field abnormalities and elevated intraocular pressure. Of the two major types of glaucoma—POAG and Primary Closed Angle Glaucoma (PCAG)—POAG is more common. In POAG, pharmacotherapy forms the mainstay of treatment. Until recently, beta-blockers were the drugs of choice for POAG; however, with the advent of PG analogues, which have the advantages of better efficacy, once-daily dosing and a relatively better safety profile [3,4], their use has significantly declined. Other drugs, such as carbonic anhydrase inhibitors, are also used but to a lesser extent. Recently, a new class of drugs, Rho-kinase inhibitors, has been added to the list [5,6]. These drugs act via unique mechanisms (increasing trabecular outflow and decreasing episcleral venous pressure) and also have a good safety profile, offering potential advantages over other currently used medications [7].

Drug utilisation studies are important tools that aid in the cost-effective use of healthcare resources, especially in a resource-poor country like India. They provide valuable feedback to clinicians and other stakeholders regarding the marketing, distribution, prescription and use of drugs in a clinical setting, forming the basis for making amendments in policies at both regional and national levels. These studies ultimately fulfill the goals of rational prescription and use of drugs.

In the present study, the authors have evaluated the drug utilisation pattern of anti-glaucoma drugs in POAG patients and recorded the associated ADRs. Such data is lacking in the region. The authors findings will contribute to improved clinical practices, resulting in enhanced patient care and will also help optimise the allocation of resources in healthcare settings.

The aim of the study was to determine the drug utilisation pattern of anti-glaucoma drugs in POAG patients to promote their rational use. The objective of the study was to determine the ADR pattern associated with these anti-glaucoma drugs.

MATERIALS AND METHODS

The present observational, cross-sectional study was conducted in the Department of Pharmacology and the Regional Institute of Ophthalmology (RIO) at IGIMS, Patna, Bihar, India. The study included patients diagnosed with POAG who visited the Glaucoma Clinic at RIO. The study had a duration of six months, starting from December 2023 and continuing through May 2024. The study was carried out after obtaining ethics approval from the Institutional Ethics Committee and securing written informed consent from every patient (842/IEC/IGIMS/2022).

Sample size calculation: Assuming a 2.1% prevalence of POAG [8], with 90% power and a 5% alpha value, the minimum sample size was calculated to be 87.

Formula:

$$n=\frac{(Z_{\alpha/2}+Z_{\beta})^2 . P . (1-P)}{d^2}$$

where:

- n: Required sample size
- $Z_{\alpha/2}$: Z-value for the desired confidence level (Z=1.96 for 95%)
- Z_{β}: Z-value for the desired power (Z=1.28 for 90%)
- P: Prevalence (P=2.1%)
- d: Margin of error (5%)

Substituting the values, we get:

$$N=\frac{(1.96+1.28)^2 \times 0.021 \times (1-0.021)}{(0.05)^2}$$

$$=\frac{10.5 \times 0.021 \times 0.979}{(0.05)^2}$$

$$=86.3 \sim 87$$

Inclusion criteria:

- Patients willing to participate and provide informed consent for the study.
- Patients of either sex aged over 18 years.
- Patients diagnosed and treated for POAG.

Exclusion criteria:

- Patients diagnosed with angle-closure glaucoma or secondary glaucoma.
- Patients diagnosed with other ophthalmological disorders, ocular inflammation, corneal abnormalities, or cataracts that pose difficulties in applanation tonometry, visual field evaluation, or fundus evaluation.

Study Procedure

Information about the prescribing pattern of anti-glaucoma drugs, including data on the use of generic or branded drugs, route and frequency of administration, FDCs, cost of pharmacotherapy and the number of drugs per prescription, was collected from prescriptions. Data on the use of FDCs were gathered to assess their frequency and cost-effectiveness. Patients already on anti-glaucoma drugs were examined and questioned about any adverse events related to the medications.

For cost evaluation of all the drugs prescribed in the present study, including Bimatoprost (0.03%), Brimonidine (0.2%), Brinzolamide (1%), Dorzolamide (2%), Latanoprost (0.005%), Netarsudil (0.02%), Ripasudil (0.4%), Timolol (0.5%), Travoprost (0.004%) and FDCs such as Brimonidine/Brinzolamide, Brimonidine/Timolol, Brinzolamide/Timolol, Dorzolamide/Timolol and Travoprost/Timolol, authors used Drug Today (April 2024-July 2024) [9]. For Netarsudil and Ripasudil, which were not listed in this source, authors obtained cost information from an online source [10].

STATISTICAL ANALYSIS

All data were entered into Microsoft Excel and statistically analysed. Descriptive statistics were performed and the data were presented as numbers, mean±Standard Deviation (SD) and percentages.

RESULTS

Out of a total of 87 patients enrolled in the study, 48 (~55.17%) were males and 39 (~44.83%) were females. The mean age of the patients was 53.75±14.83 years. The demographic characteristics of the enrolled patients are shown in [Table/Fig-1].

Parameters	n (%)
Age group (in years)	
18-30	8 (9.20%)
31-40	12 (13.79%)
41-50	16 (18.39%)
51-60	18 (20.69%)
61-70	20 (22.99%)
>70	13 (14.94%)
Gender	
Female	39 (44.83%)
Male	48 (55.17%)

[Table/Fig-1]: Demographic characteristics of study population.

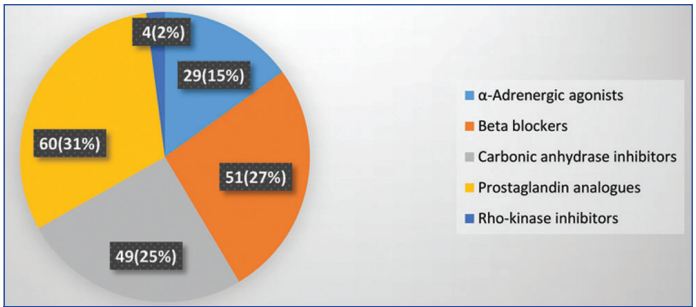
A total of 147 drugs/FDCs were prescribed, of which only 2 (1.36%) were prescribed via the oral route (Acetazolamide tablet), while 145 (98.64%) were topical (eye drops). The rest were all prescribed as topical formulations (eye drops), as shown in [Table/Fig-2].

Drug name	Route/Formulation	n (%)	Total n (%)
α-Adrenergic agonists			
Brimonidine	Topical/Eyedrops	29 (15.03%)	29 (15.03%)
Beta blockers			
Timolol	Topical/Eyedrops	51 (26.42%)	51 (26.42%)
Carbonic anhydrase inhibitors			
Acetazolamide	Oral/Tablet	1 (0.52%)	49 (25.39%)
Brinzolamide	Topical/Eyedrops	17 (8.81%)	
Dorzolamide	Topical/Eyedrops	31 (16.06%)	
Prostaglandin (PG) analogues			
Bimatoprost	Topical/Eyedrops	43 (22.28%)	60 (31.09%)
Latanoprost	Topical/Eyedrops	8 (4.15%)	
Travoprost	Topical/Eyedrops	9 (4.66%)	
Rho-kinase inhibitors			
Netarsudil	Topical/Eyedrops	3 (1.55%)	4 (2.07%)
Ripasudil	Topical/Eyedrops	1 (0.52%)	

[Table/Fig-2]: Pattern of drug usage (including FDCs) by route and class in the present study (n=193).

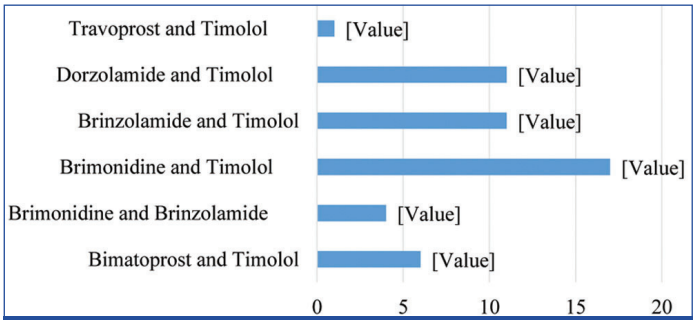
The pattern of drug usage by pharmacological class in the present study is demonstrated in [Table/Fig-3].

A single drug was prescribed to 24 patients (27.59%), while a single FDC was prescribed to 10 patients (11.5%). The rest were on combination therapy with more than one drug/FDC. A total of



[Table/Fig-3]: Pattern of drug usage (including FDCs) by class in the present study (n=193).

50 FDCs were prescribed [Table/Fig-4]. The average number of drugs per prescription was calculated to be 2.3. The prescriptions were complete in terms of dose, dosage form and frequency of administration.



[Table/Fig-4]: Pattern of usage of FDCs (topical/eyedrops) in the present study (n=50.)

All the medications were prescribed using their brand names (branded generics). The average monthly cost of various drugs and FDCs and their relative costs are shown in [Table/Fig-5,6], respectively.

A total of nine patients were started on anti-glaucoma medication during the study period, while 78 patients were already on treatment. As such, 78 patients were examined and questioned about any ADRs they were currently experiencing or had experienced after the initiation of treatment. A total of 23 patients out of 78 (29.5%) experienced various ADRs. Dryness, burning and grittiness were the most common complaints (23.4%) and the drug most commonly associated with these complaints was Timolol. The pattern of ADRs and the corresponding drugs/FDCs associated with them are shown in [Table/Fig-7,8], respectively. Timolol and FDCs containing Timolol accounted for 18 (78.3%) ADRs. No systemic adverse effects were observed except for frequent urination with the oral administration of acetazolamide.

DISCUSSION

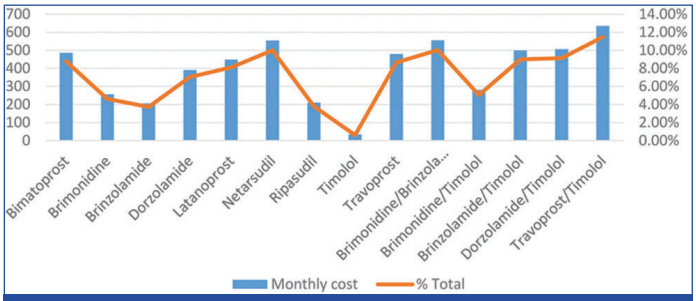
The mean age of patients in the present study was 53.75±14.83 years, with the majority in the age group of 61-70 years, which is similar to findings in previous studies [8,11,12]. This supports the fact that POAG primarily affects the elderly.

Of the participants, 48 (~55.17%) were males and 39 (~44.83%) were females, reflecting a slight male predominance in the present study population. This finding is consistent with previously conducted studies in India [8,11,12]. However, current literature suggests that no clear evidence exists for gender predilection in glaucoma. It is possible that cultural beliefs, access to healthcare, socio-economic conditions and literacy levels could influence this ratio [13].

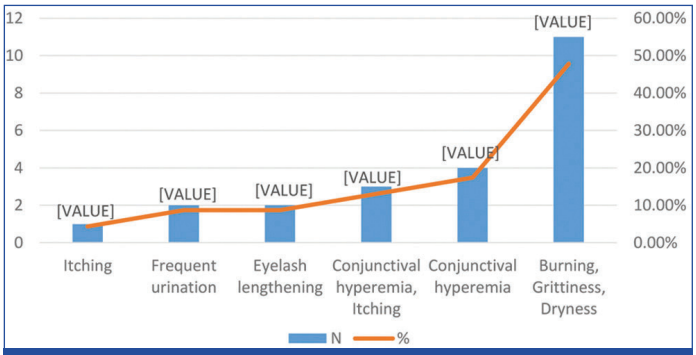
Only two patients were prescribed anti-glaucoma medication in tablet (oral) form; the rest were prescribed eye drops (topical). This finding is consistent with that reported in a previous study [12]. The preference for the topical route is justified as it minimises the chances of systemic adverse effects [14] and also allows for more localised treatment, which can be more effective in managing IOP.

Drug/FDC	Dosage and frequency	Monthly usage (No. of drops)	Monthly usage (No. of 5 mL vials) (α)	Cost per Vial (5 mL) in INR (Average)[$] (β)	Monthly treatment cost in INR (Average)[#] (α×β)
Bimatoprost (0.03%)	1 drop OD	60	0.6 vials	810	486
Brimonidine (0.2%)	1 drop BD	120	1.2 vials	225	256
Brinzolamide (1%)	1 drop BD	120	1.2 vials	172	206
Dorzolamide (2%)	1 drop BD	120	1.2 vials	326	391
Latanoprost (0.005%)	1 drop OD	60	0.6 vials	741	449
Netarsudil (0.02%)	1 drop OD	60	0.6 vials	923	554
Ripasudil (0.4%)	1 drop OD	60	0.6 vials	351	211
Timolol (0.5%)	1 drop BD	120	1.2 vials	40	48
Travoprost (0.004%)	1 drop OD	60	0.6 vials	800	480
Brimonidine/ Brinzolamide	1 drop BD	120	1.2 vials	463	555
Brimonidine/Timolol	1 drop BD	120	1.2 vials	233	280
Brinzolamide/ Timolol	1 drop BD	120	1.2 vials	416	499
Dorzolamide/Timolol	1 drop BD	120	1.2 vials	422	506
Travoprost/Timolol	1 drop OD	60	0.6 vials	529	635

[Table/Fig-5]: Monthly cost of different drugs (topical) used in the present study.
*Note: The calculations have been done assuming 20 drops in 1 mL of solution
[$]Average cost for 5 mL vial has been calculated by calculating the cost for 5 mL solution for every brand given in the Drug Today (April-July 2024) and then taking its average (except Netarsudil 0.02% and Ripasudil 0.4% which have not been mentioned in the above said source; Tata 1 mg was used for the cost calculation of these two drugs). This has been done for every single drug and FDC
[#]Monthly treatment cost has been calculated by multiplying the average cost per 5 mL vial and the required number of vials per month (e.g., for Bimatoprost 0.03%, the average monthly treatment cost would be 810×0.6=486 INR); [†]OD: Once daily, BD: Twice daily



[Table/Fig-6]: Relative cost of various drugs/FDCs (in INR) in the present study.



[Table/Fig-7]: ADR pattern in the study population.

ADR	Drugs or FDCs associated with ADR
Eyelash lengthening	Bimatoprost
Burning, Grittiness, Dryness	Timolol/Bimatoprost/Brimonidine/Dorzolamide/Brinzolamide and Timolol/Brimonidine and Timolol/Bimatoprost and Timolol
Conjunctival hyperemia	Latanoprost/Bimatoprost/Netarsudil/Brimonidine and Timolol/Brinzolamide and Timolol
Itching	Bimatoprost/Travoprost/Netarsudil/Brimonidine and Timolol/Dorzolamide and Timolol
Frequent urination	Acetazolamide

[Table/Fig-8]: ADR and the drugs/FDCs associated.

In the present study, PG analogues were the most frequently prescribed drugs, with 60 (31.09%) prescriptions, followed by beta-blockers (Timolol), which accounted for 51 (26.42%) prescriptions. Other drugs, in decreasing order of frequency, were carbonic anhydrase inhibitors 49 (25.39%), α-adrenergic agonists 29 (15.03%) and Rho-kinase inhibitors 4 (2.07%). Timolol has historically been the most frequently prescribed anti-glaucoma drug, as seen in previous studies [12,15,16], where it accounted for 82.22%, 55% and 58.15% of prescriptions, respectively. PG analogues, on the other hand, had limited usage in these studies—8.88%, 1% and 4.9%, respectively. In contrast, the present study reported 60 prescriptions of PG analogues, representing 31.09% of the total. This marks a significant increase compared to earlier findings. The relative decrease in Timolol usage and the increased prescription of PG analogues could possibly be attributed to the better safety and efficacy profile of the latter, aligning with evolving treatment guidelines.

The newly added group of drugs, Rho-kinase inhibitors, contributed to a very small fraction of the prescribed drugs (2.07%), likely due to limited clinical experience. FDCs accounted for 34% of the total prescribed drugs, which is higher than the 26.66% and 14.89% reported in previous studies [12,16]. In one study, no FDCs were prescribed [15]. This increasing trend is positive and could be attributed to the greater convenience and cost-effectiveness of FDCs compared to prescribing drugs separately, as summarised in [Table/Fig-4]. Additionally, the safety profile of FDCs is assumed to be better, as the number of drops and the frequency of instillation are reduced with their use [17].

Brimonidine and Timolol were the most commonly prescribed FDCs in the present study, accounting for 34% of all FDCs. This differs from previous studies, where Dorzolamide and Timolol were reported as either the only prescribed combination [16] or the most frequently prescribed one [12]. The preference for Brimonidine and Timolol in the present study could be attributed to their lower cost compared to other FDCs [Table/Fig-4]. Similar findings were reported in another study, where Brimonidine and Timolol were the most commonly used FDC in the public sector, while Brimonidine and Brinzolamide—a costlier alternative—were preferred in the private sector [18].

All 147 drugs (including FDCs) in the present study were prescribed by brand names (branded generics). This contrasts with findings from previous studies, where 53% and 78% of drugs were prescribed using generic names [16,19]. Conversely, another study reported that only 10% of drugs were prescribed by generic names [15]. Additionally, one study conducted to assess prescribing patterns and drug usage in the Outpatient Department of Ophthalmology noted that only 1% of prescriptions carried the generic names of drugs [20]. The preference for branded drugs over generic alternatives remains a subject of debate, warranting further research to explore the underlying attitudes and preferences of clinicians.

The average number of drugs per prescription was 2.3, which is higher than the 1.36 reported in a previous study [16]. All prescriptions were complete in terms of dose, dosage forms and frequency, which is consistent with previous studies [12,15].

Regarding the safety profile of the drugs, Timolol and FDCs containing Timolol were the most commonly associated with adverse effects (78.3%). No systemic adverse effects were observed with the topical route, justifying their increased use. Frequent urination was the only systemic adverse effect noted, which was attributable to the orally prescribed drug, acetazolamide.

Limitation(s)

Being a cross-sectional study, our research had inherent limitations associated with this design, especially the lack of follow-up, which limited the data on the long-term efficacy and safety of the listed drugs. Additionally, the ADRs reported here were partly based on patient-reported symptoms, which could be subject to recall bias; minor ADRs might have been under-reported. The cost analysis relied on available sources, which cannot account for regional variations, potential pricing discrepancies, unregulated marketing and discounts. The usage of newer drugs (Netarsudil and Ripasudil) was very low, limiting the data on their utilisation and safety profiles.

CONCLUSION(S)

Continued monitoring of prescribing trends is essential to ensure that prescribing practices evolve in line with the latest guidelines and recommendations, ultimately leading to improved patient outcomes and optimal resource utilisation. The present study highlights the current prescribing practices in POAG. Notable changes include a decreasing trend in the prescription of beta-blockers (Timolol) and an increasing trend in the prescription of PG analogues, indicating that clinicians are aligning with current drug choice recommendations. Additionally, the increased prescription of rational FDCs compared to single drugs is a positive trend, as it offers advantages in terms of cost-effectiveness and patient convenience. However, the choice of branded generics over generic drugs remains debatable. Future studies assessing the perceptions and preferences of Ophthalmologists could help clarify this issue. These findings have significant implications for clinical practice as well as policymaking and emphasise the need for awareness among healthcare providers regarding the cost-effective prescription of anti-glaucoma drugs.

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PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Pharmacology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India.
2. Associate Professor, Department of Ophthalmology, Nalanda Medical College and Hospital, Patna, Bihar, India.
3. Senior Resident, Department of Ophthalmology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India.
4. Senior Resident, Department of Pharmacology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Rinky Thakur,
Senior Resident, Department of Pharmacology, Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna-800014, Bihar, India.
E-mail: rinkythakur09@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 20, 2024
- Manual Googling: Dec 24, 2024
- iThenticate Software: Dec 27, 2024 (9%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Sep 14, 2024**
Date of Peer Review: **Nov 15, 2024**
Date of Acceptance: **Dec 29, 2024**
Date of Publishing: **Apr 01, 2025**