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Is tolerance in glaucoma therapy overestimated and drug effectiveness underestimated?

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HIGHLIGHTS

Optimal pharmacotherapy for glaucoma involves finding an individual compromise: maximum effectiveness with no or acceptable side effects.

ABSTRACT

Glaucoma pharmacotherapy is a long-term process in which subjective symptoms (related to medication intolerance) are being reported by patients with increasing frequency. As a result, therapeutic decisions made by clinicians may favor better-tolerated agents, even if they are potentially less effective. Intensification of glaucoma therapy is required when the target intraocular pressure is not achieved. This can be accomplished by adding another medication, switching to a fixed-combination preparation, or replacing the current drug with a more effective agent within the same class. The last approach is particularly relevant for prostaglandin analogues – a group that includes four active substances. Comparative analyses consistently show that bimatoprost provides a statistically significant, though relatively modest, additional intraocular pressure reduction compared with latanoprosts.

Key words: glaucoma therapy, treatment tolerance, treatment efficacy

INTRODUCTION

Pharmacotherapy for glaucoma is a long-term process in which the primary therapeutic goal is to lower intraocular pressure (IOP) to an individualized target level. Over the past four decades, substantial therapeutic progress has been achieved in this field. Glaucoma management has evolved from a limited number of poorly tolerated treatment options to advanced, patient-centered strategies that provide effective treatment, improved tolerability, and enhanced quality of life.

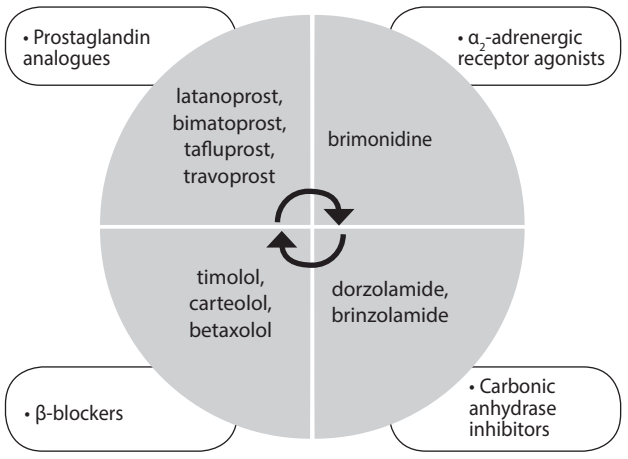
The discussion on the tolerability and efficacy of antiglaucoma therapy remains highly relevant and continues to raise concerns. The potential discrepancy between tolerability (i.e., the acceptability and safety of treatment) and efficacy (i.e., adequate IOP reduction and prevention of glaucomatous progression) is discussed below.

TOLERABILITY VERSUS EFFICACY

The pharmacological agents currently used in glaucoma therapy are presented in figure 1. The availability of multiple drugs across different therapeutic classes raises the question of how to select the optimal treatment for an individual patient. This leads to a dilemma regarding the balance between treatment tolerability and efficacy.

FIGURE 1

Classes of medications used in glaucoma pharmacotherapy in Poland.



Tolerability is often overestimated, as in routine clinical practice physicians must consider that patients use topical medications for many years and that subjective symptoms (such as burning, hyperemia, and ocular dryness) are frequently reported. Moreover, lack of efficacy is typically perceived by patients as less important than treatment tolerability. Consequently, therapeutic decision-making may favor better-tolerated agents, even if they are less potent and provide lower neuroprotective efficacy.

However, glaucoma progression is typically slow and asymptomatic; therefore, neither patients nor physicians perceive the immediate consequences of insufficient IOP reduction. In clinical practice, less intensive treatment is sometimes employed, maintaining IOP at an acceptable level, though not necessarily sufficient to halt disease progression. As a result, the efficacy of antiglaucoma therapy may be underestimated.

INTENSIFICATION OF ANTIGLAUCOMA THERAPY

When the target IOP is not achieved or glaucoma progression is observed, intensification of IOP-lowering treatment is indicated. Lower IOP levels may be achieved by:

- adding a new agent to the current regimen
- switching to a fixed-dose combination of two active compounds
- replacing the current medication with a more effective agent within the same pharmacological class.

(This approach is particularly relevant for prostaglandin analogues, which include four active substances.)

EFFICACY OF PROSTAGLANDIN ANALOGUES

The following prostaglandin analogues are commonly used: latanoprost, bimatoprost, travoprost, and tafluprost. The mean IOP reduction achieved with these agents is approximately 25–33%. Comparative analyses and systematic reviews consistently demonstrate that bimatoprost provides a statistically significant, albeit modest, advantage in IOP reduction compared with latanoprost.

Numerous studies support this observation. In 2004, Simmons et al. compared the efficacy and safety of bimatoprost and latanoprost in lowering IOP in patients with glaucoma and ocular hypertension [1]. Their analysis included 4 randomized clinical trials. The authors reported that bimatoprost was associated with a greater mean IOP reduction, as well as a higher proportion of patients achieving target IOP. The difference in mean IOP ranged between 0 and 1.5 mmHg [1]. In 92% of measurements, mean IOP was lower in patients receiving bimatoprost than in those treated with latanoprost, while in the remaining 8% of cases, values were comparable.

Holmstrom et al. conducted a meta-analysis evaluating various efficacy endpoints of IOP-lowering agents from the prostaglandin analogue class [2]. The analysis included 9,295 patients across 42 studies. Assessed parameters included mean IOP reduction and the proportion of patients achieving specific IOP thresholds. The results showed

that latanoprost achieved a mean IOP reduction of 26.7%, whereas bimatoprost reduced IOP by 30.3%.

In the most recent meta-analysis (August 2025), the efficacy of prostaglandin analogues (latanoprost, bimatoprost, travoprost, and tafluprost) was also compared [3]. This analysis included 25 studies published between 2001 and 2024, involving a total of 4,045 participants. All included studies evaluated monotherapy with the respective agents. Bimatoprost was more effective in reducing IOP than latanoprost and demonstrated significantly greater IOP-lowering efficacy than travoprost. No statistically significant differences were observed in the remaining pairwise comparisons of prostaglandin analogues in terms of IOP reduction.

Kammer et al. investigated the effect of switching prostaglandin analogues (from latanoprost to bimatoprost) on intraocular pressure (IOP) [4]. The authors showed that mean IOP was significantly lower with bimatoprost than with latanoprost at both 1 month ($p = 0.009$) and 3 months ($p = 0.024$) [5]. The additional mean IOP reduction (relative to baseline values during latanoprost treatment) was 2.1 mmHg (11.0%).

A 1 mmHg reduction in IOP has been shown to decrease the risk of glaucoma progression by approximately 10% (as reported in the Early Manifest Glaucoma Trial) [5, 6]. Therefore, the greater IOP-lowering efficacy of bimatoprost may have clinically meaningful implications.

TREATMENT TOLERABILITY

The cited meta-analyses have shown that all agents are generally well tolerated [1]; however, both bimatoprost and travoprost are associated with a higher risk of conjunctival hyperemia than latanoprost [1, 3]. Conjunctival hyperemia as a treatment-related adverse event was reported in 3.1% of patients treated with bimatoprost and in 1.5% of those receiving travoprost [4]. In the remaining patients, treatment was well tolerated.

The term 'tolerability' in pharmacotherapy encompasses several distinct concepts. Clinical tolerability refers to the extent to which a patient accepts a given treatment and implies the absence of significant adverse effects that may lead to treatment discontinuation or limit its real-world effectiveness. In contrast, pharmacodynamic tolerability, also referred to as tachyphylaxis, denotes a gradual reduction in drug efficacy with prolonged use.

Tachyphylaxis has been described primarily in association with β-blockers and α_2-agonists. Proposed mechanisms include receptor regulation and desensitization of α_2- and β-adrenergic receptors, as well as compensatory processes within the eye. Tachyphylaxis is rarely observed with prostaglandin analogues; in this class, the IOP-lowering effect is typically maintained over many years.

Table 1 summarizes clinical and pharmacodynamic tolerability across different classes of medications used in glaucoma therapy.

TABLE 1

Pharmacodynamic and clinical tolerability across different classes of medications used in glaucoma therapy.

Drug class	Pharmacodynamic tolerability	Clinical tolerability
Prostaglandin analogues	Rare – effect remains stable over years	Good; most commonly conjunctival hyperemia, cosmetic changes (hyperpigmentation, eyelash growth)
β-blockers	Yes – tachyphylaxis occurs in some patients	Good, but limited in patients with asthma/COPD and cardiovascular disease; possible bradycardia and hypotension
α_2-agonists	Yes – reduced efficacy after months of use	Frequent conjunctival and eyelid reactions; somnolence, dry mouth → frequent discontinuation
Carbonic anhydrase inhibitors	Generally stable efficacy	Burning sensation, dysgeusia (bitter taste)

CONCLUSIONS

Both tolerability and efficacy are of critical importance in the management of glaucoma. However, excessive emphasis on tolerability may lead to undertreatment. Optimal glaucoma pharmacotherapy requires achieving an individualized balance between maximizing efficacy and minimizing adverse effects while maintaining them at an acceptable level, taking into account factors such as patient age, prognosis, risk of disease progression, and comorbidities.

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