Clinical Issues:
Fixed Combinations in Treatment Algorithms and Guidelines

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Core Concepts
• Glaucoma treatment should be started with a topical monotherapy
• If the first choice monotherapy is not effective or tolerable, a switch to a different monotherapy is to be considered
• If the first choice monotherapy is effective, but does not yield target IOP, an adjunctive therapy is to be considered
• When two or more actives are necessary a fixed combination should be considered.
• Fixed combinations may offer several advantages, such as improved efficacy and tolerability – through less exposure to preservatives – as well as improved patient compliance and quality of life.

There’s a general consensus to start glaucoma medical therapy with one topical intraocular pressure (IOP) lowering medication. If the first choice monotherapy alone is not effective to reduce IOP or is not tolerated, it is preferable to switch to another molecule that is initiated as monotherapy. Adjunctive therapy should be considered whenever a monotherapy does not reach target IOP or the target must be lowered as the disease is progressing (1,2) (Fig.1). Usually fixed-combinations are not ideal as a first choice product, unless an large reduction in IOP is needed quickly.

In such cases, fixed-combination drug preparations may have advantages if compared with two separate instillations of the same agents (1) (Fig.1).

Improved compliance. Compliance with any given medical therapy in glaucoma, like other chronic diseases, is better when regimens are simple rather than complex (3). In most patients it is not recommended to use more than two drugs in two separate bottles or to add more than one single drug to a fixed-combination. Besides complexity, the higher costs from more bottles seem to promote non-compliance and reduce persistence (4).

Reduced daily amount of exposure to preservatives and side effects: There may be a direct correlation between the presence of preservatives and the surface symptoms provoked by anti-glaucoma therapy (5); reducing such exposure could improve the patient’s comfort and thus compliance. Long-term use of topical drugs may be detrimental as a dose- and time-dependent consequence to benzalkonium chloride exposure (5). Such changes may reduce the success rate of subsequent filtration surgery (6). Although no definitive data exist, at least some of the currently available fixed combination have shown a better safety profile and tolerability when compared with the same molecules used separately (1,7).

Possibly more efficacy. Several open-label replacement studies have suggested an additional IOP lowering effect when switching from dorzolamide and a betablocker to the fixed-combination dorzolamide/timolol, but no definitive data is available (7). Increased compliance and elimination of the dilution effect if drops are instilled from different bottles without sufficient time between, could explain such fixed-combination benefit.

A substantial proportion of patients on a multiple drops regimen wait less than 3 minutes before instilling the second medication. The dilution effect occurs when patients consecutively instill multiple eye drops too closely, so that the first drop is washed away by the second drop before the first can achieve maximal ocular penetration and thus efficacy (8).

Possible cost savings. The cost of a fixed combination is not necessarily less

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![Figure 1. Treatment algorithm of OAG. Fixed combinations are a viable option when monotherapy fails in reaching the target IOP (1,2).](image-url)
than the cost of the single components. However, fixed combinations reduce the number of purchased bottles, which may reduce costs for patients whose prescription drug coverage requires a co-payment for each prescription filled.

Quality of life. The goal of glaucoma treatment is to maintain the patient’s visual function and related quality of life (1). Besides the functional loss and having the diagnosis of a potentially blinding disease, other factors alone or in combination may affect patients’ quality of life: inconvenience of the treatment, side effects and therapy costs. By reducing drops and bottles without losing efficacy, fixed combinations represent an important tool in order to maintain a good quality of life, which is one of the most important aspects for patients.

Conclusions
When two or more active molecules are necessary to obtain an adequate IOP, fixed-dose combination eye drops may offer advantages for patients, while maintaining at least the same effect on IOP than separate instillation of the same two products. Reducing the number of daily drops may improve compliance and quality of life, save costs and reduce detrimental effects to the ocular surface.

REFERENCES