Abstract
Glaucoma is a serious eye disease that affects a large number of people and potentially leads to permanent visual impairment. Currently, the first-line therapy is the use of topical medications in an attempt to control intraocular pressure levels and prevent further damage to ganglion cells. Over the decades, a number of agents have been introduced; most recently, the development of fixed combination therapies has signalled a new era in treating glaucoma. Although these formulations provide advantages in terms of convenience and increased quality of life, they are also associated with certain drawbacks. The novel fixed combination of latanoprost 0.005% and timolol 0.5% has been studied extensively, and overall this medication has proved effective in controlling symptoms and has become a viable option for the treatment of glaucoma.

Keywords
Glaucoma, latanoprost, timolol, combination therapy, intraocular pressure, prostaglandin analogues, alpha 2-adrenergic agonists, topical carbonic anhydrase inhibitors

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Glaucoma is a progressive optic disc neuropathy that has become one of the leading causes of irreversible vision loss worldwide. It is characterised by optic disc damage and functional losses in the visual field, and is associated with an elevated intraocular pressure (IOP). If left untreated, glaucoma will cause progressive injury to retinal ganglion cells and their axons, damaging the optic nerve and ultimately leading to permanent blindness (see Figure 1). In the US, over 2 million adults suffer from glaucoma, and with a growing ageing population this number is expected to rise to over 3 million by 2020. Estimates of the incidence of glaucoma around the world have shown comparable or higher prevalence depending on the region investigated.

Due to the severe consequences of glaucoma, early treatment is critical for preventing further disease progression. However, with no dramatic or painful symptoms, early detection is challenging. Once diagnosed, treatment is administered to reduce the IOP to an acceptable level in an attempt to minimise further damage.

Currently, topical medication is the first-line therapy against this disease, followed by laser trabeculoplasty and/or surgery. Specifically, prostaglandin analogues (PGAs) have become the first-line agents in glaucoma treatment due to their potency and safety. However, it was recently found that nearly 40% of patients require two or more medications to achieve a modest target IOP reduction. As a result, fixed or unfixed combination therapies are now often used in the management of glaucoma and are recommended when single agents prove inadequate for reaching acceptable IOP levels.

History of Glaucoma Therapies
Research and development of fixed combinations of glaucoma treatments began as early as the 1960s. Nevertheless, the introduction of new medications since that time has been hindered by many issues, including the different pharmacokinetics of the various drugs, the cumulative nature of adverse effects when using multiple products and the potential negative drug–drug interactions. To be a viable treatment option for glaucoma, a fixed combination must show a greater reduction in IOP than either of the two component drugs as monotherapies and similar efficacy and safety profiles to the concomitant use of the two drugs.

Despite these obstacles, several fixed-dose combination therapies have emerged over the past few decades. Originally, adrenergic and cholinergic agents were the only classes of drug available for topical treatment and, during that time, it was found that the IOP-reducing effects of these drugs were additive. Furthermore, a number of patients required both medications to adequately control their disease; as a result, interest arose in combining the two components. Pilocarpine/epinephrine was the first fixed combination to be available commercially, in the early 1970s. Since then, the β-blocker timolol has been introduced and has become the first-line treatment for glaucoma, leading to the development of such combinations as pilocarpine/timolol and epinephrine/timolol in the 1980s.

As research progressed, PGAs overtook timolol as first-line therapy due to their potency and safety. However, β-blockers remain the most popular class of drug for both fixed and unfixed adjunctive therapy.
Glaucoma

Table 1: Studies Conducted on the Fixed Combination of Latanoprost 0.005% and Timolol 0.5%

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment A</th>
<th>Treatment B</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diestelhorst and Almegard 25</td>
<td>Latanoprost/timolol-FC</td>
<td>Timolol</td>
<td>A&gt;B</td>
</tr>
<tr>
<td>Pfeiffer et al. 14,15</td>
<td>Latanoprost/timolol-FC</td>
<td>Timolol</td>
<td>A&gt;B</td>
</tr>
<tr>
<td>Higginbotham et al. 17</td>
<td>Latanoprost/timolol-FC</td>
<td>Timolol</td>
<td>A&gt;B</td>
</tr>
<tr>
<td>Konstas et al. 17,16</td>
<td>Latanoprost/timolol-FC</td>
<td>Timolol</td>
<td>A&gt;B</td>
</tr>
<tr>
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</tr>
<tr>
<td>Higginbotham et al. 17</td>
<td>Latanoprost/timolol-FC</td>
<td>Latanoprost</td>
<td>A&gt;B</td>
</tr>
<tr>
<td>Olander et al. 18</td>
<td>Latanoprost/timolol-FC</td>
<td>Latanoprost</td>
<td>A&gt;B</td>
</tr>
<tr>
<td>Konstas et al. 17,16</td>
<td>Latanoprost/timolol-FC</td>
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<tr>
<td>Magacho et al. 18</td>
<td>Latanoprost/timolol-FC</td>
<td>Latanoprost</td>
<td>A&gt;B</td>
</tr>
<tr>
<td>Diestelhorst and Larsson 22</td>
<td>Latanoprost/timolol-FC</td>
<td>Latanoprost +</td>
<td>A&gt;B</td>
</tr>
<tr>
<td></td>
<td>timolol-UFC</td>
<td>timolol-UFC</td>
<td>Non-inferiority</td>
</tr>
<tr>
<td>Diestelhorst and Larsson 22</td>
<td>Latanoprost/timolol-FC</td>
<td>Latanoprost +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>timolol-UFC</td>
<td>timolol-UFC</td>
<td></td>
</tr>
</tbody>
</table>

FC = fixed combination; UFC = unfixed combination. Adapted from Tabet et al., 2008.

Table 1: Studies Conducted on the Fixed Combination of Latanoprost 0.005% and Timolol 0.5%

Overall, studies with alpha-adrenergic agonists and TCAIs have shown variable results in unfixed combinations with PGAs. While some investigations have demonstrated the addition of brimonidine tartrate or brimonidine purite BID to latanoprost to be effective in lowering IOP by a further 2.1–3.1mmHg compared with latanoprost alone, others have demonstrated different results with travoprost. These studies showed that brimonidine adjunctive therapy with travoprost was less effective in reducing IOP than brinzolamide or timolol with travoprost. Furthermore, the addition of dorzolamide to latanoprost resulted in an additional 2.8mmHg (15%) reduction in IOP compared with latanoprost alone. The combination of brinzolamide with travoprost led to IOP reductions of 2.7–4.2mmHg.

Fixed combination therapies are the most recent addition to the assortment of available glaucoma treatments. Many data have been collected for these drugs with comparisons against the separate components as monotherapies and the concomitant use of the constituent drugs in an unfixed manner. Although no clear result has been revealed in terms of an optimal treatment method, fixed combinations do provide patients with several advantageous features.

Advantages of Fixed Combination Therapy

Although in general combining therapies has proved effective in glaucoma over the years, there are certain advantages to using a pre-prepared fixed combination treatment. The primary benefit of these medicines is convenience, as a single drug can replace numerous bottles and multiple drops at various times of day. This reduces the burden of therapy and improves patient quality of life. Ease of medication administration is also associated with better compliance, which is important since adherence to a treatment regime is crucial for its success.

In addition to improving convenience, using fewer drops also avoids exposing the ocular surface to excessive preservatives such as benzalkonium chloride, which has been associated with toxicity to the eye. Furthermore, such preservatives can potentially lead to poor surgical outcomes for patients who eventually require filtering surgery. Instillation of sequential topical medications over a short period of time (less than five minutes) also results in the suboptimal absorption of each medication. This washout effect may be minimised or eliminated completely with fixed combination therapies. Finally, fewer solutions may lower the cost of treatment for patients with prescription drug benefits.

with PGAs. Various fixed combination drugs have been approved in the last decade in different countries, most of which contain timolol. Examples include timolol 0.5% in combination with dorzolamide 2%, latanoprost 0.005%, travoprost 0.004%, bimatoprost 0.03% or brimonidine 0.2%.

Studies of Unfixed and Fixed Combination Treatments

As the administration of combination therapies became more popular, many studies emerged to test the efficacies of both unfixed and fixed treatments.

While the β-blocker timolol remains the most commonly used agent for additive therapy in glaucoma, other classes of drug can be prescribed, such as alpha 2-adrenergic agonists and topical carbonic anhydrase inhibitors (TCAIs). A study was conducted to compare these three categories of drug and attempt to determine their relative efficacies as adjunctive therapies. Using one eye from each of 73 patients who were responding inadequately to latanoprost treatment alone, O’Connor et al. performed a retrospective review to evaluate the different classes in combination with this PGA. When administered twice or three times daily (BID or TID, respectively), the TCAI dorzolamide lowered IOP to a greater extent than the addition of β-blockers or the alpha 2 agonist brimonidine. When added to latanoprost, dorzolamide reduced IOP by a further 3.9mmHg (19.7%; p<0.001) compared with 2.0mmHg (12.3%; p<0.001) for β-blockers and 2.0mmHg (9.3%; p=0.0011) for brimonidine. This study revealed that addition of medications other than β-blockers to PGAs may prove to be effective as well. By contrast, in a randomised cross-over trial Konstas et al. demonstrated that dorzolamide and brimonidine purite had equal additional hypotensive effects over a 24-hour period.

Overall, studies with alpha-adrenergic agonists and TCAIs have shown variable results in unfixed combinations with PGAs. While some investigations have demonstrated the addition of brimonidine tartrate or brimonidine purite BID to latanoprost to be effective in lowering IOP by a further 2.1–3.1mmHg compared with latanoprost alone, others have demonstrated different results with travoprost. These studies showed that brimonidine adjunctive therapy with travoprost was less effective in reducing IOP than brinzolamide or timolol with travoprost. Furthermore, the addition of dorzolamide to latanoprost resulted in an additional 2.8mmHg (15%) reduction in IOP compared with latanoprost alone. The combination of brinzolamide with travoprost led to IOP reductions of 2.7–4.2mmHg.

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Efficacy of the Fixed Combination of Latanoprost 0.005% and Timolol 0.5%

The fixed combination of latanoprost 0.005% and timolol 0.5% (Xalacom™, Pfizer) was first approved in the EU in 2000 and is now available in several countries. It is given once daily and is indicated for IOP reduction in patients with open-angle glaucoma or ocular hypertension who are inadequately treated with β-blockers, PGAs or other IOP-lowering agents and when Xalacom is considered appropriate. Xalacom is contraindicated in patients with reactive airway disease, cardiovascular issues and known hypersensitivity to the product ingredients. This combination has been investigated by a number of researchers to determine its efficacy compared with the constituent drugs as monotherapies and the concomitant administration of the two components as an unfixed combination. The results of some of these studies are summarised in Table 1. For the most part, the fixed combination of latanoprost 0.005% and timolol 0.5% showed superior efficacy compared with either of the monotherapies or the unfixed combination. The reductions shown with the fixed combination were more substantial with timolol monotherapies or the unfixed combination. The reductions shown in Table 1.5 For instance, some patients may benefit from a timolol 0.25% solution, allowing physicians to individualise treatment by varying the doses of the components. For patients who were not adequately controlled with monotherapy, the fixed combination showed a reduction in their mean diurnal IOP or an increase within 1mmHg relative to baseline. However, the mean reductions observed were not statistically significant and three patients developed an IOP higher than the target.

Based on these findings, it is advisable for patients with inadequate IOP control with monotherapy to switch to the fixed combination treatment. Furthermore, patients already exhibiting adequate IOP levels with concomitant medications may benefit from a change to the fixed therapy. As with any type of medication, there are disadvantages associated with the use of fixed combination topical IOP-lowering drugs. First, there is no clear evidence confirming the superiority of such fixed combinations; in fact, at certain time-points, fixed combinations have appeared less effective than their individual components. Furthermore, when using fixed combinations physicians cannot individualise treatment by varying the doses of the components. For instance, some patients may benefit from a timolol 0.25% solution, but all fixed solutions contain timolol 0.5%, leading to over-dosing in these patients. Similarly, the drugs cannot be split to optimise treatment times. These fixed combinations are also limited by the fact that prostaglandin medications are best administered in the evening whereas β-blockers are recommended for morning.

Disadvantages of Fixed Combination Therapy

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### Table 2: Mean Intraocular Pressures for the Three Groups at Each Time-point and Mean Diurnal Intraocular Pressure During the Study

<table>
<thead>
<tr>
<th>Time of Day</th>
<th>Previous Latanoprost Group</th>
<th>Previous Timolol Group</th>
<th>Previous Unfixed Combination Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>08:00</td>
<td>12:00</td>
<td>16:00</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.13±</td>
<td>4.97</td>
<td>15.65±</td>
<td>1.87±</td>
</tr>
<tr>
<td>20.57±</td>
<td>14.57±</td>
<td>2.19±</td>
<td>1.93±</td>
</tr>
<tr>
<td>19.43±</td>
<td>9.59</td>
<td>14.78±</td>
<td>1.68±</td>
</tr>
<tr>
<td>20.38±</td>
<td>5.33</td>
<td>14.88±</td>
<td>1.86±</td>
</tr>
<tr>
<td>21.19±</td>
<td>5.33</td>
<td>14.78±</td>
<td>1.68±</td>
</tr>
<tr>
<td>20.88±</td>
<td>4.10±</td>
<td>2.68±</td>
<td>1.63±</td>
</tr>
<tr>
<td>18.94±</td>
<td>2.18±</td>
<td>2.42±</td>
<td>2.56±</td>
</tr>
<tr>
<td>20.33±</td>
<td>2.56±</td>
<td>2.34±</td>
<td>2.56±</td>
</tr>
</tbody>
</table>

*Statistical significance when p<0.001.

Adapted from Polo et al., 2008.
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