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Efficacy and safety of brimonidine and dorzolamide for intraocular pressure lowering in glaucoma and ocular hypertension

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Key words: Adjunctive – Brimonidine – Dorzolamide – Glaucoma – Intraocular pressure

Background: Brimonidine and dorzolamide are intraocular pressure (IOP)-lowering medications most commonly used in second-line treatment of glaucoma and ocular hypertension.

Scope: An evidence-based review of comparative clinical trials of brimonidine and dorzolamide was undertaken to determine the relative efficacy and safety of these drugs in reducing IOP. Using the keywords ‘brimonidine’ and ‘dorzolamide’, all articles describing such trials from September 1966 to July 2007 were found in MEDLINE and EMBASE.

Findings: In all identified studies, brimonidine and dorzolamide were both found to provide significant IOP reduction from treated or untreated baseline levels. Results of eight trials reported to date indicate that brimonidine produced either a lower treated IOP or greater pressure reduction from baseline than dorzolamide at one or more measured timepoints, and provided comparable IOP lowering over all other measurements. Differences between the IOP reductions provided by brimonidine and dorzolamide were more pronounced when the medications were used adjunctively with other classes of drugs. Six other trials showed similar efficacy, and one additional monotherapy study showed lower IOP with dorzolamide treatment. Ocular burning was noted with dorzolamide more than any other adverse event with either drug. Trials ranged widely in duration of therapy and the time of day IOP measurements were taken, and many were too small for sufficient statistical power.

Conclusion: Brimonidine and dorzolamide are both efficacious and reasonably well tolerated. Possible overall distinctions in efficacy were obscured by differences in study designs and treatment regimens, but adjunctive therapy with brimonidine may reduce IOP as effectively or more effectively than adjunctive or fixed combination dorzolamide therapy. In certain patients with glaucoma and ocular hypertension brimonidine may be a better choice than dorzolamide for second-line treatment.

Introduction

Many classes of drugs are available to reduce intraocular pressure (IOP) in the treatment of glaucoma and ocular hypertension (OHT). Dorzolamide and brimonidine are representative members of two of these drug classes.

Dorzolamide is a topical carbonic anhydrase inhibitor that reduces IOP by suppressing aqueous humor production. Dorzolamide hydrochloride
2.0% ophthalmic solution (Trusopt*), available in a buffered isotonic solution of pH 5.6 preserved with benzalkonium chloride (BAK) 0.0075%, is indicated in the treatment of elevated IOP in patients with OHT or open-angle glaucoma. It can be used safely in pediatric patients between the ages of 2 and 6 years.\(^3,4\)

In its pivotal trials for drug approval, dorzolamide TID reduced IOP by 3–5 mmHg\(^5\) but was less effective than timolol in lowering IOP at both peak and afternoon trough effect\(^6,7\). Dorzolamide is labeled for TID dosing but is often used BID in clinical practice. There is a warning on the label that dorzolamide is a sulfonamide that is systemically absorbed after topical application, so adverse reactions attributable to sulfonamides, including fatal reactions, are theoretically possible but have not been reported. Dorzolamide is contraindicated in patients with hypersensitivity to any component of the medication. Common side effects associated with dorzolamide treatment include ocular burning and stinging, bitter taste, and allergy.

Brimonidine is a selective alpha2-adrenergic receptor agonist that has a dual mechanism of IOP lowering: it both reduces aqueous production and stimulates uveoscleral outflow.\(^8\) In its pivotal trials for drug approval, topical brimonidine tartrate 0.2% (Alphagan†), reduced IOP at least as well as timolol at peak effect (2 h after dosing) but less effectively than timolol at morning trough.\(^9,11\) Brimonidine is indicated for reducing IOP in patients with open-angle glaucoma or OHT. It is contraindicated in patients with hypersensitivity to any component of the medication and in patients receiving monoamine oxidase inhibitor therapy, and it should not be used in children under the age of 3 years.\(^12,13\) The label recommends TID dosing, but brimonidine is most commonly used BID in clinical practice. Common side effects associated with brimonidine treatment include conjunctival hyperemia, allergic conjunctivitis, eye pruritus, lethargy, and dry mouth.\(^14\)

New formulations of brimonidine contain brimonidine tartrate 0.1 or 0.15% in a buffered solution of pH 6.6–7.4 preserved with Purite\(‡\) 0.005%.\(^15\) Although the new formulations contain a reduced concentration of brimonidine, they were shown in clinical trials to have the same IOP-lowering efficacy and better tolerability compared with the brimonidine 0.2% formulation because the change in pH provides better bioavailability.\(^15,16\) In contrast to the more commonly used preservative BAK, Purite has not been associated with ocular surface side effects after repeated exposure.\(^17,18\)

Both brimonidine and dorzolamide are less efficacious than the once-daily prostaglandin analogue drugs (latanoprost, bimatoprost, travoprost) in reducing IOP,\(^19,20\) but they are sometimes used as monotherapy and are frequently used as adjunctive therapy with a prostaglandin analogue or a beta-blocker such as timolol.\(^21,22\) Both brimonidine and dorzolamide are commonly considered drugs for second-line therapy.\(^23\) In choosing between these medications, it is important to consider their relative efficacy and safety profiles.

A literature search of the MEDLINE database from 1966 through July 2007 and EMBASE from 1988 through July 2007 using the search terms ‘brimonidine’ and ‘dorzolamide’ revealed multiple studies that directly compared these drugs in the treatment of glaucoma and OHT. All reports of studies that compared the IOP-lowering efficacy and/or safety of these two medications were included in this review. The most relevant reports of studies that used just one of the medications were included as background information. References cited in articles elicited by the search were reviewed and included when appropriate. Relevant articles in languages other than English were translated. This review summarizes and discusses the results of those comparison studies, which are divided into three treatment situations: brimonidine and dorzolamide monotherapy, brimonidine and dorzolamide as adjunctive therapy, or brimonidine–timolol and dorzolamide–timolol fixed combinations.

### Brimonidine and dorzolamide as monotherapy

Three separate prospective, randomized studies with crossover designs have evaluated the efficacy and safety of brimonidine compared with dorzolamide as monotherapy in glaucoma and OHT.\(^24–26\) The results of these studies, described below, suggest that there is no overall difference between the drugs in the frequency of side effects, but ocular stinging and burning are more often associated with dorzolamide treatment. When used as monotherapy, brimonidine and dorzolamide show similar efficacy.

A prospective, double-masked, randomized, crossover study\(^24\) compared brimonidine 0.2% and dorzolamide 2.0%, each dosed TID for 6 weeks, in 40 patients with glaucoma or OHT. The study design included a 2-week washout between treatment periods. IOP was measured at 8 a.m. and 10 a.m. at the study baseline and after 6 weeks of treatment. Mean baseline IOP for all patients was 24.1 mmHg. After treatment, mean IOP was similar between groups at 8 a.m. (20.8 mmHg with brimonidine and 20.7 mmHg with dorzolamide, \(p = 0.99\)). At 10 a.m. (peak effect), mean IOP was 17.8 mmHg with

*Trusopt is a registered trade name of Merck & Co, Inc; Whitehouse Station, NJ, USA
† Alphagan is a registered trade name of Allergan Inc; Irvine, CA, USA
‡ Purite is a registered trade name of Allergan Inc; Irvine, CA, USA
brimonidine treatment and 18.6 mmHg with dorzolamide treatment ($p = 0.10$). In safety analyses, there was no significant difference in incidence of ocular adverse events during treatment ($18$ on dorzolamide vs. $10$ on brimonidine, $p = 0.10$). The only individual adverse event with a significant difference in incidence between treatments was stinging/burning, which was reported for $15$ patients on dorzolamide ($38\%$) and one patient on brimonidine ($2.5\%$, $p < 0.01$). One patient discontinued from brimonidine treatment because of ocular adverse events and two did so because of systemic adverse events not necessarily related to treatment. The results of this industry-sponsored short-term study suggest that brimonidine and dorzolamide are both well tolerated when dosed thrice daily as monotherapy, and they provide similar IOP lowering. However, dorzolamide use was associated with a higher incidence of stinging/burning.

Whitson and associates$^{25}$ reported a prospective, double-masked, randomized, crossover comparison of brimonidine $0.2\%$ and dorzolamide $2\%$ each given TID for $6$ weeks in $43$ glaucoma or OHT patients with a $2$-week washout between treatment periods. IOP was measured at $8$ a.m. (morning trough), $9$ a.m., and $11$ a.m. at baseline before each treatment period and at Week $6$ of treatment. Over both baselines, mean IOP ($8$ a.m.) was $24.3$ mmHg for patients on dorzolamide, and $24.6$ mmHg for those on brimonidine ($p = 0.9$). Mean baseline IOP for the first treatment period was $24.3$ mmHg for the brimonidine group and $26.1$ mmHg for patients initially receiving dorzolamide ($p = 0.1$). Patients who received brimonidine in the second treatment period entered it with a mean IOP of $24.9$ mmHg, and those in the dorzolamide group had a mean second baseline IOP of $22.1$ mmHg ($p = 0.06$). The mean IOP reductions from treatment period baseline to Week $6$ of brimonidine treatment at $8$ a.m., $9$ a.m., and $11$ a.m. were $3.0$ mmHg, $3.1$ mmHg, and $2.6$ mmHg, respectively. The corresponding mean IOP reductions with dorzolamide treatment were $3.0$ mmHg, $2.4$ mmHg, and $2.9$ mmHg, respectively, and none of the differences between treatment groups were statistically significant ($p ≥ 0.96$). These results should be interpreted with caution for several reasons, primarily because the order of treatment periods effect was statistically significant. Baseline IOP was reported for only the $8$ a.m. measurements, but at this timepoint, baseline mean IOP for patients initially treated with brimonidine was $2.2$ mmHg higher at the start of the first period than at the start of the second treatment period, and baseline mean IOP for patients initially treated with dorzolamide was $1.2$ mmHg higher. This order effect might have been caused by an inadequate washout period ($2$ weeks) between treatment periods and could partially explain both the unexpectedly low efficacy of both drugs in this study ($8$–$12\%$ mean IOP reduction) and the lack of significant differences between drugs. The order effect had minimal impact on the IOP-lowering results at trough (without correction, the mean IOP reduction was $3.0$ mmHg with both drugs; after correction for the order effect, the mean IOP reduction was $3.1$ mmHg on brimonidine and $2.9$ mmHg on dorzolamide, $p < 0.001$). The true peak effect of the medications may not have been measured at $9$ a.m. ($1$ h after dosing), but the uncorrected mean IOP reduction at this time was $3.1$ mmHg on brimonidine compared with $2.4$ mmHg on dorzolamide. The order effect on the $9$ a.m. results was not reported. The most common adverse event was ocular burning, reported for over $40\%$ of patients during dorzolamide treatment but less than $10\%$ of brimonidine patients. Burning and stinging were more frequent with dorzolamide ($p ≤ 0.017$), and dry eye was more frequent with brimonidine ($p = 0.04$). Four patients dropped out of the study because of adverse events not necessarily related to treatment (one during dorzolamide treatment because of burning and three during brimonidine treatment because of conjunctival hyperemia, lethargy, and a non-specified adverse event). The results of this industry-sponsored study demonstrate that brimonidine and dorzolamide dosed TID are both well tolerated and have similar IOP-lowering efficacy. However, once again, dorzolamide use was associated more frequently with ocular burning and stinging.

Sharpe and associates$^{26}$ performed a prospective, double-masked, randomized, crossover comparison of brimonidine–Purite $0.15\%$ and dorzolamide $2\%$, each given BID for $4$ weeks in $33$ glaucoma and OHT patients with a $4$-week washout between treatment periods. In this industry-sponsored study, IOP was measured at $8$ a.m. (morning trough), $10$ a.m. (peak), $6$ p.m., and $8$ p.m. (evening trough) at baseline before each treatment period and at Week $4$ of treatment. Mean baseline IOP before brimonidine treatment was $22.9$ mmHg and $22.2$ mmHg before dorzolamide treatment ($p = 0.46$). The primary efficacy measure was mean IOP after $4$ weeks of treatment. At $10$ a.m. (peak effect), brimonidine–Purite provided a mean IOP of $18.1$ mmHg while that for dorzolamide was $19.5$ mmHg ($p = 0.10$). With a difference in mean IOP of $1.4$ mmHg, statistical significance could not be expected because the study was not powered to detect a difference of that magnitude. Mean IOP at other times of the day was similar between treatments: $21.0$ mmHg with both treatments at $8$ a.m. ($p = 0.9$), $19.0$ mmHg with brimonidine–Purite and $19.4$ mmHg with dorzolamide at $6$ p.m. ($p = 0.59$), and $19.0$ mmHg with brimonidine–Purite and $19.2$ mmHg with dorzolamide at $8$ p.m. ($p = 0.69$). Mean diurnal IOP was $19.3$ mmHg with brimonidine–Purite and...
19.8 mmHg with dorzolamide (p = 0.46). The mean IOP reduction from treatment-period baseline was significantly greater with brimonidine–Purite than with dorzolamide at peak (5.3 mmHg vs. 3.6 mmHg, p = 0.03) and at evening trough (3.3 mmHg vs. 1.7 mmHg, p = 0.04), as well as in the mean diurnal measurements (3.6 mmHg vs. 2.4 mmHg, p = 0.03). The mean reduction from baseline IOP results should be interpreted with caution, however, because there was a possible effect of treatment order on baseline IOP associated with dorzolamide treatment, and the authors suggested that the 4-week washout used between treatment periods may have been inadequate26. All enrolled patients completed the study as planned. The only significant difference in adverse events between treatments was a much higher incidence of burning upon instillation with dorzolamide (24%) than with brimonidine (3%, p = 0.02). The results of this study indicate that brimonidine–Purite and dorzolamide dosed BID are comparable in effectiveness and both were generally well tolerated, although the degree of discomfort was substantially greater with dorzolamide.

Recently, Quaranta and associates27 reported a study comparing the effects of brimonidine, dorzolamide, timolol, and latanoprost on blood pressure and 24-h IOP control in 27 treatment-naive patients with newly diagnosed moderate or advanced glaucoma. This was a prospective, investigator-masked, randomized, crossover comparison with 6-week treatment periods and a 4-week washout between treatments. Mean baseline IOP was 24.2 mmHg (24-h mean). Mean IOP across 24 h was 18.3 mmHg with brimonidine and 17.4 mmHg with dorzolamide. Dorzolamide produced lower IOP than brimonidine from 10 p.m. to 6 a.m. (p ≤ 0.003), but the treatments did not differ significantly from 6 a.m. to 8 p.m. It is possible that the different dosing schedules used for the two drugs – dorzolamide 2% was dosed three times daily, whereas brimonidine 0.2% was dosed twice daily – can account for the difference in IOP level. Of note, although mean changes in blood pressure were small and not clinically significant in the pivotal trials of brimonidine11, brimonidine treatment was associated with consistently lower blood pressure compared with both baseline and the other treatments in the 24-h study (p < 0.0001)27. Mean baseline systolic blood pressure was 125.1 mmHg and diastolic pressure was 73.6 mmHg. With brimonidine treatment, mean systolic pressure was reduced to 116.8 mmHg and diastolic to 64.5 mmHg. The clinical significance of these findings is not clear and the investigators suggested that longer-term studies will be needed to evaluate effects of the treatments on nocturnal hypotension and ocular perfusion pressure27.

In a recent study, a connection was noted between dorzolamide or brimonidine use and induction of ectropion28. Based on systematic drug discontinuation and rechallenge in 13 patients presenting with ectropion, dorzolamide was found to be the cause in seven of eight patients who were initially on the drug. Of five patients that had been using brimonidine, three ectropion cases were attributed to its use. Although this adverse effect has not been noted in a significant number of treated patients, this study suggests that certain patients may be susceptible to eyelid ectropion with use of either dorzolamide or brimonidine.

**Brimonidine and dorzolamide as adjunctive therapy**

Several head-to-head randomized controlled trials29–33 have compared the efficacy and safety of brimonidine and dorzolamide as adjunctive therapy with beta-blockers or other pre-existing therapy (Table 1). With adjunctive brimonidine providing IOP reductions similar to or greater than those provided by adjunctive dorzolamide in each study (Table 1), efficacy results from the studies tended to favor brimonidine.

**Adju nctive therapy with beta-blockers**

Because beta-blockers reduce IOP by inhibiting aqueous humor production34, it has been deemed important to determine whether medications that lower IOP in whole or in part by suppressing aqueous production, such as dorzolamide and brimonidine, have additive effects with beta-blockers. A short-term study in normal subjects showed that combined treatment with brimonidine and timolol caused a further inhibition of aqueous flow and decrease in IOP compared to treatment with brimonidine or timolol (15.4%, p < 0.001) alone35. Similarly, in a study reported by Toris and associates, aqueous flow and IOP were reduced more by combined treatment with dorzolamide and timolol than by treatment with either dorzolamide (p < 0.04) or timolol (p = 0.001) alone36. Further, many longer-term clinical studies in patients with glaucoma or OHT have confirmed that both brimonidine32,30,37,38 and dorzolamide30,36–42 provide significant additional mean decreases in IOP when added to ongoing beta-blocker therapy.

Stewart and associates21 reported a retrospective study of brimonidine (n = 24), dorzolamide (n = 67), and latanoprost (n = 50) given as adjunctive therapy with a beta-blocker in patients with glaucoma or OHT. Baseline patient characteristics were similar between the treatment groups, with brimonidine patients at 21.7 mmHg, dorzolamide patients at 23.0 mmHg and latanoprost patients at 22.9 mmHg (stated non-significant). Almost all of the patients on brimonidine...
Table 1. Randomized controlled trials of brimonidine and dorzolamide in adjunctive therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Treatment duration</th>
<th>Pre-existing therapy</th>
<th>Adjunctive therapy</th>
<th>Mean baseline IOP (mm Hg)</th>
<th>p-value</th>
<th>IOP reduction</th>
<th>Statistical significance (brim vs dorz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>92</td>
<td>3 months</td>
<td>Beta-blocker</td>
<td>Brim 0.2% BID</td>
<td>22.37</td>
<td>0.96</td>
<td>4.4 mmHg</td>
<td>(Month 1 peak)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dorz 2% BID</td>
<td>22.38</td>
<td></td>
<td>3.3 mmHg</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>106</td>
<td>3 months</td>
<td>Beta-blocker</td>
<td>Brim 0.2% BID</td>
<td>21.56</td>
<td>0.284</td>
<td>Peak: 6.0 mmHg</td>
<td>(Month 1)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Dorz 2% TID</td>
<td>20.89</td>
<td></td>
<td>Trough: 2.9 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Peak: 4.1 mmHg</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Trough: 1.9 mmHg</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>146</td>
<td>12 weeks</td>
<td>Timolol</td>
<td>Brim 0.2% BID</td>
<td>NA</td>
<td>NA</td>
<td>2.8 mmHg</td>
<td>(8-h diurnal Week 12)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Dorz 2% BID</td>
<td>NA</td>
<td>NA</td>
<td>3.1 mmHg</td>
<td>p-value not reported for brim vs dorz</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Unoprostone BID</td>
<td>NA</td>
<td>NA</td>
<td>2.7 mmHg</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>272</td>
<td>1 year</td>
<td>Various regimens</td>
<td>Brim 0.2% BID</td>
<td>22.8</td>
<td>0.31</td>
<td>30.8%</td>
<td>p ≤ 0.018 brim vs dorz; lat vs dorz</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dorz 2% BID</td>
<td>22.7</td>
<td></td>
<td>27.3%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Latanoprost QD</td>
<td>23.2</td>
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<td>30.6%</td>
<td></td>
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<tr>
<td>33</td>
<td>33</td>
<td>6 weeks</td>
<td>Latanoprost</td>
<td>Brim P 0.15% BID</td>
<td>19.0</td>
<td>0.52</td>
<td>2.2 mmHg</td>
<td>(24-h circadian Week 6)</td>
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<td></td>
<td></td>
<td></td>
<td>Dorz 2% BID</td>
<td>19.0</td>
<td></td>
<td>2.2 mmHg</td>
<td>p = 0.74</td>
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</table>
(92%) used the adjunctive drug BID, and most of the patients on dorzolamide also used their adjunctive therapy BID (81%) rather than TID. The study results showed significantly lower mean IOP values after 3 months with adjunctive brimonidine (17.4 mmHg) compared with adjunctive dorzolamide (20.1 mmHg, \( p = 0.03 \)), but no between-group difference in the reduction from beta-blocker-treated baseline (4.2 mmHg for brimonidine vs. 3.1 mmHg for dorzolamide, stated non-significant). Treatment was successfully maintained for 3 months in 58% of brimonidine patients versus 40% of dorzolamide patients (among-group \( p < 0.005 \); pairwise between-group \( p \)-value not reported); the higher success rate with brimonidine occurred primarily because many more dorzolamide patients (49%) than brimonidine patients (21%) had a change in medical regimen or had surgery prior to Month 3 because their IOP was not low enough. The percentage of patients who discontinued treatment because of adverse events did not vary significantly among the treatment groups (21% for brimonidine vs. 13% for dorzolamide, \( p > 0.05 \)). This study had several limitations: patients were not randomized to treatment, there was a 1.3 mmHg mean difference between brimonidine and dorzolamide treatment groups in baseline IOP which was not accounted for in overall statistical comparisons, there was no control for diurnal IOP, and Month 3 efficacy data were not available for a large percentage of patients. Nonetheless, the results of this industry-sponsored study suggest that IOP lowering with brimonidine is as or more effective than with dorzolamide, and may be associated with higher success rates as an adjunctive with a beta-blocker.

A prospective, randomized, crossover comparison study was initiated to investigate the capacity for adjunctive brimonidine or dorzolamide to acutely lower IOP\(^4\). A single drop of brimonidine or dorzolamide was given to 28 advanced glaucoma patients who had uncontrolled IOP after at least 2 weeks of beta-blocker therapy. The washout period between treatment periods was 1 month. IOP was measured at 2, 4, 6, and 8 h after the administration of adjunctive medication. Each of the study medications reduced IOP significantly from baseline at every timepoint. At two of the four timepoints (4 and 8 h after dosing), the mean IOP reduction was significantly larger with brimonidine (5.6–7.0 mmHg) than with dorzolamide (3.5–4.1 mmHg, \( p = 0.04 \)). At the other two timepoints, the mean IOP reduction was comparable between drugs (3.0–4.0 mmHg with dorzolamide and 2.9–4.4 mmHg with brimonidine, stated non-significant). This study was limited because it was a single drop study and the run-in on timolol therapy may not have been long enough for timolol to achieve maximal effects. The results show that both brimonidine and dorzolamide have the potential to produce IOP lowering additive to that achieved with timolol.

In a prospective, randomized, parallel-group clinical comparison, brimonidine or dorzolamide was given twice daily for 1 month as adjunctive therapy with a beta-blocker in 180 eyes of 92 patients with glaucoma or OHT who had IOP uncontrolled on beta-blocker therapy alone\(^3\). Treatment success was determined by the achievement of at least a 15% IOP reduction from beta-blocker-treated baseline. Patients who were successfully treated at Month 1 were continued on their therapy for another 2 months, while those who did not demonstrate at least 15% IOP lowering were switched to the other treatment arm and seen at visits after 1 and 3 months of crossover therapy. IOP was measured at study visits in the morning 1.5–2 h after instillation of dorzolamide or brimonidine. Mean baseline beta-blocker-treated IOP was 22.4 mmHg in each treatment group. After 1 month of treatment, significantly more brimonidine-treated eyes (78.3%) demonstrated at least a 15% reduction from baseline IOP compared with dorzolamide-treated eyes (71%, \( p = 0.05 \)). Moreover, of the nine patients (19.6%) on brimonidine who had less than a 15% IOP reduction, five were crossed over to dorzolamide, and none of these five patients had a successful IOP lowering response on dorzolamide either. In contrast, 13 patients (28.3%) had inadequate IOP lowering on dorzolamide, and five were crossed over to brimonidine treatment where all five subsequently showed at least a 15% reduction from baseline IOP. Six patients on dorzolamide and seven on brimonidine discontinued treatment because of adverse effects not necessarily related to treatment. It should be noted that patients who failed treatment on one medication at Month 1 and crossed over to the other treatment arm were included in the Month 1 mean IOP evaluation of both drugs. The mean IOP reduction at Month 1 was significantly greater in patients treated with adjunctive brimonidine (4.4 mmHg) than in patients treated with adjunctive dorzolamide (3.3 mmHg, \( p < 0.05 \)). In this study, brimonidine provided an additional 15% IOP reduction in a higher percentage of patients than did dorzolamide, and a greater mean IOP reduction from baseline at peak effect when used as adjunctive therapy for 1 month with a beta-blocker. At Month 3, there was no significant difference in mean IOP between patients treated with adjunctive brimonidine and patients treated with adjunctive dorzolamide. Although the number of patients who dropped out of the study between Month 1 and Month 3 was not reported, the crossover study design and the discontinuation of patients from treatment at Month 1 because of an inadequate IOP-lowering response may account for the lack of difference between treatments in mean IOP reduction from baseline to Month 3.
A prospective, investigator-masked, randomized, parallel-group, 3-month trial compared brimonidine BID (n = 54) with dorzolamide TID (n = 52) as adjunctive therapy with beta-blockers in patients with glaucoma or OHT who had IOP uncontrolled on beta-blocker therapy. IOP was measured at 8 a.m. (trough effect, just prior to study drug instillation) and 10 a.m. (peak effect) at baseline, Month 1, and Month 3 in this industry-sponsored study. Patients who failed to achieve at least a 15% reduction from beta-blocker-treated baseline IOP at 10 a.m., Month 1 or who failed to tolerate treatment were switched to the other treatment arm. The efficacy results in the trial favored brimonidine over dorzolamide. Baseline mean IOP was comparable between treatment groups (21.6 mmHg for brimonidine and 20.9 mmHg for dorzolamide, p = 0.284), but at Month 1, the mean IOP reduction from beta-blocker-treated baseline was significantly larger in the brimonidine group than in the dorzolamide group at peak effect (6.0 mmHg vs. 4.1 mmHg, p = 0.007). The mean IOP reduction from baseline at trough effect was 2.9 mmHg with brimonidine versus 1.9 mmHg with dorzolamide (p = 0.120). More patients achieved the target 15% additional IOP reduction at 10 a.m. Month 1 with brimonidine adjunctive therapy than with dorzolamide adjunctive therapy (86% vs. 62%, p = 0.005). However, at Month 3 in this study, significantly more brimonidine patients (78%) achieved the target IOP reduction at 10 a.m. than did dorzolamide patients (44%, p = 0.007). Even after patients who had inadequate IOP lowering at Month 1 had been switched to the other treatment arm, brimonidine continued to provide a larger mean IOP reduction compared with dorzolamide at peak effect (6.4 mmHg vs. 4.1 mmHg, p = 0.059). After 3 months, trough IOP reductions were comparable between the treatment groups, with brimonidine providing a mean reduction of 2.82 mmHg, and dorzolamide a mean of 2.40 mmHg (p = 0.54). Of five unsuccessful patients on brimonidine who were crossed over to dorzolamide and returned for follow-up 1 month later, none achieved the target 15% IOP reduction with dorzolamide therapy. In contrast, of 13 unsuccessful patients on dorzolamide who were switched to brimonidine, six (46%) achieved the target 15% IOP reduction on brimonidine. Few adverse events were reported in either treatment group. Five patients discontinued each therapy (9.2% of brimonidine patients and 9.8% of dorzolamide patients) and were crossed over to the other study arm or exited early from the study because of adverse events. The results of this trial suggest that brimonidine and dorzolamide are both well tolerated when used as adjunctive therapy with a beta-blocker, but brimonidine provides greater IOP-lowering efficacy. Furthermore, patients are more likely to achieve a clinically relevant additional IOP reduction with brimonidine adjunctive treatment.

Hommer et al. reported a prospective, double-masked, randomized, parallel-group comparison of brimonidine (n = 48), dorzolamide (n = 48), and unoprostone (n = 50) each given as adjunctive therapy BID for 12 weeks to glaucoma and OHT patients who had uncontrolled IOP after a 2-week run-in on timolol. The main outcome measure was the change from timolol-treated baseline IOP measured over 8 h at Week 12. No significant differences in the mean diurnal IOP reduction from baseline were found between unoprostone and brimonidine (p = 0.154) or between unoprostone and dorzolamide (p = 0.101). Statistical comparisons were not made between brimonidine and dorzolamide treatment groups directly. The mean diurnal IOP reduction at Week 12 was 2.7 mmHg (12.3%) in the unoprostone group, 2.8 mmHg (12.5%) in the brimonidine group, and 3.1 mmHg (14.4%) in the dorzolamide group. The overall incidence of treatment-related adverse events was 23% in the brimonidine group compared with 29% in the dorzolamide group and 22% in the unoprostone group. The most common adverse event was burning/stinging, which was reported by 14.6% of patients receiving dorzolamide, versus 4.2% of brimonidine patients and 4.0% of unoprostone patients. The study results suggest similar IOP-lowering efficacy and tolerability of brimonidine and dorzolamide as adjunctive therapy with timolol. These results should be interpreted with caution, however, because baseline IOP was not reported, and it is unclear whether baseline diurnal IOP was similar among the treatment groups. A further limitation of the study is that the 2-week washout of previous medications and 2-week run-in on timolol before baseline IOP measurements may have been inadequate in duration.

A randomized, double-masked, 1-year clinical comparison of brimonidine BID (n = 90), dorzolamide BID (n = 91), and latanoprost QD (n = 91) added to pre-existing therapy was performed in Indian patients with primary open-angle glaucoma and uncontrolled IOP. Baseline IOP was 22.8 mmHg for brimonidine patients, 22.7 mmHg for dorzolamide patients, and 23.2 mmHg for latanoprost patients (p = 0.31). The authors reported that IOP lowering from baseline at Year 1 was significantly greater in patients treated with brimonidine than in those treated with dorzolamide (mean IOP reduction of 30.8% vs. 27.3%, p = 0.018), based on a model that adjusted for pretreatment IOP, fundus changes, visual field changes, laser treatment, and surgery. By comparison, latanoprost QD provided an adjusted mean IOP reduction of 30.6% (p = 0.76 vs. brimonidine and p = 0.002 vs. dorzolamide). Data were not available for the five or six patients in each...
group who discontinued from the study prior to Year 1, but none of these patients exited the study early because of poor IOP control. The overall incidence of side effects was similar between the brimonidine (36.6%) and dorzolamide (24.1%) treatment groups \((p = 0.067)\); the most common side effects were ocular stinging and burning in the brimonidine group (11.9%) and bitter taste in the dorzolamide group (9.4%). This study was limited because the pre-existing therapy was not required to be a beta-blocker, or indeed, to be limited to medical therapy. Although most patients in each group were treated with a beta-blocker, some were treated with pilocarpine or dipivefrine alone or in multiple-drug therapy, and it is possible that some patients had received only laser or surgical therapy when they were randomized to brimonidine, dorzolamide, or latanoprost treatment. This limitation in the study design makes it difficult to draw strong conclusions, but the results are supportive of other studies that suggest better adjunctive IOP lowering with brimonidine compared with dorzolamide.

**Adjunctive therapy with latanoprost**

Only two reports of studies comparing brimonidine and dorzolamide as adjunctive therapy with medications other than beta-blockers were identified, and both dealt with the use of these drugs as adjunctive therapy with the prostaglandin prodrug latanoprost\(^{33,47}\). Latanoprost, available since 1996, reduces IOP more effectively than timolol when used as monotherapy\(^{48}\) and in 2002 received FDA approval for first-line use in glaucoma and OHT. Other once-daily prostaglandin analogues (bimatoprost and travoprost) are as efficacious or more efficacious than latanoprost\(^{49-52}\) and bimatoprost received a first line indication in 2006 when long-term safety data became available. The once-daily prostaglandin analogues lower IOP by increasing aqueous outflow: latanoprost and travoprost reduce IOP by increasing uveoscleral outflow\(^{52,53}\) and bimatoprost has been demonstrated to reduce IOP by increasing trabecular meshwork as well as uveoscleral outflow\(^{54,55}\).

O’Conner and associates\(^{47}\) reported a retrospective study of brimonidine, dorzolamide, and beta-blockers used as adjunctive therapy with latanoprost in 73 eyes of 73 glaucoma patients with IOP uncontrolled on latanoprost alone. This chart review included patients who were treated for 1 year with no change in medical regimen or surgical intervention within that period. The average IOP reductions reported from latanoprost-treated baseline after 1 year of adjunctive treatment were 3.9 mmHg with dorzolamide BID or TID \((n = 25)\), 2.0 mmHg with brimonidine \((n = 25)\), and 2.5 mmHg with beta-blockers \((n = 23)\). Each of these mean IOP reductions was significantly different from baseline \((p \leq 0.001)\). This study was limited because patients were excluded if they discontinued therapy before the end of the year because of lack of efficacy or adverse events. Also, no information was provided on baseline characteristics of the treatment groups other than IOP (such as demographics, diagnosis, or treatment history), and treatment was not assigned randomly, so it is likely that patient selection bias might have influenced the comparative efficacy of the medications that was observed. Nonetheless, the results of the study suggest that brimonidine, dorzolamide, and beta-blockers may all effectively reduce IOP when used as adjunctive therapy with latanoprost.

Konstas and associates\(^{33}\) recently reported a prospective, double-masked, randomized, crossover comparison of brimonidine–Purate 0.15% and dorzolamide as adjunctive therapy in 33 glaucoma patients who had uncontrolled IOP after at least a 3-week run-in on latanoprost monotherapy. Each study drug was given twice daily as adjunctive therapy with latanoprost for 6 weeks, with a 6-week washout between treatment periods. The primary outcome measure was circadian IOP, measured at seven timepoints over 24 h after 6 weeks of adjunctive therapy. Of the 33 enrolled patients, one discontinued early because of an allergic reaction while on dorzolamide, and one was not included in the analysis because of protocol violations. Of the 31 patients who had data available, one (3.2%) had the same circadian IOP (average of all seven measurements) on both drugs, 19 (61.3%) had lower circadian IOP with brimonidine–Purate, and 11 (35.5%) had lower circadian IOP with dorzolamide. There were no statistically significant differences in mean IOP reduction from baseline between brimonidine–Purate and dorzolamide at any individual timepoint or in the circadian curve \((p \geq 0.05)\). The mean circadian IOP was 16.9 mmHg with brimonidine–Purate and 16.8 mmHg with dorzolamide. At the 8 a.m. timepoint when IOP reached its highest levels, mean IOP was 18.4 mmHg with brimonidine–Purate and 18.9 mmHg with dorzolamide. The results of this industry-sponsored study suggest that brimonidine–Purate is at least as effective as dorzolamide in providing 24-h IOP control when used as adjunctive therapy with latanoprost. The only significant difference between treatments in the incidence of adverse events was a statistically higher incidence of bitter taste with dorzolamide treatment (24% vs. 0% with brimonidine, \(p = 0.01\)).

**Fixed combinations with timolol**

A fixed combination of dorzolamide 2.0%/timolol 0.5% (Cosopt, Merck & Co, Inc.; Whitehouse Station,
IOP with timolol BID and brimonidine BID in reducing timolol BID was as effective as concomitant therapy monotherapy, the fixed combination of brimonidine/timolol overall (confidence level > 0.96)\(^{45,48}\), but it is equivalent in efficacy to concomitant dorzolamide and timolol when each medication is dosed twice daily\(^{45}\).

In some countries, a fixed combination of brimonidine 0.2%/timolol 0.5% (Combigan, Allergan Inc; Irvine CA, USA) is also available. In a controlled 3-month clinical study in patients with glaucoma or OHT, the fixed combination of brimonidine/timolol BID (\(n = 385\)) reduced IOP significantly more than did either timolol BID (\(n = 392, p \leq 0.026\)) or brimonidine TID (\(n = 382, p < 0.001\)) alone\(^{45}\). These findings were verified in a 12-month trial\(^{45}\) in which mean IOP reductions were greater with fixed brimonidine/timolol than timolol 0.5% BID alone at all measured timepoints (\(p \leq 0.002\)), and greater than brimonidine 0.2% TID alone at all but one measured timepoint (\(p < 0.001\)). In another randomized controlled trial in 371 glaucoma and OHT patients with inadequate IOP control after at least 3 weeks run-in on any monotherapy, the fixed combination of brimonidine/timolol BID was as effective as concomitant therapy with timolol BID and brimonidine BID in reducing IOP\(^{45}\). Differences between the fixed combination and concomitant therapy were \(\leq 0.35\) mmHg for mean IOP and \(\leq 0.30\) mmHg for mean change from baseline IOP at all timepoints over the 12-month study, and none of the differences were statistically significant (\(p \geq 0.274\)).

**Brimonidine plus timolol versus dorzolamide/timolol fixed combination**

Two studies that compared the fixed combination of dorzolamide/timolol with brimonidine plus timolol concomitant therapy were found\(^{49,62}\). Following similar designs, these studies showed that the two treatments have comparable tolerability and efficacy.

Sall and associates reported a prospective, investigator-masked, randomized, parallel-group 6-month comparison study of concomitant brimonidine 0.2% BID and timolol 0.5% BID (\(n = 149\)) versus fixed-combination dorzolamide 2%/timolol 0.5% BID (\(n = 144\)) in glaucoma and OHT patients with IOP uncontrolled after a 3-week run-in on timolol\(^{48}\). IOP was measured at 9 a.m. (trough, just before dosing) and 11 a.m. (peak) at baseline and Months 1, 3, and 6 for this industry-sponsored study. Baseline mean IOP on timolol was similar between the treatment groups (24.44 mmHg for fixed combination dorzolamide/timolol vs. 24.29 mmHg, \(p = 0.659\)). Adjusted mean IOP reductions took treatment group, study site, and baseline IOP into account using analysis of covariance models. In the modified intent-to-treat patient population, the adjusted mean IOP reduction over follow-up ranged from 3.7 to 5.5 mmHg with brimonidine plus timolol and 3.1 to 5.0 mmHg with dorzolamide/timolol, but none of the between-group differences were statistically significant (\(p \geq 0.062\)). In the per-protocol patient population, the primary efficacy endpoint (mean IOP reduction from baseline at 11 a.m. at Month 3) was statistically significant in favor of concomitant brimonidine and timolol therapy (an adjusted mean IOP reduction of 5.77 mmHg with brimonidine and timolol vs. 4.87 mmHg with dorzolamide/timolol, \(p = 0.046\)). The overall incidence of treatment-related adverse events was 64% for fixed combination dorzolamide/timolol and 60% for concomitant brimonidine plus timolol (stated non-significant). Ocular burning, ocular stinging, and taste perversion occurred at significantly different rates between treatment groups; each of these adverse events was more common in the dorzolamide/timolol group: ocular burning was reported by 41% of dorzolamide/timolol patients versus 20% of brimonidine plus timolol patients (\(p < 0.001\)), stinging was reported by 22% in the dorzolamide/timolol group and 12% on brimonidine plus timolol (\(p = 0.024\)), taste perversion was noted by 26% of dorzolamide/timolol patients and by 10% of patients using brimonidine plus timolol (\(p < 0.001\)). Five percent of patients in each group discontinued from the study because of adverse events. The results of this study suggest that concomitant treatment with brimonidine and timolol is associated with less stinging, burning, and taste perversion than the dorzolamide/timolol fixed combination over 6 months and may provide better efficacy at peak effect.

A prospective, investigator-masked, randomized, parallel-group, industry-sponsored 3-month comparison trial of concomitant brimonidine BID and timolol BID (\(n = 250\)) versus fixed-combination dorzolamide/timolol BID (\(n = 242\)) was performed in glaucoma and OHT patients with IOP uncontrolled after a 3-week run-in on timolol\(^{48}\). IOP was measured at 8:30 a.m. (trough) and 10:30 a.m. (peak) at baseline, Month 1, and Month 3. Patient convenience and satisfaction were also evaluated at Month 1 and Month 3 using a survey. Baseline mean IOP on timolol was 24.1 mmHg for both treatment groups (\(p\)-value not given). The primary efficacy outcome measure (mean IOP reduction from baseline at 10:30 a.m. at Month 3) was statistically significant in favor of
concomitant brimonidine and timolol therapy (mean IOP reduction of 5.3 mmHg with brimonidine and timolol vs. 4.3 mmHg with dorzolamide/timolol, p < 0.001). The mean IOP reduction at 8:30 a.m. at the Month 3 visit was similar between treatment groups (3.5 mmHg with brimonidine and timolol vs. 3.3 mmHg with dorzolamide/timolol). There were no significant differences between treatment groups in the overall incidence of treatment-related adverse events (21% with brimonidine and timolol vs. 28% with dorzolamide/timolol, stated non-significant) or in discontinuations because of adverse events not necessarily related to treatment (7% with brimonidine and timolol vs. 5% with dorzolamide/timolol). Burning was reported by 14% of the dorzolamide/timolol group versus 2.4% of the brimonidine plus timolol group, stinging occurred at a rate of 4.9% for dorzolamide/timolol versus 1.6% for brimonidine plus timolol, and taste distortion occurred in 4.5% of dorzolamide/timolol patients versus 0% of those on brimonidine plus timolol, but none of these means were significantly different. There were no significant differences between treatment groups in patient-reported convenience or satisfaction with treatment after either 1 or 3 months (p ≥ 0.056). The results of this study suggest that both treatments are well tolerated, and that concomitant therapy with brimonidine and timolol provides better efficacy at peak effect and similar efficacy at trough effect compared with fixed-combination dorzolamide/timolol therapy.

Brimonidine/timolol fixed combination versus dorzolamide/timolol fixed combination

One study that compared fixed combination dorzolamide/timolol with fixed combination brimonidine/timolol was identified. In this prospective, multicenter, masked-observer, crossover comparison, 30 primary open-angle glaucoma or OHT patients were washed out from their previous medication for 4 weeks. They were next randomized to begin the first 4-week treatment period on either fixed combination brimonidine/timolol BID or fixed combination dorzolamide/timolol BID. After a second 4-week wash-out period, they were switched to the second medication for a final 4-week period. Baseline mean diurnal IOP was 22.9 mmHg, and both fixed combinations significantly reduced IOP relative to baseline (p < 0.00001). Both the mean diurnal IOP (p = 0.510) and mean diurnal reduction from baseline (p = 0.430) were comparable for the fixed combinations. The incidence of reported ocular adverse events was the same for each drug (p = 0.359), but fixed combination dorzolamide/timolol was associated with more ocular stinging upon instillation (30%) than fixed combination brimonidine/timolol (3.3%; p = 0.027). Both fixed combinations effectively reduce IOP, but brimonidine/timolol may be more comfortable to use.

Discussion

Comparison studies of brimonidine and dorzolamide cover a range of treatment combinations, durations of therapy, and measurement timepoints. Many are too small for statistical power. On the whole, however, the studies show that when used either as monotherapy or as adjunctive therapy, brimonidine tends to reduce IOP more than dorzolamide at peak effect, and brimonidine and dorzolamide show similar IOP-lowering efficacy at trough effect. The overall incidence of adverse events was similar between drugs; however, burning, stinging and bitter taste were often more common with dorzolamide than with brimonidine in the studies reviewed here. There was no difference in the incidence of treatment-related ocular allergy between brimonidine and dorzolamide, even in the longer-term (6-month) study.

Efficacy findings are consistent with a meta-analysis of these drugs when used as monotherapy. The meta-analysis included data from randomized controlled trials published through December 2003. The average percentage reduction of IOP from baseline after 1 month of treatment was 25% (95% confidence interval (CI): 28–22%) for brimonidine 0.2% and 22% (95%CI: 24–20%) for dorzolamide 2% at peak effect (2h after morning dosing) and 18% (95%CI: 21–14%) for brimonidine and 17% (95%CI: 19–15%) for dorzolamide at morning trough (just prior to dosing).

The reason for the greater IOP reduction with brimonidine at peak effect might involve the physiological mechanism of the actions of the drugs. Dorzolamide reduces IOP by inhibiting aqueous production; there are no reports in the literature that it affects outflow. On the other hand, brimonidine reduces IOP by a dual mechanism involving both inhibition of aqueous production (the predominant effect with short-term treatment) and stimulation of aqueous outflow through the uveoscleral pathway (the predominant effect with chronic treatment). The ability of brimonidine to increase aqueous outflow might confer better additivity with aqueous suppressants such as beta-blockers. Data directly comparing the effects of brimonidine and dorzolamide on aqueous dynamics are limited. In a randomized, double-masked, placebo-controlled study in 20 normal subjects dosed BID with each drug, aqueous flow was measured after three doses of drug. The study was limited because brimonidine was compared to placebo in the fellow eye, and dorzolamide...
was compared to prior placebo treatment of the same eye while the fellow eye was treated with brimonidine and dorzolamide, making a contralateral eye effect possible. The results of the study, nonetheless, showed a trend for greater reduction of aqueous flow with brimonidine (28.2%) compared with placebo than with dorzolamide (19.3%; p < 0.09).

Larger IOP variation, as well as higher IOP, is associated with increased risk of glaucoma progression. None of the comparison studies discussed in this review evaluated IOP variation or the ability of dorzolamide and brimonidine to provide stable IOP over time or protect against glaucomatous progression. However, in a study in which glaucoma patients on monotherapy were given a water drinking test, patients treated with brimonidine BID showed a significant elevation in IOP over baseline (p ≤ 0.05) for only 45 min after drinking 1 L of water, and their IOP levels peaked at 20% over the baseline value. In contrast, patients treated with dorzolamide TID showed a significant elevation in IOP (p ≤ 0.05) for at least 105 min after drinking the water, and their IOPs peaked at 29% over the baseline value. Although the study was limited in that patients were not randomized to treatment, the results suggest that brimonidine may be more effective than dorzolamide in stabilizing IOP in particular stress conditions, and the authors suggested that the effect of brimonidine on aqueous outflow explains its ability to stabilize IOP better than aqueous inhibitors such as dorzolamide.

Because the once-daily prostaglandin analogues and non-selective beta-blockers reduce IOP more effectively as primary agents, dorzolamide and brimonidine are not usually used as first-line therapy. However, many patients receive adjunctive therapy with these drugs, and alpha agonists and carbonic anhydrase inhibitors may be preferred second-line therapy. It is important to choose an effective medication when adding to ongoing therapy, because if IOP is not low enough on a 2-drug regimen, the long-term success rates associated with the addition of a third or fourth medication are not high. Almost all comparative studies of brimonidine and dorzolamide in adjunctive therapy have added them to a beta-blocker. The results have generally shown better peak IOP lowering with brimonidine and similar IOP lowering with the drugs at trough, even when brimonidine was dosed BID and dorzolamide was dosed TID. Only one randomized controlled trial evaluated brimonidine and dorzolamide as adjunctive therapy with a prostaglandin analogue (latanoprost). In that study, no significant differences were found between the drugs. However, the study was small, with sample sizes chosen to give a power of 80% to detect a 1.5 mmHg difference between treatment groups, and differences on the order of 1 mmHg would likely go undetected. Additional studies are needed to determine the relative efficacy of brimonidine and dorzolamide as adjunctive therapy with prostaglandin analogues.

Fixed-combination therapy offers several potential advantages over concomitant therapy with two drugs. The fixed-combination regimen is more convenient, and this simpler regimen might enhance compliance. Use of fixed combinations might also be associated with decreased corneal exposure to preservatives and decreased costs. Studies have demonstrated that concomitant treatment with brimonidine and timolol lowers IOP significantly more than fixed combination dorzolamide/timolol at peak effect and is as well tolerated as the dorzolamide/timolol combination over 6 months of treatment. A recent study showed that the fixed combinations are at least equally effective, and overall findings reviewed here suggest that replacement of the dorzolamide/timolol combination with the brimonidine/timolol combination may provide better efficacy. Over longer periods of use, allergic blepharocconjunctivitis associated with chronic brimonidine treatment may become an additional concern. Interestingly, the combination of brimonidine and timolol is associated with lower incidence of allergy than brimonidine alone. Long-term direct comparison studies of dorzolamide/timolol and brimonidine/timolol will be needed to determine the relative efficacy and tolerability of these fixed combinations for chronic treatment.

Conclusions

Brimonidine and dorzolamide are both good choices for second-line therapy in glaucoma. With studies showing comparable or greater efficacy in reducing IOP, and less incidence of discomfort, brimonidine may prove to be a more effective choice for many patients.

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