Expert Opinion

Brimonidine for glaucoma

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Importance of the field: Brimonidine is a drug used in the management of glaucoma throughout the world and is the most modern α_2-adrenoceptor agonist available. This review comprehensively discusses the use of brimonidine for glaucoma.

Areas covered in this review: A historical insight into the development of selective adrenergic glaucoma drugs is given, followed by a description of the mechanisms of action and a discussion of the main clinical trials investigating clinical applications. The safety of brimonidine is evaluated, and our expert opinion is provided on how brimonidine is used in our clinical practice. The most relevant literature on the role of brimonidine in glaucoma is discussed.

What the reader will gain: A clear understanding of the role of brimonidine for glaucoma treatment, with an explanation of its efficacy, limitations and use in clinical practice.

Take home message: Brimonidine is an effective drug for lowering intraocular pressure. It has potentially serious systemic effects in children, in whom it is contraindicated. Its use in adults is limited by its ocular side effects such as allergy. Brimonidine is, however, an important part of the range of intraocular pressure lowering drugs available to prescribers.

Keywords: α_2-adrenoceptor agonist, brimonidine, combigan, glaucoma, neuroprotection

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1. Introduction

Glaucoma is a group of slowly progressive diseases affecting the optic nerve. Many patients are unaware that they have the condition until irreversible damage to the optic nerve has occurred [1]. Untreated, progressive visual field loss can occur, and glaucoma is the second leading cause of blindness worldwide [2]. Glaucoma is considered to be a multifactorial disease and intraocular pressure (IOP) is a significant risk factor associated with the development of optic nerve neuropathy [3,4].

High IOP may be controlled both medically and surgically. Surgical treatments for glaucoma are only used when medical or laser treatments have failed to reach a satisfactory IOP. An in-depth discussion of the surgical treatments of glaucoma is beyond the scope of this review, but the current 'gold standard' surgical treatment is trabeculectomy. Surgical treatments are continually evolving with recent developments such as the use of expanded polytetrafluoroethylene implants [5] and Ologen™ implants [6]. There are also some reports that some novel devices such as the Trabectome (Neomedix, Inc., USA), iStent (Glaukos, USA) and Solx shunt (Solx, USA) (suprachoroidal shunt) may control IOP satisfactorily and without the need for antifibrotic agents or external filtering bleb formation [7].

Medical therapy has been used to lower IOP for many years, and the earliest glaucoma therapies were drugs that stimulated either the parasympathetic or the sympathetic system. The oldest recorded glaucoma medications were topical cholinergic agents, with pilocarpine and physostigmine being used in the late 19th century [8,9] and ecothiopate iodide in the 1950s [10]. Epinephrine (adrenaline) as a repeated subconjunctival injection, or as a topical drop, has been used to treat glaucoma from the 1920s, but variable IOP lowering results and adverse side effects such as cardiac

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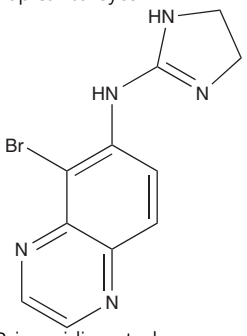
Box 1. Drug summary.

Drug name	Brimonidine
Phase	Post marketing
Indication	Raised intraocular pressure
Pharmacology description/mechanism of action	α_2-Adrenoceptor agonist
Route of administration	Topical to eyes
Chemical structure	
Pivotal trial	Brimonidine study group trials [41-45,59,60]

arrhythmias caused the avoidance of its use [11,12]. Renewed interest in sympatheticomimetic agents eventually led to the development of dipivalyl epinephrine (dipivefrine, DPE), a prodrug of epinephrine that penetrates the eye about 17 times better than its parent compound [13]. Due to its superior topical penetration, a concentration of 0.1% DPE was found to be as effective as 1 – 2% epinephrine hydrochloride [14,15], but DPE's systemic and topical side effects also caused it to fall out of use.

The search continued to develop a drug that would have the ability to lower IOP, whilst minimizing systemic sympatheticomimetic side effects. This led to the development of selective adrenergic agents. The first agent of this emerging class of drugs was clonidine (**Figure 1A**), an α_2-adrenoceptor agonist [16]. Although the topical form lowered IOP, it also significantly lowered blood pressure, and it has only been approved for glaucoma treatment in Europe and not in the US. In the 1980s, a second generation α_2-adrenoceptor agonist, apraclonidine, was produced (**Figure 1B**). It contains a para-amino group that makes it more hydrophilic, limiting its transport through the BBB, and thereby limiting CNS-mediated systemic adrenergic affects. However, apraclonidine was found to have a high rate of tachyphylaxis and topical side effects such as conjunctivitis [17], and it is now only used to control short-term IOP spikes such as following yttrium aluminium garnet laser iridotomies.

Brimonidine is a third generation α_2-adrenoceptor agonist introduced in 1996 (**Box 1**). Its chemical nomenclature is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate, and it was formerly known as UK-14304-18 and AGN 190342-LF (**Figure 1C**). It differs from clonidine and apraclonidine by containing a quinoxaline ring system and bromine as a side group, instead of chlorine. It has been found to have a significantly higher α_2-adrenoceptor affinity, in the order of 23- to 32-fold [18]. The purpose of this paper is to review the use of brimonidine as a modern drug for the treatment of glaucoma.

2. Mechanism of action

Brimonidine exerts its effects in the eye due to its high α_2-adrenoceptor affinity, for which it is considered a standard reference compound [19]. In radioligand binding assays using human colonic cell lines (α_2-adrenoceptors) and human cerebral cortex neurons (α_1-adrenoceptors), the ratio of α_2:α_1-adrenoceptor selectivity was 974 for brimonidine, 151 for clonidine and 30 for aparaclonidine, thus, indicating that brimonidine was 6 – 32 times more selective for α_2-adrenoceptors than clonidine and apraclonidine, respectively [18]. Studies using *in vitro* ligand binding and autoradiography have demonstrated a large number of specific brimonidine binding sites on human iris and ciliary epithelium, with a smaller number of binding sites on human ciliary muscle [20].

Brimonidine lowers IOP by both reducing aqueous humor production and increasing aqueous outflow via the uveoscleral pathway [21]. Both of these mechanisms are mediated by stimulation of ocular α_2-adrenoceptors. Topical application of brimonidine reduced aqueous production in monkeys [22] and increased uveoscleral outflow in rabbits [23]. In humans, aqueous production (measured by fluorophotometry) was reduced by 20% in the treated eyes and by 12% in the contralateral untreated eyes of patients with ocular hypertension receiving brimonidine 0.2% twice daily for 1 week [21]. Furthermore, a fivefold increase in uveoscleral outflow was evident in treated eyes only. In this study, brimonidine did not appear to affect the episcleral venous pressure, fluorophotometric outflow facility or tonographic outflow facility [21].

Brimonidine may also have a neuroprotective effect independent of its ability to lower IOP. The mechanisms underlying this are not fully understood but may include an upregulation of basic fibroblast growth factor [24], causing a cell hyperpolarization and a reduction in the release of glutamate from neurons [25], or an upregulation of antiapoptotic genes [26]. Previous studies in human tissue have identified a number of brimonidine binding sites in the retina, retinal pigment epithelium and choroid [20], and α_2-adrenoceptors have also been identified in the retina and retinal pigment epithelium [27]. Moreover, one study has demonstrated that vitreous samples from patients taking brimonidine contained mean concentrations of the drug of 185 nM [28], and this is in excess of the 2 nM level previously determined to activate α_2-adrenoceptors [18]. It has been found that intraperitoneal injections of brimonidine produced a dose-dependent reduction in the secondary degeneration of retinal ganglion cells in an acute optic nerve crush model [29]. Similarly, a previous study using a model of chronic ocular hypertension in rats in

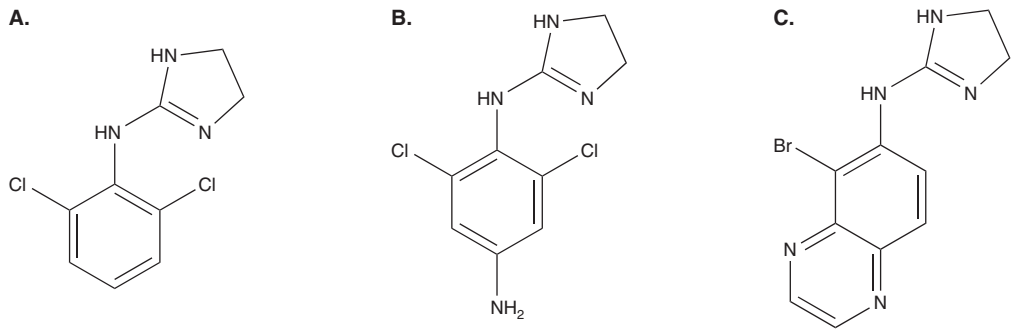


Figure 1. The α-adrenoceptor agonists. A. Clonidine, the first α-adrenoceptor agonist used in glaucoma. **B.** Apraclonidine, a second generation α-adrenoceptor agonist. Note the para-amino group that differentiates it from clonidine. **C.** Brimonidine, the latest third generation α-adrenoceptor agonist which differs from apraclonidine by containing a quinoxaline ring system and bromine as a side group, instead of chlorine.

which the episcleral and limbal veins were photocoagulated to increase IOP revealed that systemic application of brimonidine was associated with a statistically significant reduction in the loss of retinal ganglion cells [30]. However, there is no definitive evidence in the current literature that brimonidine has a neuroprotective effect in humans; studies to investigate this are currently ongoing [31,32].

The topical application of brimonidine results in IOP reduction within 1 h. The peak effect is achieved within 2 – 3 h and the trough drug effect occurs 10 – 14 h after installation [33]. Animal studies, and a few studies involving human subjects, have suggested that mainly the cornea, and to a lesser extent the sclera and conjunctiva, are the major pathways for intraocular absorption of brimonidine [34]. The retention and absorption of brimonidine may be increased by drug binding to ocular melanin [35]. Brimonidine has been demonstrated to have marked affinity for melanin containing ocular tissues *in vivo* with peak concentrations of the drug in the iris-ciliary body, being fourfold higher in pigmented than in albino rabbits [36]. Brimonidine undergoes extensive hepatic metabolism. Oxidation of the drug by liver aldehyde oxidase has been implicated as the major metabolic pathway in humans resulting in the formation of 2-oxobrimonidine, 3-oxobrimonidine and 2,3-dioxobrimonidine [37]. The elimination half-life in human plasma after a single topical dose has been found to be about 2 h [38].

3. Clinical applications

Initial clinical studies of brimonidine investigated its role in the prevention of laser trabeculoplasty pressure spikes, and these showed that the efficacy of brimonidine in 0.5 and 0.2% concentrations was similar to that of apraclonidine [39]. An early study found that brimonidine in concentrations of 0.08, 0.2 and 0.5% with twice daily dosing lowered IOP by 20 – 30% in glaucoma and ocular hypertension patients [40]. The study was, however, limited in its scope as it was nonrandomized, and only 1 month in duration. The 0.2% concentration had the least ocular and systemic side effects and was at the peak of the dose–response curve.

This report was followed by more robust studies. Two large, 1 year, randomized, double-masked, multi-center clinical trials comparing brimonidine tartrate 0.2% with timolol maleate 0.5% reported that IOP was significantly lower at peak (2 h after instillation) in the brimonidine group, but that the ocular hypotensive effect was not as great as timolol at trough (12 h after instillation) [41]. Overall, brimonidine showed sustained IOP lowering efficacy comparable with timolol, but with significantly fewer negative chronotropic effects on the heart. Data from trials after 3 or 4 years of continuous use demonstrated that brimonidine maintained an IOP lowering efficacy comparable with timolol, and assessment of long-term visual field preservation was similar with both drugs [42,43].

A further 3 month, multi-centered, randomized, double-blind, parallel group study compared brimonidine with betaxolol 0.25% and reported that brimonidine had significantly higher decreases in IOP at both peak and trough with greater tolerability [44]. A later study also judged that brimonidine had a higher clinical success rate than betaxolol when comparing factors such as IOP reduction, adverse effects and quality of life effects [45]. It must, however, be noted that this study had a relatively small sample size and was carried out over a short period of time; adverse effects and allergic reactions might not have had time to manifest fully.

A large meta-analysis of 15 publications on 14 trials comparing latanoprost 0.005% to brimonidine 0.2% found that once daily dosage of latanoprost lowered IOP more effectively than brimonidine used twice daily up to 1 year after initial treatment for normal tension glaucoma, ocular hypertension and open angle glaucoma [46]. Moreover, this meta-analysis found that brimonidine had a higher association with fatigue than latanoprost.

Three separate studies have evaluated the efficacy and safety of brimonidine compared with dorzolamide when used as

monotherapy, and whilst there was no overall difference in IOP lowering efficacy, ocular burning and stinging were more common with dorzolamide [47-49]. These studies are, however, limited by their low patient numbers and relatively short periods of follow-up.

A direct ranking of the efficacy of IOP reduction by glaucoma drugs is difficult as not all studies compare all drugs directly, but a recent study using network meta-analysis of 28 randomized control trials of eight different glaucoma drugs (brimonidine, bimatoprost, travoprost, latanoptost, timolol, dorzolamide, betaxolol and brinzolamide) found that brimonidine had the fourth highest drop in IOP at peak, but had the lowest IOP reduction of the eight drugs investigated at trough [50].

The efficacy and safety of brimonidine as an adjunctive therapy has also been investigated in several randomized controlled studies. The addition of brimonidine to ongoing β-blocker therapy [51,52] and to latanoprost [52,53] both result in significant further IOP reduction. Brimonidine 0.15% has also been found to give the most reduction in IOP when used as adjunctive therapy with a prostaglandin analogue than either brinzolamide or dorzolamide [54]. Similarly, the addition of brimonidine 0.2% to maximum tolerated medical therapy in patients with several different types of glaucoma resulted in a decrease in IOP from 16 to 32% [55].

In 2007, a novel fixed combination of timolol 0.5% and brimonidine 0.2% (Combigan, Allergan, Irvine, CA, USA) was introduced. Two 12 month, randomized, double masked multi-center clinical trials investigated the efficacy of Combigan in comparison with either of the component drugs separately, and it was found that Combigan had a superior IOP lowering effect than monotherapy. Adverse effects were found to be lower with Combigan than with brimonidine, but higher than with timolol [56]. A recent 3 month randomized control trial comparing Combigan with 2% dorzolamide–0.5% timolol (Cosopt, Merck, Whitehouse Station, NJ, USA) fixed combination therapy found that Combigan had both greater efficacy in lowering IOP and was better tolerated with fewer patients complaining of ocular burning, stinging or unusual taste than with dorzolamide–timolol [57]. However, no significant difference in either efficacy or tolerability was found between Combigan and 2% dorzolamide–0.5% timolol in an earlier study [58]. The reason for this discrepancy is not entirely clear but the earlier study had a more robust methodology and included the effect of diurnal variation on IOP; this was not done in the later study.

These clinical studies show that brimonidine is an effective ocular hypotensive agent as a monotherapy, an adjunctive agent and a combination therapy and that the effect is sustained over time.

4. Safety evaluation

Several studies have reported the overall safety and efficacy of brimonidine 0.2% after 1, 3 and 4 years. Brimonidine is not known to be associated with clinically significant effects on mean heart rate, lung function or blood pressure [42,59,60] and is not contraindicated in patients with cardiopulmonary disease. The most common systemic side effects include fatigue or drowsiness, dry mouth and headache [42,59,60]. There is laboratory evidence that α_2-adrenoceptor agonists may potentiate smooth muscle vasoconstriction in arteries [61], and brimonidine is, therefore, contraindicated in cerebral or coronary insufficiency, postural hypotension and Raynaud's disease. Post-mortem studies in the brains of depressed suicide victims have found an increase in the density and affinity of α_2-adrenoceptors [62,63], and brimonidine is, therefore, contraindicated in depression. Due to its extensive hepatic metabolism, brimonidine use is also contraindicated in patients with hepatic insufficiency.

Long-term administration of brimonidine is limited by its propensity to cause ocular allergic reactions. The incidence of blepharitis and belpharoconjunctivitis has been reported as 9 – 12.7% [41,59,64], follicular conjunctivitis has been found in 7.8 – 12.7% of patients [41,59] and conjunctival hyperemia has an incidence of 26.3 – 30.3% [65,66]. However, allergic reactions may take several years to manifest, and there is evidence from a recent 26 year surveillance of glaucoma medical therapy that these 1 year studies may have significantly underestimated the true incidence of ocular allergy with brimonidine, which may be as high as 32.3% [65].

Brimonidine may also increase the likelihood of allergy to subsequently used preparations. It has been reported that in patients allergic to both brimonidine and another drug, the mean time interval between the first and second drug allergies was shorter when brimonidine was used initially and allergy to it occurred first [66]. This is of clinical significance, as this suggests that an allergy to brimonidine may jeopardize the future medical management of patients with glaucoma, resulting in the need for surgery.

Such ocular allergic reactions may be due to a class effect as similar problems are seen with other α-adrenoceptor agonists such as apraclonidine [17]. The reasons for this are unclear, but it has been hypothesized that adrenergic agents may reduce the volume of conjunctival cells, thus, producing a widening of intercellular spaces through which potential allergens may reach the subepithelial tissues causing allergy [67]. It may, therefore, be advisable to avoid adrenergic agents such as brimonidine in patients with a known history of other ocular surface allergies such as atopy and hay fever.

In an attempt to reduce ocular surface allergy, Allergan, Inc. have also released a reformulated solution of brimonidine with chlorine dioxide as a preservative (Purite™), in place of benzalkonium chloride (BAK), and reduced the concentration of brimonidine to 0.15%. Whilst this appears to have similar efficacy in reducing IOP as brimonidine 0.2% preserved with BAK, one early study demonstrated a reduction in adverse effects [68], but another has shown no difference [69]. Moreover, a recent meta-analysis of two Phase III studies showed that although reducing the concentration of

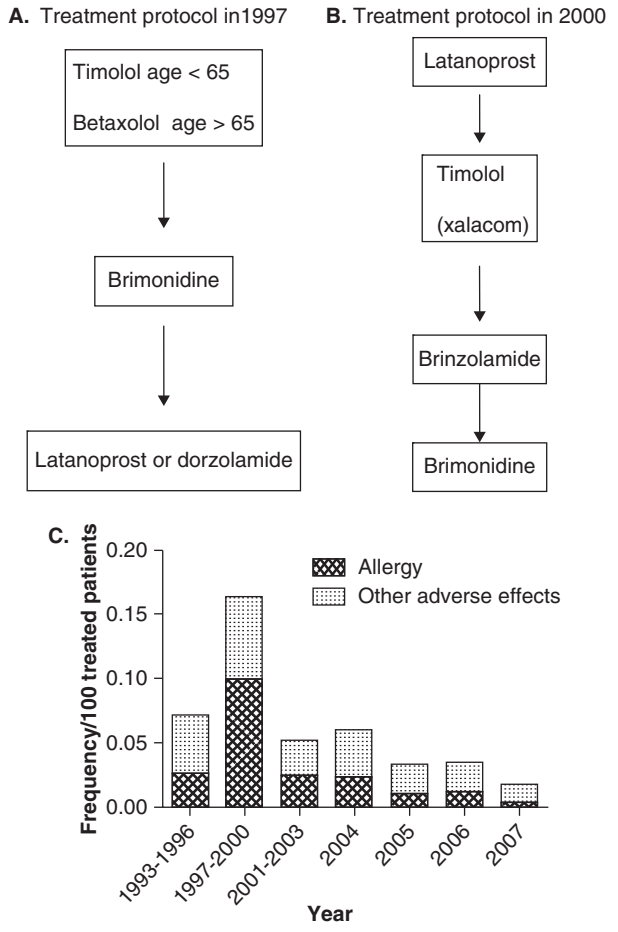


Figure 2. Drug treatment protocols and the number of discontinuations per treatment year. A. The initial treatment protocol in 1997 with brimonide as favored second-line agent. **B.** The modified treatment protocol in 2000 after our initial audit of adverse effects. **C.** The number of drug discontinuations per year. Note the dramatic decline following the change of protocol in 2001 – 2003.

brimonidine purite to 0.1% reduced the systemic side effects, no difference was made to the ocular surface side effects [70].

The fixed combination of timolol 0.5% and brimonidine 0.2% (Combigan) dosed twice daily has, however, shown lower rates of allergy compared with brimonidine alone, but higher than with timolol [56,71]. This may be because timolol's β-blocker effects may cause vasoconstriction and reduced conjunctival hyperemia. It may also be attributable to the lower concentration of BAK present in Combigan than in brimonidine alone [56].

There are also several case reports linking brimonidine to granulomatous uveitis [72-74]. These episodes occurred 10 – 15 months after topical administration, and all resolved following cessation of administration. In several cases, rechallenging the patient with brimonidine caused a recurrence [72,73]. Although these cases are sporadic and the lack of similar episodes being reported with other sympatheticomimetic drugs is not enough to establish absolute causality [75], the potential occurrence of this sight threatening problem is worth noting.

Importantly, brimonidine is absolutely contraindicated in children. It has been linked with side effects associated with CNS depression in neonates and infants, with several infants requiring hospitalization after its use [76,77]. In one series, two young children (aged <4 years) were unarousable after its administration, and five other children experienced extreme fatigue [78]. These effects may occur because children have a less mature BBB to stop brimonidine and prevent CNS effects. Moreover, CNS depression mimicking opioid toxicity with apnea and bradycardia has been reported in a young child after accidental ingestion [79], and similarly, sedation, cardiorespiratory depression and hyperglycemia have been reported within minutes of an accidental ingestion of a single drop of brimonidine in a neonate [80].

5. Conclusion

Brimonidine is a third generation α_2-adrenoceptor agonist whose efficacy in IOP reduction has been confirmed in several studies. It is available both as a monotherapy and as a fixed combination therapy with timolol, in the form of Combigan. In adults, its use is limited by its high incidence of ocular side effects, such as allergy. Its serious systemic side effects in young patients mean that it is absolutely contraindicated in children. Although it is now rarely used as a first-line glaucoma drug, brimonidine remains an important part of the range of IOP reducing drugs available to physicians as an adjunctive agent or in patients in whom other classes of drugs may not be suitable.

6. Expert opinion

Our evidence based practice is largely governed by results from a large and unique computerized database that has been established at a single consultant's (D Montgomery) glaucoma clinic at Glasgow Royal Infirmary, with the main aim of investigating the tolerability of glaucoma medications in patients with primary open angle glaucoma, ocular hypertension and normal tension glaucoma [65]. This contains complete treatment histories of >950 patients, with data collected from 1981 to the present day, representing >7000 patient treatment years. This has shown that there has been a decline in the use of brimonidine over the past decade.

With the introduction of novel drugs such as brimonidine in the mid-1990s, our clinic adopted the treatment protocol shown in **Figure 2A**. This attempted to arrange the newer agents in a hierarchy, with brimonidine selected as the favored second-line agent following β-blockers. Initial audit using the database, however, quickly revealed an unacceptable increase in the discontinuation rate due to adverse effects in the years that followed. It was clear that brimonidine was particularly

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