

# Optimum VA

NAVAO Newsletter

January 2003

## President's Report

*VA Optometry news.*

Happy New Year! I hope everyone had a nice Holiday Season. It seems like ages ago that we were together in San Diego when in reality it was 4 weeks ago! Time flies when you're having fun.

Our annual NAVAO Dinner this year had record attendance of about 135 folks. The gala is becoming an annual bash at the AAO and its gratifying that the leaders in our profession understand the contribution of VA Optometry. At our dinner, we happily awarded **Dr. Charlie Mullen** a **Lifetime Achievement Award** for his many contributions not only to the **Department of Veterans Affairs** and our nation's veterans but to all of optometry for his pro-active approach and vision of optometry as the primary eye care profession as early as 1970!

Our guest speaker, **Dr. Linda Johnson** gave an excellent presentation of the history of the VA and academic affiliations. Dr. Johnson's remarks were very well received and it was a pleasure to meet her.

Having spent some great years at **West Los Angeles VAMC**, I was happy to see that **Dr. Pauline Ilsen** (one of my former residents I might add) won the **Eagle Award** for the best VA publication in **Optometry, Journal of the American Optometric Association**. I'm sure my fellow residency program directors and supervisors can appreciate the pride one feels when your former trainees achieve the right kind of success. Congratulations Pauline!

Now its 2003 and the profession and VA Optometry moves forward. We have an excellent leader in John Townsend, we have great support in Central Office, and we are on the threshold of moving to the logical next level and will lead the profession where it needs to go. What I'm referring to of course is **Advanced Competency Recognition** for VA Residency Trained individuals. We are working with all the stakeholders in optometry under the AAO/AOA umbrella. We're also working with ASCO and NBEO. The end result should be a credible procedure to recognize advanced competence that can stand up to scrutiny from anyone.

Residency recruitment is critical in any year and I urge all of you to get out there and make sure you have quality candidates. This may mean reaching out rather than waiting for candidates to come to you. Our residency program is critical to the profession and VA Optometry....protect it like the treasure it is.

Enjoy the winter and I'll see you in the spring!

- Jerry

## Clinical Pearls

*Highlights from recent publications.*

### **THE AGIS STUDY: RISK FACTORS FOR FAILURE OF TRABS AND ALT**

779 eyes from the original 591 patients aged 35-80 years old that participated in the Advanced Glaucoma Intervention Study were included in this study. The risk of ALT failure was associated with younger age and higher pre-intervention intraocular pressure. Failure of trabeculectomy was associated with younger age, higher pre-intervention IOP, diabetes and postoperative complications such as elevated IOP and inflammation

*The AGIS Investigators. AJO October 2002: 481-498.*

## **THE AGIS STUDY: RISK FACTORS FOR VISUAL FIELD LOSS AND VISUAL ACUITY**

747 eyes from the original 591 patients aged 35-80 years old that participated in the Advanced Glaucoma Intervention Study were included in this study. Being male was associated with sustained visual field loss in both treatment arms. In the ALT/Trab/ALT sequence arm, baseline visual acuity was associated with sustained visual field loss while diabetes was a risk factor in the Trab/ALT/Trab treatment arm. The risk factors for sustained visual acuity loss in both treatment arms was better baseline visual acuity, older age and less formal education.

*The AGIS Investigators. AJO October 2002: 499-512*

## **XALATAN VS RESCULA IN PATIENTS WITH ELEVATED IOP**

165 patients who had previously been treated due to an elevated IOP of > 25 mm Hg in one or both eyes underwent a washout and were randomly assigned to latanoprost 0.005% once daily in the evening or unoprostone 0.15% twice daily. The mean IOP reduction for latanoprost was 28% compared to 15% for unoprostone.

*Jampel H, Bacharach J, Sheu W, et al. AJO December 2002: 863-71*

## **THE EARLY MANIFEST GLAUCOMA TRIAL**

250 patients aged 50-80 years with early glaucoma (median mean deviation = -4 dB and median IOP of 20 mm Hg) were identified through a population screening. 129 patients underwent ALT plus topical betaxolol hydrochloride while 126 patients received no treatment. 5.1 mm Hg or 25% reduction of IOP was maintained throughout the follow-up. After 6 years, progression was less frequent in the treatment group (45%) compared to the control group (62%).

*Heijl A, Leske MC, Bongtsson B, et al. Archives October 2002: 1268-1279*

## **LUMIGAN COMPARED TO TIMOLOL IN PATIENTS WITH GLAUCOMA AND OC HTN**

Patients were randomized to 0.03% bimatoprost once daily, twice daily or 0.5% timolol maleate twice daily. Bimatoprost once daily showed significantly lower mean IOP compared to timolol twice daily at every time of day and was more efficacious than the twice a day regimen of bimatoprost. 58% of bimatoprost patients received IOP at or below 17 mm Hg compared to 37% of timolol patients. The most common side effect of bimatoprost was hyperemia.

*Higginbotham EJ, Schuman JS, Goldberg I, et al. Archives October 2002: 1286-1293*

## **EFFECTIVENESS OF PDT AFTER 3 YEARS**

320 of the original 402 participants initially enrolled were available for evaluation. For the 105 patients with a predominantly classic baseline lesion composition who completed the month 36 examination, an average of 1.3 treatments were given from the month 24 examination up to, but not including, the month 36 examination. Verteporfin-treated patients had little change in the mean visual acuity lost and few or no additional instances of infusion-related back pain or photosensitivity reactions from month 24 to month 36.

*TAP Study Group. Archives October 2002: 1307-1314*

## **SMOKING AND AGE-RELATED MACULOPATHY**

According to investigators involved in the Blue Mountains Study, incidence rates for any late ARM lesions were 3.1%, 1.2%, and 1.4%, respectively, among baseline current, past, or never smokers. The mean age for cases was 67 years for baseline current smokers, 73 years for past smokers, and 77 years for those who had never smoked. After adjusting for age, current smokers, compared with never smokers, had an increased risk of incident geographic atrophy and any late ARM lesions. Current smokers had an increased risk of incident retinal pigmentary abnormalities with the risk higher in men.

*Mitchell P, Wang JJ, Smith W, et al. Archives October 2002: 1357-1363*

## **PDT FOR SUBFOVEAL CNVM IN PATIENTS WITH AMD**

Patients with predominantly classic CNV had a worse initial mean visual acuity and smaller lesions and were more likely to have lesions that included blood or blocked fluorescence. In the subgroup with predominantly classic lesions, visual acuity outcomes were consistently better in verteporfin-treated patients. Outcomes for patients with predominantly classic lesions without occult CNV tended to be better than outcomes for patients with predominantly classic lesions with occult CNV, although the former tended to have smaller lesions and lower levels of visual acuity at baseline. Contrast sensitivity and fluorescein angiographic outcomes (total lesion size, progression of classic CNV, and absence of classic CNV) were better in verteporfin-treated patients than in placebo-treated patients in the predominantly classic and the

minimally classic CNV subgroups. The authors conclude that Verteporfin therapy can safely reduce the risk of moderate and severe vision loss in patients with subfoveal lesions that are predominantly classic CNV secondary to AMD. While this benefit seemed to be even greater in the absence of occult CNV, the effect may be related to the smaller lesions and worse visual acuity associated with predominantly classic lesions without occult CNV and not solely to the lesion composition itself. The authors suggest that further investigations should be performed to determine if lesions with a minimally classic composition might benefit when they are smaller and have lower levels of visual acuity.

*TAP Study Group. Archives November 2002: 1443-1454*

### **OUTCOME ESTIMATES FOR INTRAOCULAR MELANOMA IRRADIATION**

A review of 2069 patients treated with radiation for intraocular melanoma between 1975 and 1997 found tumor regrowth occurred in 60 patients, and 95% of tumors were controlled locally at 15 years. Overall, the treated eye was retained by 84% of patients at 15 years. The probabilities for visual acuity worse than 20/200 ranged from 100% to 20% at 10 years and for death from tumor metastases from 95% to 35% at 15 years, depending on the risk group. The authors conclude that in most cases, the eye was salvaged, and functional vision was retained in many patients. The mortality rate was high in an identifiable subset of patients who may benefit from adjuvant therapies directed at microscopic liver metastases.

*Gragoudas E, Li W, Goitein, M, et al. Archives December 2002: 1665-1671*

### **COMBINED VS SEPARATE SURGERIES FOR CATARACT AND GLAUCOMA**

The authors performed an evidence-based review of the literature for this study. Long-term IOP is lowered more by combined glaucoma and cataract operations than by cataract operations alone. On average, the IOP was 3 to 4 mmHg lower in the combined groups with fewer medications required. The evidence was weak that short-term IOP control was better with ECCE or PECE combined with an incisional glaucoma procedure compared with ECCE or PECE alone. There was weak evidence that combined PECE and trabeculectomy produces slightly worse long-term IOP control than trabeculectomy alone, and there was fair evidence that the same is true for ECCE combined with trabeculectomy.

*Friedman DS, Jampel HD, Lubomski LH, et al. Ophthalmology October 2002: 1902-1913*

### **TREATMENT OF RETINAL CAPILLARY HEMANGIOMA**

Among 68 patients with RCH with von Hippel-Lindau disease (n = 31) and without von Hippel-Lindau disease (n = 37), we identified 174 RCH in 86 eyes. The overall median age at diagnosis of RCH was 30.8. The RCH was bilateral in 26% of cases, and a family history of von Hippel-Lindau disease was positive in 28% of cases. The RCH were initially managed by observation (46%), laser photocoagulation (25%), or cryotherapy (23%). 82% of the 77 RCH that were initially observed remained stable for a median follow-up of 84 months. The remaining 14 progressed and were successfully controlled with laser photocoagulation or cryotherapy. Either laser photocoagulation or cryotherapy was effective as the sole method of treatment in controlling 74% and 72% of extrapapillary tumors, with a mean number of 1.2 and 1.1 sessions, respectively. The only variables that were significantly related to final vision of  $\leq 20/400$  were poor initial and the presence of retinal/vitreous hemorrhage. The authors conclude that RCH can be safely observed initially in selected cases. Laser photocoagulation and cryotherapy are the mainstays of treatment in most cases. Early detection of RCH and treatment before the onset of severe visual loss is recommended.

*Singh AD, Nouri M, Shields CL et al. Ophthalmology October 2002: 1799-1806*

### **PLAQUE RADIOTHERAPY FOR LARGE CHOROIDAL MELANOMAS**

Three hundred fifty-four patients each of whom had a posterior uveal melanoma measuring 8 mm or greater in thickness were treated with plaque radiotherapy. Final visual acuity was poor in 57% at 5 years and 89% at 10 years follow-up. The most important risk factors for poor visual acuity included retinal invasion by melanoma, increasing patient age, iodine 125 ( $I^{125}$ ) isotope, and <2 mm distance to the optic disc. Treatment-related complications at 5 years included proliferative retinopathy, maculopathy, papillopathy, cataract, neovascular glaucoma, vitreous hemorrhage, and scleral necrosis. Enucleation was necessary in 24% at 5 years and 34% at 10 years follow-up. The risk factors for enucleation included left eye, peripheral tumor margin anterior rather than posterior to the equator, increasing tumor thickness, and ruthenium 106 ( $Ru^{106}$ ) isotope. Local tumor recurrence was found in 9% at 5 years and 13% at 10 years follow-up. Risk factors for tumor recurrence included  $Ru^{106}$  radioisotope and ciliary body involvement with tumor. Tumor-related metastases were found in 30% at 5 years and 55% at 10 years follow-up. Risk factors for metastases included inferotemporal meridian, anterior extension of the tumor to the iris root, increasing tumor base, and posterior margin < 2 mm from the optic nerve.

*Shields CL, Naseripour M, Cater J, et al. Ophthalmology October 2002: 1838-1849*

### **INCIDENCE AND PROGRESSION OF AMD AFTER 10 YEARS**

The 10-year incidence of early age-related maculopathy was 12.1% and of late age-related maculopathy it was 2.1%. Individuals 75 years of age or older at baseline had significantly higher 10-year incidences of: larger sized, soft indistinct drusen, retinal pigment abnormalities, exudative macular, and pure geographic atrophy than people 43 to 54 years of age. Compared with those with small numbers of only small, hard drusen, those with large numbers of only hard drusen (8 or more) had an increased 10-year incidence of both soft drusen and pigmentary abnormalities. Eyes with soft indistinct drusen or retinal pigmentary abnormalities at baseline, were more likely to develop late age-related macular degeneration at follow-up than eyes without these lesions.

*Klein R, Klein BEK, Tomany SC, et al. Ophthalmology October 2002: 1767-1779*

### **CENTRAL SEROUS CHORIORETINOPATHY AND STEROIDS**

A total of 50 patients was recruited. Twenty-six patients had a history of exogenous steroid use, including oral, intravenous, intranasal, and intraarticular administration. Two additional patients had a history of Cushing's syndrome. In a matched control group, eight patients had a history of steroid use. The authors conclude that the study is consistent with previous reports associating steroid use with CSC. It identifies corticosteroids as a significant risk factor for the development of acute, exudative macular manifestation and implicates hypercortisolism as a factor in the pathogenesis of this disorder. Susceptible patients in need of corticosteroids should be advised of the risk of developing acute manifestations of CSC.

*Carvalho-Recchia CA, Yannuzzi LA, Negrão S, et al. Ophthalmology October 2002: 1834-1837*

### **SIXTH NERVE PALSIES IN YOUNG ADULTS**

All patients aged 20 to 50 years with a nontraumatic sixth nerve palsy seen in a neuro-ophthalmic practice from 1994 to 2000 were reviewed. The most common cause for a sixth nerve palsy in this age group was a central nervous system (CNS) mass lesion, although the most common cause for an isolated sixth nerve palsy in this age group was multiple sclerosis. Deferring neuroimaging or other appropriate investigations presuming a microvascular cause for the palsy in this age group is not recommended.

*Peters GB, Bakri SJ, Krohel GB. Ophthalmology October 2002: 1925-1928*

### **MYOPIA AND GLAUCOMA**

Higher myopic refraction was significantly associated with more damage at a point just temporal and inferior to the fixation point in POAG eyes, whereas it was significantly associated with less damage at test points just temporal and superior to the fixation point in NTG eyes. After correcting for the influence of refraction, POAG eyes had significantly more damage at a test point just temporal and inferior to the fixation point, whereas NTG eyes had significantly more damage at those test points nasal and inferior to the fixation point. The authors conclude that high myopia constitutes a threat to the remaining lower central visual field and is one of the factors that interfere with the quality of vision in advanced OAG with high IOP but not low IOP.

*Mayama C, Suzuki Y, Araie M, et al. Ophthalmology November 2002: 2072-2077*

### **WHICH VISUAL FIELD TEST FOR FIRST TIME TEST TAKERS?**

Normal individuals with no perimetric experience may present more significantly depressed points on the pattern deviation probability map when the SS strategy is used, reducing the test specificity in comparison with FT. These findings are probably due to a lower interindividual variability observed with SS. However, these differences disappeared in a second examination, suggesting that both strategies perform similarly in perimetrically experienced individuals.

*Rui Barroso Schimiti RB, Avelino RR, Kara-Jose N, et al. Ophthalmology November 2002: 2084-2092*

### **VISUAL FIELD PROGRESSION**

One hundred fifty-two patients undergoing bilateral treatment for at least 2 years for OAG and who were followed with standard automated perimetry were included in the study. After a mean follow-up period of 7.5 +/- 3.6 years, fifty-four patients showed progression of the more severely affected of the two eyes (worse eye), and 37 patients had progression in the better eye. Among these patients, 24 had bilateral. The authors conclude that patient-specific factors may play an important role in visual field progression in OAG. Documented progression of visual field loss in one eye may prompt the physician to consider reducing the target intraocular pressure in both eyes.

*Chen, P. Ophthalmology November 2002: 2093-2099*

### **SIDE EFFECTS OF RADIOTHERAPY FOR GRAVE'S DISEASE**

Forty-two patients with Grave's disease were included in the study. Half of the patients elected to have a surgical procedure on their eyes or orbits. Among patients who were not decompressed, the authors found only slight improvement in some of the main outcome measures. After orbital decompression, the volumes of both muscle and fat increase, but bony orbital volume increases more and proptosis diminishes. Retinal microvascular abnormalities consistent with radiation retinopathy developed de novo in five eyes of three patients within 3 years of radiation therapy. The authors conclude that limited evidence for a clinically significant improvement was observed, which may be the result of treatment or of natural remission. In either case, the changes are of little clinical significance. Because it is neither effective nor innocuous, radiotherapy does not seem to be indicated for treatment of mild to moderate ophthalmopathy.

*Gorman CA, Garritty JA, Fatourechhi V, et al. Ophthalmology November 2002: 2100-2107*

### **EFFECT OF TECHNIQUE ON IOP IN COMBINED CATARACT AND GLAUCOMA SURGERY**

In the literature on surgical techniques and adjuvants used in the management of coexisting cataract and glaucoma, the strongest evidence of efficacy exists for using MMC, separating the incisions for cataract and glaucoma surgery, and removing the nucleus by phacoemulsification.

*Jampel HD, Friedman DS, Lubomski LH, et al. Ophthalmology December 2002: 2215-2224*

### **COMS: BRACHYTHERAPY WITH IODINE 125**

638 of the 650 patients randomized to brachytherapy and so treated had been followed up for 1 year or longer, and 411 had been followed up for at least 5 years. Tumors measured 2.5 to 10.0 mm in apical height and no more than 16.0 mm in longest basal dimension. Sixty-nine eyes were enucleated during the first 5 years after brachytherapy, and treatment failure was reported for 57 eyes. The Kaplan-Meier estimate of proportion of patients undergoing enucleation by 5 years was 12.5; the risk of treatment failure was 10.3. Treatment failure was the most common reason for enucleation within 3 years of treatment; beyond 3 years, ocular pain was most common. Risk factors for enucleation were greater tumor thickness, closer proximity of the posterior tumor border to the foveal avascular zone, and poorer baseline visual acuity in the affected eye. Risk factors for treatment failure were older age, greater tumor thickness, and proximity of the tumor to the foveal avascular zone. The authors conclude that the COMS randomized trial documented the absence of a clinically or statistically significant difference in survival for patients randomly assigned to enucleation versus brachytherapy. This analysis documents the efficacy of brachytherapy to achieve sustained local tumor control and to conserve the globe.

*Jampol LM, Moy CS, Murray TG, et al. Ophthalmology December 2002: 2197-2206*

### **CHRONIC ANGLE CLOSURE GLAUCOMA**

Eyes diagnosed with CACG with glaucomatous optic nerve head and visual field damage underwent laser peripheral iridotomy (LPI). The mean presenting IOP was higher in the Singapore compared with the New York. All 80 New York eyes and 78 of 83 Singapore eyes required further treatment to control IOP during follow-up. Of the eyes with a subsequent rise in IOP, 33 of 80 eyes compared with 34 of 83 eyes of the Singapore patients were controlled with additional topical medication. Of the New York eyes, 25 of 80 eventually underwent filtering surgery, compared with 44 of 83 in the Singapore study. The other 22 eyes in the New York group went on to additional laser procedures, peripheral iridoplasty, laser trabeculoplasty, or a combination thereof, after which IOPs were controlled and no surgery was required. There was no similar comparison for the Singapore group, because these eyes went directly on to surgery. The authors conclude that despite the presence of a patent LPI, most eyes with CACG presenting with elevated IOP and having both optic disc and visual field damage in both populations required further treatment to control IOP. Results in the American population are similar to that reported in Asian patients.

*Rosman M, Aung T, ANG LPK et al. Ophthalmology December 2002: 2227-2231*

### **RATE AND PATTERN OF VISUAL FIELD DECLINE IN POAG**

Forty eyes of 40 patients with primary open-angle glaucoma that were followed longitudinally with serial Goldmann visual fields for a minimum period of 8 years in an academic institution were evaluated. Eyes with any other ocular disease except for mild cataract were excluded. The rate of visual field change was -1.3% per year for the entire visual field. About half the patients showed symmetric visual field decline, whereas others showed a more asymmetric pattern. Asymmetric visual field progression was associated with the presence of disc hemorrhage, overall rate of visual field progression, and surgical intervention for glaucoma. The authors conclude that in this group of selected patients with primary open-angle glaucoma with a long-term follow-up, all sections of the visual field declined over time. Disc hemorrhage was associated with more asymmetric visual field progression, implicating focal damage to the optic disc.

*Pereira MLM, Kim C, Zimmerman MB, et al. Ophthalmology December 2002: 2232-2240*

## **PHACO AFTER FILTERING SURGERY**

49 eyes underwent phacoemulsification after successful trabeculectomy, with at least 12 months of follow-up. The IOP before phacoemulsification was  $12.24 (\pm 4.68)$  mmHg, and it increased on the first postoperative day, after 1, 6, and 12 months, and at the last visit, respectively. At each interval, the mean IOP was significantly higher than the preoperative. Nevertheless, the mean IOP after phacoemulsification was always lower than before trabeculectomy. At the last visit, glaucoma medication was required in 34.7% of eyes. The number of glaucoma medications used increased at all follow-up visits. Bleb size decreased after phacoemulsification. An IOP before phacoemulsification of greater than 10 mmHg was associated with postoperative failure. Similarly, bleb failure and the need for glaucoma medication were associated with higher IOPs before phacoemulsification.

*Rebolleda G, Muñoz-Negrete FJ. Ophthalmology December 2002: 2248-2255*

## **BAERVELDT IMPLANT FOR UVEITIC GLAUCOMA**

Twenty-four eyes underwent implantation of Baerveldt glaucoma drainage devices between 1996 and 2000 for the treatment of uveitic glaucoma refractory to medical therapy. Success rates were 95.8% at 3 months and 91.7% at 6 months, 12 months, and 24 months. The mean postoperative follow-up was 20.8 months. The IOP was reduced from a preoperative mean of  $30.5 \pm 8.96$  mmHg with  $3.1 \pm 0.99$  antiglaucoma medications to a postoperative mean at 6 months or 1 year of  $13.0 \pm 4.6$  mmHg with  $0.8 \pm 0.8$  antiglaucoma medications. At last follow-up 58.3% of eyes required no antiglaucoma medications. Best-corrected visual acuity improved or remained within 2 lines of preoperative visual acuity in 79.2% of eyes. The most common complications were choroidal, hypotony, cystoid macular edema and failure of corneal grafts. Seven of 22 eyes in which successful control of IOP with the Baerveldt implant was achieved underwent subsequent nonglaucoma-related incisional surgery. None of these eyes lost IOP control after the subsequent procedure.

*Ceballos EM, Parrish RK, Schiffman JC. Ophthalmology December 2002: 2256-2260*

## **DIETARY ANTIOXIDANTS AND THE INCIDENCE OF AGE-RELATED MACULOPATHY**

From 1992 through 1994, 3654 persons aged 49 years or more were examined for the Blue Mountains Eye Study baseline. Five years later, 75% were reexamined. A 145-item Food Frequency Questionnaire (FFQ) was used to assess nutrient intakes. Of the 2335 people who attended a follow-up visit, 1989 (85%) had completed a FFQ at baseline. The nutrients examined in this study included:  $\alpha$ -carotene,  $\beta$ -carotene,  $\beta$ -cryptoxanthin, lutein and zeaxanthin, lycopene, retinol, vitamin A, vitamin C, and zinc. Early ARM developed in 8.7% who did not have either late or early ARM at baseline. Of these, 159 persons completed the FFQ at baseline. After adjusting for age, gender, family history of ARM, and smoking status at baseline, no associations, or any trends suggesting possible association, were found between baseline intake of the nutrients examined, apart from vitamin C, and the 5-year incidence of early ARM. Compared with the lowest quintile, increasing baseline intakes of vitamin C, from diet and supplements, was associated with an increased risk of incident early ARM. The authors conclude that they could not find evidence of protection associated with usual dietary antioxidant or zinc intakes (including use of supplements) on the 5-year incidence of early ARM.

*Flood V, Smith W, Wang JJ et al. Ophthalmology December 2002: 2272-2278*

## **IOP AND PERFUSION PRESSURE FOR XALATAN AND ALPHAGAN IN NTG PATIENTS**

Latanoprost and brimonidine reduced the average IOP by  $3.6 \pm 1.9$  mmHg and  $2.5 \pm 1.3$  mmHg, respectively, with a significant difference between the two regimens. Both drugs significantly reduced IOP at each time point. Latanoprost decreased IOP significantly more than did brimonidine at 8 am ( $11.7 \pm 2.2$  mmHg vs.  $13.7 \pm 2.1$  mmHg) and 4 pm ( $11.4 \pm 2.1$  mmHg vs.  $13.2 \pm 2.9$  mmHg), but IOP was equal between the two agents at 12 noon ( $11.5 \pm 2.6$  mmHg vs.  $11.5 \pm 2.3$  mmHg). IOP was maintained at 12 mmHg or lower in 66.7% of 27 patients after treatment with latanoprost and in 33.3% of 27 patients after treatment with brimonidine. Latanoprost monotherapy reduced IOP by 30% in 29.6% of patients, but brimonidine monotherapy did not reduce IOP by that much in any of the patients. OPP increased after latanoprost treatment but did not increase after brimonidine treatment. There was no significant change in pulse rate or blood pressure. The authors conclude that latanoprost and brimonidine reduce IOP in NTG patients. Brimonidine has a peak IOP-lowering effect equal to that of latanoprost but produces a higher mean diurnal IOP than does latanoprost because of its shorter effect. Latanoprost might favorably alter optic disc blood perfusion by increasing OPP.

*Liu CJ, Ko YC, Cheng CY, et al. Ophthalmology December 2002: 2241-2247*

# Original Article

Submitted by :

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## ABSTRACT:

Latanoprost (Xalatan) is a prostaglandin-F<sub>2</sub>α isopropyl-ester derivative. It was the first prostaglandin (PG) analogue used in the treatment of glaucoma in the United States. The efficacy of xalatan has been shown to be equal or better than timolol in clinical trials. The mechanism of action of xalatan, like the other PGs, is reduced intra-ocular pressure (IOP) primarily via increased uveoscleral outflow.

Prior to the development of xalatan, the Prostaglandin-F<sub>2</sub>α derivatives that were studied lowered IOP but were accompanied by intolerable side effects, such as hyperemia, foreign body sensation and headache. Xalatan, on the other hand, was well tolerated and rarely caused these side effects due to its being a selective FP-agonist with little affinity for the EP receptor (which mediates ocular inflammation).

Several new prostaglandin agents have been developed recently. Although these new PG agents show similar efficacy to xalatan, they do display more ocular side effects such as conjunctival hyperemia and foreign body sensation.

PGs are becoming the most commonly used agents in the treatment of glaucoma due to their greater efficacy and minimal side effects in comparison to topical beta-blockers. Xalatan is the most commonly prescribed glaucoma drug by Optometrists in the United States today and is being used more often as a first line agent due to its greater safety profile and compliance factor.

## DISCOVERY OF PROSTAGLANDINS:

Prostaglandin F<sub>2</sub>-alpha-isopropyl ester (PGF<sub>2</sub>α-IE) was the initial prototype prostaglandin used on human subjects to effectively reduce intra-ocular pressure (IOP) in the treatment of glaucoma (1). However, this lowering of IOP was accompanied by conjunctival injection, ocular irritation, and headache that rendered this drug intolerable for continued use.

Research then focused on separating the IOP lowering effect from the side effects (i.e.- irritation and hyperemia) by changing the receptor profile of PGF<sub>2</sub>α via chemical modification. Attempts to modify the PGF<sub>2</sub>α by alterations in the carboxylic acid end of the molecule or by changing the stereochemistry and functional groups of the cyclopentane ring yielded no change in pharmacology of PGF<sub>2</sub>α.

Alterations and substitutions to parts of the omega-chain (i.e.- double bond between carbon-13 and carbon-14) resulted in improved reduction in IOP and more tolerable side effects. These alterations included substitution of the phenyl ring in the C-17 position and saturation of the double bond at C-13 and C-14 position. In addition, it was determined that a large number of modifications of the ring structure are possible while still producing useful compounds for glaucoma treatment.

Saturation of the carbon -13,14-trans double bond in PGF<sub>2</sub>α-IE further improved its receptor profile, chemical stability and therapeutic index. This dihydro PGF<sub>2</sub>α-IE analogue was then selected as the new candidate drug (called "PHXA34"). Since the 15R epimer is more potent than the 15S epimer, the 15R epimer became the final candidate drug, known as "PHXA41" or Latanoprost.

Structure-activity studies indicate that latanoprost exhibits a good therapeutic index due to its receptor profile. Latanoprost is a much more selective FP receptor agonist than PGF<sub>2</sub>α since it has less "spill-over" effects on the EP<sub>1</sub> and TP receptors (4). Therefore, unlike other PG<sub>2</sub>α derivatives that caused intolerable side effects (i.e.- hyperemia, headache, foreign body sensation), latanoprost is well tolerated due to its weak affinity for the EP receptor; a receptor which mediates ocular inflammation.

## OTHER PROSTAGLANDIN DERIVATIVES:

Latanoprost, travoprost, unoprostone and bimatoprost are all synthetic analogues of PG-F<sub>2</sub>α and have affinity for the FP receptor. The activation of the FP receptor increases the actions of matrix metalloproteinases (MMPs) which cause an alteration in the collagen content of the ciliary muscle, thereby reducing resistance in the uveoscleral pathway (5). The makers of bimatoprost claim that it does not have affinity for the FP receptor or any other known receptor in the eye (this issue is controversial) (6). It is widely accepted that all these PG agents primarily lower IOP by increased uveoscleral outflow.

## EFFICACY OF PGs VS OTHER IOP LOWERING AGENTS:

Timolol has been the standard agent used for comparison of IOP reduction for the all glaucoma drugs. The agent unoprostone has not demonstrated significantly greater IOP reduction than timolol. Unoprostone with its twice a day dosing makes it less desirable as an alternative to timolol.

Latanoprost has been shown to be more effective than timolol twice a day for IOP reduction in POAG and ocular hypertension patients (7). Additionally, more latanoprost treated patients reached their target IOP than timolol treated patients. A study (8) comparing once daily dosing of timolol gel versus latanoprost revealed greater IOP reduction with latanoprost over a 24 hour period. Bimatoprost and travoprost taken once a day have also shown equal or greater efficacy to timolol taken twice daily (9).

A number of clinical trials have shown that latanoprost can be successfully combined with other glaucoma drops, such as timolol, diamox, propine and pilocarpine, since latanoprost has a unique mechanism of action.

#### MECHANISM OF ACTION OF PGs:

Latanoprost induced minimal change in blood flow in the rabbit eye on topical administration, in contrast PGF<sub>2</sub>α-IE which caused a marked increase blood flow to ocular surface structures and anterior uvea. The hyperemic effect of PGF<sub>2</sub>α-IE appears to be due to nitric oxide (NO) release (13). The mechanism of nitric oxide release does not involve FP receptors. These effects correspond with the absence of a nociceptive response with FP-prostanoid receptor agonists like latanoprost.

In aphakic monkeys with intact posterior lens capsules, latanoprost induced no capillary leakage in the retina, as revealed by fluorescein angiography (FA) during six months of treatment. Similar results were also obtained during shorter treatment times with pseudophakic patients (14). From these studies it appears that the FP receptor plays little role in regulation of vessel tone and capillary permeability in the eye.

In the lungs, PGE, PGE-2 and Prostacyclin (PGI-2) relax respiratory smooth muscle while Thromboxane (TXA-2) and PGF<sub>2</sub>α are strong bronchoconstrictors. Studies on the effects of Xalatan on pulmonary function in healthy and asthmatic patients revealed no negative effects on pulmonary function (15).

One disadvantage of prostaglandins is that their receptors are widely distributed in the eye (i.e.- the FP receptor is also present in the corneal epithelium and endothelium, lens epithelium, ciliary muscle, iris melanocytes and different layers of the retina.), causing its tissue selectivity to be low. In addition, prostaglandins have a wide range of functions as a result of their many receptor subtypes. All of these side effects attributed to PGs can therefore be minimized by using selective prostaglandin analogues such as xalatan for the treatment of glaucoma.

#### IMPLICATIONS OF LOWER IOP BASED ON RECENT CLINICAL TRIALS

Several major clinical studies were conducted to demonstrate the importance of lower IOP in reducing progression of glaucoma:

The Ocular Hypertensive Treatment Study (OHTS) was the first large scale study to demonstrate that treatment of elevated IOP will effectively delay or prevent the onset of POAG in susceptible individuals. This study also concluded that in addition to IOP; age, cup to disc ratio and Pattern Standard Deviation (PSD) were good predictors for the onset of POAG in OHT patients. Central corneal thickness was also found to be a predictor for the development of POAG, since patients with thinner corneas are at much greater risk for developing glaucoma (16). Therefore, from this study it can be concluded that it is imperative to consider initiating treatment on those patients with OHT who are at moderate to severe risk for developing glaucoma.

The Advanced Glaucoma Intervention Study (AGIS) investigated the association between control of IOP after surgical treatment and visual field deterioration. Results confirmed that low IOP is associated with reduced progression of visual field defects, thereby demonstrating the protective role of lower IOP in visual field loss (17).

The Collaborative Initial Glaucoma Treatment Study (CIGTS) was performed to determine the effects of initial treatment of newly diagnosed open angle glaucoma with either topical glaucoma medications or trabeculectomy. Results in both the initial medical or surgical treatment groups revealed approximately the same visual field outcome after 5 years of follow-up (18). This again reiterates the benefits of IOP reduction in the control of glaucoma.

The Collaborative Normal Tension Glaucoma Study (CNTGS) determined that IOP is part of the pathogenesis in NTG and that treatment to lower IOP, without adverse side effects, would be beneficial. This study revealed that by aggressively reducing IOP by 30% in patients with NTG, one can slow the rate of visual field deterioration (19).

#### SAFETY PROFILE OF PROSTAGLANDINS

Some common ocular side effects of PGs include: ocular discomfort, conjunctival hyperemia, increased iris pigmentation and eyelash growth. The hyperemia may cause the most discomfort and irritation to these patients. In a recent study (20) comparing the side effects of the different PG ophthalmic agents, latanoprost had the lowest incidence of hyperemia compared to bimatoprost and travoprost. Discontinuation of treatment due to hyperemia was slightly higher with bimatoprost and travoprost than latanoprost.

The increase iris pigmentation is due to the stimulation of melanocytes in the iris stroma to produce increased melanin. This increased pigmentation was observed only in irides of mixed green-brown or blue/gray-brown. Iris freckles or nevi do not change shape, color or size during treatment. These iris pigment changes are permanent and do not recede after discontinuation of treatment (21). The increased melanin content in iris stromal melanocytes is not excessive. There is no evidence of significant melanin release into the stroma that could result in iris inflammation or pigmentary glaucoma.

Additional ocular side effects include: dry eye, blurry vision, excessive tearing, burning, stinging, itching and foreign body sensation. There were no significant differences in these side effects among the different PG agents.

Several studies have been conducted to determine the incidence of cystoid macular edema (CME) associated with PG treatment after cataract surgery. Best visual acuity reduction of two or more Snellen lines was considered as significant visual acuity reduction. The incidence of CME in aphakic and pseudophakic patients was extremely low. However, in those patients who had complicated cataract extraction with posterior capsule rupture requiring anterior vitrectomy, the incidence of CME was more significant. Therefore, extra care is required in the follow-up of pseudophakic patients with ruptured posterior capsules due to their greater risk of developing CME.

Other less frequent ocular side effects associated with PG use include exacerbation of uveitis or herpes simplex keratitis. Although no casual relationship has ever been established between PG treatment and these side effects, PGs should be used with caution in patients with a history or at risk of these conditions.

There have been few reported systemic side effects with these PG ophthalmic agents. No changes in heart rate, blood pressure or respiratory function were encountered during the clinical trials of these agents.

## CONCLUSIONS

The PGs are steadily becoming the most widely used glaucoma agents. PGs have been shown to be an improvement over timolol due to their greater efficacy, improved therapeutic index, better diurnal control and more convenient once-a-day dosing.

Until recently, xalatan was the only available PG analogue used for the treatment of glaucoma in the United States. All of the newer agents, with the exception of unoprostone, have shown superior efficacy to timolol for lowering IOP. Although their IOP lowering effects have been reported to be similar to latanoprost, both bimatoprost and travoprost have displayed more ocular side effects than latanoprost which may limit their clinical usefulness.

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## Thoroughbreds

*Kudos to the lecturers / writers within the VA Optometry Service.*

### Lectured:

**Sheila Anderson**, [American Academy of Optometry](#), 12/02, Fluorescein Angiography Injection  
**Rex Ballinger**, [American Academy of Optometry](#), 12/02, Pressure Independent Glaucoma and Its Management and Ocular Inflammation: Diagnosis and Management  
**Loren Bennett**, [American Academy of Optometry](#), 12/02, The Ocular Ischemic Syndrome  
**David Bright**, [American Academy of Optometry](#), 12/02, Skin Cancer: Pathogenesis, Recognition And Treatment and Update on HIV Disease Management  
**Bernard Dolan**, [American Academy of Optometry](#), 12/02, Treatable Macular Disorders  
**Steve Ferrucci**, [American Academy of Optometry](#), 12/02, Care of the Diabetic Patient: Case Reports  
**Murray Fingeret**, [American Academy of Optometry](#), 12/02, A New Look at Visual Fields in Glaucoma And New Ideas in Glaucoma  
**Shelly Hay**, [American Academy of Optometry](#), 12/02, Essentials For Interpretation of Fluorescein Angiography: Correlating Fluorescein Angiography to Clinical Entities  
**Anthony Litwak**, [American Academy of Optometry](#), 12/02, Glaucoma Case Analysis 2002  
**Wesley Ota**, [American Academy of Optometry](#), 12/02, Diabetes Mellitus for the Optometrist  
**Stuart Richer**, [American Academy of Optometry](#), 12/02, AREDS and Emerging Trends in the Treatment Of AMD and Diet Wars: Ornish vs Atkins and Prevention of Eye Disease  
**John Spalding**, [American Academy of Optometry](#), 12/02, Glaucoma Case Analysis 2002  
**Clifford Stephens**, [American Academy of Optometry](#), 12/02, Physical Diagnosis and Ancillary Testing  
**Katherine Wang**, [American Academy of Optometry](#), 12/02, Systemic Medications With Adverse Ocular Reactions

### Published:

**Harshman D.** Corneal Melt Hints at Systemic Disease. [Review of Optometry](#). November 2002; 83-89.  
**Mick AB (1<sup>st</sup> co-author).** A Cost Analysis of the Prostaglandin Analogs. [Optometry](#). October 2002; 73: 614-619.

## Calendar

*Important dates to remember.*

### **February 19-23, 2003**

SECO International 2003, Atlanta, GA, [www.secointernational.com](http://www.secointernational.com)

### **March 5-9, 2003**

Ocular Therapeutics in Cancun, Cancun, Mexico, [www.oculartherapeutics.com](http://www.oculartherapeutics.com)

### **March 20-23, 2003**

International Vision Expo East, New York, New York, [www.vision.reedexpo.com](http://www.vision.reedexpo.com)

**May 4-9, 2003**

ARVO, Ft. Lauderdale, FL, [www.arvo.org/Meetings/meetgrid.asp](http://www.arvo.org/Meetings/meetgrid.asp)

**June 18-23, 2003**

AOA Congress, San Diego, CA, [www.aoa.org/corp/congress2003.asp](http://www.aoa.org/corp/congress2003.asp)

**July 16-20, 2003**

Florida Optometric Association Annual Convention, West Palm Beach, FL, [www.floridaeyes.org](http://www.floridaeyes.org)

**November 15-18, 2003**

American Academy of Ophthalmology, Anaheim, CA, [www.aao.org/annual\\_meeting/](http://www.aao.org/annual_meeting/)

**December 4-8, 2003**

American Academy of Optometry, Dallas, TX, [www.aaopt.org](http://www.aaopt.org)

## Internet Links

*Suggested web sites.*

### JOURNALS

Archives of Ophthalmology, <http://archophth.ama-assn.org/>

American Journal of Ophthalmology, <http://www.ajo.com/>

British Journal of Ophthalmology, <http://bjo.bmjournals.com/contents-by-date.0.shtml>

Clinical and Experimental Optometry, <http://www.optometrists.asn.au/ceo/ceo.html>

Ocular Surgery News, <http://www.osnsupersite.com/>

Ophthalmology, <http://www.aaojournal.org/>

Primary Care Optometry News, <http://www.slackinc.com/eye/pcon/pconhome.asp>

Review of Optometry, <http://www.revoptom.com/>

Review of Ophthalmology, <http://www.revophth.com/>

### MISCELLANEOUS

Medscape Ophthalmology, <http://www.medscape.com/ophthalmologyhome>

Ophthoguide, <http://www.ophthoguide.com/ophtho/>

OphthoLinx, <http://www.ophtholinx.com/>

### ORGANIZATIONS

American Academy of Optometry (AAO), <http://www.aaopt.org/>

American Academy of Ophthalmology, <http://www.aao.org/>

American Optometric Association (AOA), <http://www.aoanet.org/>

National Association of VA Optometrists (NAVAO), <http://www.navao.org/>

National Board of Examiners in Optometry (NBEO), <http://www.optometry.org/>

National Eye Institute (NEI), <http://www.nei.nih.gov/>

Optometry Residency Matching Service (ORMS), <http://www.optometryresident.org/>

VA Optometry Service, <http://vaww.va.gov/optometry/>

### EDUCATIONAL

Bascom Palmer Eye Institute, <http://129.171.73.73/prod06.htm>

Massachusetts Eye and Ear Infirmary, <http://www.djo.harvard.edu/GRhome.html>

Optcom Grand Rounds, <http://www.optcom.com/dgr.html>

Oxford University, <http://www.mrcophth.com/oxfordpd.htm>

Wilmer Eye Institute, <http://www.wilmer.jhu.edu/training/profound/ROUNDS.HTM>

Common Cases and MCQs, <http://www.mrcophth.com/commonshortcasesindex1.html>

Eye Atlas, <http://www.eyeatlas.com/>

## Open Positions

*Positions available within the VA as of December 19, 2002.*

**Altoona, PA** 1 Position FT, James Andros 814-943-8164x7039  
**Bakersfield, CA** 1 Position FT, Dr. David Bright 310-268-3332  
**Beckley, WV** 1 Position FT, JC Crouch 304-255-2121x4460  
**Chillicothe, OH** 1 Position FT, Nate Darden 740-773-1141x7069  
**Columbia, SC** 1 Position FT, Andrea Johnson 706-733-0188x2077  
**Durham, NC** 1 Position FT, Dr. Joseph Halabis 919-286-0411  
**El-Paso, TX** 1 Position FT, Susan Parks: [slparks@hotmail.com](mailto:slparks@hotmail.com)  
**Fayetteville, NC** 2 Positions FT, Jim Turner 910-822-7077  
**Fayetteville, Arkansas** 1 Position FT, Dr. Mary Jo Horn, 479-443-4301x5678  
**Loma Linda, CA** 1 Position FT, Sharon Takayesu, 9089-825-7084x2438  
**Montgomery, AL** 1 Position FT, Fancea Garrett, 843-577-5011  
**Mount Vernon, MO** 1 Position FT, Dr. Mary Jo Horn, 479-443-4301x5678  
**Oklahoma City, Oklahoma** 2 Positions FT, Jeff Disalvatore 405-270-5161  
**Shreveport, LA** 1 Position FT, Terence Whatley 318-841-4744  
**Wichita, KS** 2 Positions FT, Deborah Brodbeck 316-685-2221x3418  
**Youngstown, OH** 1 Position FT, Dr. Bill McGann, 330-740-9200x1528

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## Miscellaneous Information

- Congratulations to New Academy Fellows

Debi Pian, O.D., VA Outpatient Clinic, Santa Barbara, CA

- NAVAO Board Members

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**Newsletter Editor:** John Spalding, O.D., [john.spalding@med.va.gov](mailto:john.spalding@med.va.gov)

- VA Optometry Mentor Program

If you are interested in being a mentor to a newly hired VA optometrist, please contact Dr. Rebecca Sterner: [rebecca.sterner@med.va.gov](mailto:rebecca.sterner@med.va.gov). Each newly hired VA optometrist will be given a list of mentors and VISN Consultants to contact should the need arise.

- NAVAO Membership

If you know of a colleague who may be interested in joining NAVAO, please have them send \$40 to NAVAO, Attention: Barb Nahlik, 1034 S. Brentwood Suite #300, St. Louis, MO 63117.

- Estimated Newsletter Publication Dates

January 15th

April 15th  
July 15th  
October 15th

- **Content Submissions / Suggestions**

Cases/photos/articles, kudos, meeting dates, etc.

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