Ocular Hypertension Treatment Study (OHTS)

Primary Goals

- Evaluate the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the development of POAG in individuals with elevated IOP

- Identify baseline demographic and clinical factors that predict which participants will develop POAG

The OHTS Exclusion Criteria

- VA worse than 20/40 in either eye
- Previous intraocular surgery other than uncomplicated CE with PCIOL
- Diabetic retinopathy
- Other disease capable of causing VF loss/ON damage

Baseline Characteristics by Randomization Group

Self-designated Race

<table>
<thead>
<tr>
<th>Race</th>
<th>Medication n=817</th>
<th>Observation n=819</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native American</td>
<td>0.1%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Asian</td>
<td>0.5%</td>
<td>1.2%</td>
</tr>
<tr>
<td>African American</td>
<td>25.0%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.9%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>70.6%</td>
<td>68.4%</td>
</tr>
<tr>
<td>Other</td>
<td>1.0%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>
Primary POAG Endpoints*
Log Rank P-value <0.001, Hazard Ratio 0.40, 95% CI (0.27, 0.59)
- Medication
- Observation

At 5 yrs, 4.4% of treated group and 9.5% observation group developed glaucoma

First POAG Endpoint (n=125)

Includes all subjects in medication and observation group

Treatment perhaps less protective in African Americans
- African Americans
  - 12.7% POAG endpoints in observation group
  - 6.9% POAG endpoints in medication group
  - Hazard Ratio 0.54
  - P value for interaction 0.26
- Others
  - 10.2% POAG endpoints in observation group
  - 3.6% POAG endpoints in medication group
  - Hazard Ratio 0.34

Significant Baseline Factors Predicting Progression to POAG

Univariate Analysis
- Age
- Black race
- Male gender
- Heart disease
- Increased IOP
- Thinner CCT
- Greater PSD
- Horizontal C/D ratio
- Vertical C/D ratio

Multivariate Analysis
- Age
- IOP
- CCT
- PSD
- Vertical C/D ratio

POAG Endpoints by Central Corneal Thickness and Baseline IOP (mmHg) in Observation Group*

Baseline IOP (mmHg)
- >25.75
- >23.75 to ≤ 25.75
- ≤ 23.75

Central Corneal Thickness (microns)
- ≤ 555
- >555 to ≤ 588
- >588

POAG Endpoints by Central Corneal Thickness and Baseline Vertical C/D Ratio in Observation Group*

Vertical C/D Ratio
- >0.50
- ≥ 0.30 to <0.50
- ≤ 0.30

Central Corneal Thickness (microns)
- ≤ 555
- >555 to ≤ 588
- >588
**PURPOSE:** To determine the relationship between office IOP and peak IOP

**METHODS (Study One):**
- 42 patients with OAG
- Treated with 3 different IOP lowering eye drops
- 24 hr IOP values obtained in sitting position with Goldmann applanation tomography at 3 hr intervals

**METHODS (Study Two):**
- 103 patients with OAG (including 35 untreated)
- 24 hr IOP values obtained at 2 hr intervals using a pneumatometer, in sitting and supine positions during the diurnal/wake period and in the supine position during the nocturnal/sleep period

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**IOP is Higher at Night**

**PURPOSE:** To characterize the 24 hr pattern of IOP in untreated patients

**METHODS:**
- 24 untreated patients with newly diagnosed glaucomatous optic discs and/or abnormal visual fields
- 24 hr IOP values obtained with a pneumatometer at 2 hr intervals, in the sitting and supine position during the diurnal/wake period and in the supine position during the nocturnal/sleep period

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**Collaborative Normal Tension Glaucoma Study**

- Treatment for IOP reduction: medication (excluding beta-blockers or alpha2 adrenal receptor agonists due to concerns of vasoactivity), ALT, or filtration surgery
Collaborative Normal Tension Glaucoma Study

- Survival analysis: time to visual field progression
- Findings At 5 years, treated patients showed overall survival of 80% compared with 40% in controls (P=.0018)
- The beneficial results of IOP reduction were found only when the impact of cataracts on visual field progression (caused mainly by filtration surgery) was removed

The Collaborative Normal-Tension Glaucoma Study Clinical Pearls

1. Therapeutic intervention (30% IOP reduction) helped prevent visual field progression. However, one must adjust for the development of cataracts, which occur commonly after filtration surgery, to detect the therapeutic benefit of IOP reduction.

2. 30% IOP reduction was achieved in 57% of patients receiving medical therapy with or without argon laser trabeculoplasty (ALT), which underscores the importance of conservative therapy. Since beta-blockers, alpha2 agonists, and prostaglandin analogs were not used in the study, currently available medical agents may achieve IOP reduction in a greater percentage of patients.

The Collaborative Normal-Tension Glaucoma Study Clinical Pearls

3. Approximately 50% of eyes without a history of progression did not progress by 7 years when untreated. However, if progression has been documented in the past, future progression is highly likely, and IOP reduction is recommended.

4. Confirmatory visual fields are essential for verifying suspected progression. For both visual function as well as structural tests, it is important to confirm suspected progression.

The Collaborative Normal-Tension Glaucoma Study Clinical Pearls

5. Disc hemorrhage is a strong, negative prognostic sign; other risk factors include migraine and female gender.
Diurnal Fluctuations in IOP: Independent Risk Factor?

**PURPOSE:** To study the risk associated with diurnal IOP variations in patients with OAG

**METHODS:**
- 64 patients with OAG and IOP below 25 mm Hg (over 5 year follow-up)
- Patients successfully performed tonometry with a self-tonometer 5 times a day for 5 days
- Baseline status and time to progression of visual field loss identified from clinical charts
- Level and variability of diurnal IOP characterized and risk of progression analyzed using a nonparametric time-to-event model

Diurnal Fluctuations Correlate with Visual Field Progression

Hazard ratio between higher quartile and lower quartile for "Range in Home IOP" was 5.7

Timolol: Nocturnal IOP

Effect of Travoprost on Diurnal and Nocturnal IOP

Measured in the usual "habitual position" of the patients during those time periods
- Diurnal period – sitting
- Nocturnal period – supine

Early Manifest Glaucoma Trial

- Compared the effect of immediately lowering the IOP vs no treatment or later treatment, on the progression of newly detected open-angle glaucoma

EMGT Participants

- 255 open angle glaucoma patients
- Ages 50-80 (median 68 years)
- Early glaucoma
- Mild VF loss (median MD, −4dB)
- Median IOP of 20
**EMGT**

- Excluded from trial
  - Patients with IOP greater than 30 mmHg
  - Patients with advanced VF loss


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**EMGT - Interventions**

- Subjects randomized to either
  - Argon Trabeculoplasty + Betaxolol (n=129)
    - OR
  - No initial treatment (n=126)
- HVF 30-2 and IOP q 3 months for 10 years
- Optic nerve photos every 6 months


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**EMGT – progression criteria**

- Visual field progression
  - Computer based criteria
  - Defined as the same 3 or more test point locations showing significant deterioration from baseline in the glaucoma change probability maps on 3 consecutive tests


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**EMGT – progression criteria**

- Optic disc progression
  - Determined by masked graders
  - Used flicker chronoscopy plus side-by-side photographs


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**EMGT- Results**

- Median follow-up of 6 years (range 51-103 months)
- Excellent retention (only 6 patients lost to follow-up for reasons other than death)
- On average, tx reduced IOP by 5.1mm Hg or 25%
- 25% IOP reduction was maintained throughout follow-up


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**EMGT- Results**

- 53 % of subjects progressed
- Progression
  - 45 % of treated patients progressed (58/129)
  - 62% of untreated patients progressed (78/126)
- Statistically significant (P=.007)
- This progression difference was evident at 11 months and increased steadily over time

EMGT- Results

◆ In multivariate analyses, progression risk was halved by treatment
◆ Progression risk decreased by about 10% with each mm of HG of IOP reduction from baseline to the first follow-up visit
◆ Progression risk increased by about 10% with each mm of HG of IOP increase from baseline at first follow-up visit

EMGT- Summary

◆ Factors Increasing Risk of Progression
  - Higher baseline IOP
  - Exfoliation
  - Bilateral disease
  - Older age
  - Worse MD on visual field
  - Presence of disc hemorrhage


PGAs: Effects on Circadian IOP

PURPOSE: To compare 24 hr reduction in IOP with latanoprost, travoprost and bimatoprost in patients with OAG and ocular hypertension (OH)

DESIGN: Randomized, double-masked, crossover study

PARTICIPANTS: 24 OAG and 20 OH patients

METHODS:
• Patients treated with randomized cross-over sequence of latanoprost, travoprost and bimatoprost for 1 month each, with 30 day washout in between
• 24 hr tonometric curves were recorded at baseline (prior to each treatment) and after each treatment period in seated and supine positions
• Baseline and post-treatment IOP measured at 3:00, 6:00, 9:00 AM and noon and 3:00, 6:00, 9:00 PM and midnight

Travoprost Appears Consistent Peak to Trough

Collaborative Initial Glaucoma Treatment Study

◆ On ongoing study to determine if newly diagnosed open-angle glaucoma is better treated with initial medical therapy or immediate filtration surgery
◆ Different study design:
  - Patient satisfaction and quality of life are determining factors in deciding patient care; enrolled patients interviewed before being assigned treatment then re-interviewed every 3-6 months
  - Allows referring ophthals to remain primary caretaker; routine biannual visits conducted at clinical center

CIGTS: Subjects

◆ Eligibility criteria
  - 25-75 years old
  - Newly diagnosed glaucoma as determined by elevated IOP, glaucomatous optic disc damage and VF loss
  - Must not have received any previous glaucoma treatment for longer than 14 days
CIGTS: Subjects

- 607 patients enrolled at 14 centers
- Of the 607 patients enrolled:
  - 90.6% had primary open angle glaucoma
  - 4.6% pigmentary glaucoma
  - 4.8% pseudoexfoliative glaucoma
- Subjects randomized to surgery or stepped medical therapy

Medications: typically BB followed in order by other monotherapy, dual therapy, triple therapy, quad therapy, ALT, Trab, meds, trab+MMC, meds

Surgical treatment arm: patients underwent immediate trab and, with documented failure, proceed to ALT, then conclude with medications

Patients rather than eyes were randomized to the two treatment arms if both eyes were eligible (the treatment course for both eyes is the same and was determined in randomization)

Advance through regimens if VF progression or failure to reach IOP target occurs

Target defined on basis of baseline IOP and degree of field damage

Criteria for failure stricter if VF worse

CIGTS: Results at 5 years

- Quality of life: Surgical vs. Medical
  - Main outcomes were Visual Activities Questionnaire and Symptom and Health Problem Checklist
  - A significantly greater level of symptoms present in surgical patients over 5 years, especially those localized to the eye (such as feeling something in the eye)

Quality of life: Surgical vs. Medical

- The medical group reported a variety of systemic symptoms that were not consistent over time, but were clearly different from the symptoms reported by the surgical group

Ophthalmology 2001; 108: 1954-65
CIGTS: Results

- Quality of life: Surgical vs. Medicine
  - The self-reported visual function of surgical patients was marginally (5%) worse than medically treated patients over 5 years
  - No difference in fear of blindness: both groups decline from 50%-25% over 5 years

*Ophthalmology* 2001; 108: 1954-65

- Clinical Results: Surgery vs. Medicine
  - Average pressure in the medically treated group 17-18 mmHg
  - Pressure in the surgical group was 3 points lower (14-15)

*Ophthalmology* 2001; 108: 1943-53

CIGTS: Results

- Clinical Results: Surgery vs. Medicine
  - VF loss did not differ over 5 years between treatment groups
  - VA was better for medically treated group over much of the study, but by 4 years, was no different than the surgical group
  - Number progressing in both groups was low (15%)

*Ophthalmology* 2001; 108: 1943-53

CIGTS: Results

- With pressure-lowering significantly better in the surgical group, why were their outcomes not superior?
  - More aggressive use of better currently available meds
  - Cataract rates higher in surgery group; could mask visual field outcomes

Glaucoma & Pregnancy

- BJO 2009; JD Ho:
- 244 pregnant women treated for glaucoma analyzed for birth weight
- 1,952 age matched controls
- No significant difference between women on BB’s vs: no Tx
- Herndon, L: D/C Brimonodine several weeks before d/t risk of apnea
Advanced Glaucoma Intervention Study

AGIS

- How effective is IOP lowering in preserving VF?
- Is there an “ideal” IOP that provides maximum benefit in reducing or eliminating pressure-related component of damage?

AGIS

- Patients enrolled 1988-1992
- 591 patients
- 789 eyes
- 8 years of follow up
- Randomized to ALT or Trab first for COAG patients inadequately controlled with meds
- Main result: no difference between the two groups

AGIS

- Evaluated 2 tx sequences in medically uncontrolled COAG patients
- Patients randomized to either ALT or Trabeculectomy first.

AGIS

- ATT or TAT
- Supplemented with meds
- Target IOP<18
- Mean pre-surgery IOP=25

AGIS 7 Report

- Analysis of the relationship b/t IOP control and VF loss over the first 6 years of F/U.
AGIS 7 Report

- Patients with IOP<18 on 100% of follow-up exams over 6 years had mean change from baseline VF close to ZERO. (Mean IOP=12.3 over 6 years)
- Patients with IOP<18 on 50% of follow-up exams showed progression

*Am J Ophthalmol 2000;130:429-440*

AGIS 7

- Does AGIS 7 apply to all patients?
- AGIS 7: Target IOP=12
- AGIS specific to COAG. May not be applicable to 2^G or OHT
- All study subjects had surgery (ALT or Trab)

AGIS 7

- Average IOP at target following initial intervention had better preservation of VF.
- Those who did not achieve target IOP during months 6-18 did worse.
- Therefore, when IOP is more resistant to surgical or medical tx, outcome is worse

AGIS

- Racial difference (7 year follow-up)
  - African Americans ATT
  - White Americans TAT
- Before Xalatan
- Trabs without MMC
- Rigid protocol is different today

A message from AGIS and CIGTS

- Aggressive IOP-lowering by any means is the best way to protect against further VF loss
Ocular Surface Disease Prevalence Study

**Purpose:** To Determine The Prevalence of OSD Symptoms in Glaucoma Patients

**Methods:**
- 10 Sites
- 630 Glaucoma Patients On IOP Lowering Medication:
  - Patients Completed an OSDI Survey While in The Office

Fechtner R, Budenz D, Godfrey D. Prevalence of ocular surface disease symptoms in glaucoma patients on IOP lowering medications. Poster presented at annual meeting of the American Glaucoma Society; March 8, 2008; Washington, DC.

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**Ocular Surface Disease Index**

Please Answer The Following Questions by Checking The Box That Best Represents Your Answer

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Half of the time</th>
<th>Some of the time</th>
<th>None of the time</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes that are sensitive to light?</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
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<tr>
<td>Eyes that feel gritty?</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Painful or sore eyes?</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burned eyes?</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

How problems with your eyes limited you in performing any of the following during the last week:

<table>
<thead>
<tr>
<th>Activity</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Half of the time</th>
<th>Some of the time</th>
<th>None of the time</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reading?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Driving at night?</td>
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<tr>
<td>Working with a computer or bank machine (ATM)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watching TV?</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Have your eyes felt uncomfortable in any of the following situations during the last week:

<table>
<thead>
<tr>
<th>Situation</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Half of the time</th>
<th>Some of the time</th>
<th>None of the time</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Windy conditions?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Places or areas with low humidity (very dry)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Areas that are air conditioned?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**OSDI Severity Grading**

<table>
<thead>
<tr>
<th>Score</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12</td>
<td>13-22</td>
<td>23-32</td>
<td>33-100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Total OSDI Score = (Sum of Score for All Questions Answered) x (25) / (Total # of Questions Answered)


**OSD Prevalence Study: Results**

**OSDI Scores in Glaucoma Patients**

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>325</td>
<td>134</td>
<td>84</td>
<td>87</td>
</tr>
<tr>
<td>Percentage</td>
<td>51.6%</td>
<td>21.3%</td>
<td>13.3%</td>
<td>13.8%</td>
</tr>
</tbody>
</table>

48.4%

Fechtner R, Budenz D, Godfrey D. Prevalence of ocular surface disease symptoms in glaucoma patients on IOP lowering medications. Poster presented at annual meeting of the American Glaucoma Society; March 8, 2008; Washington, DC.

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**OSD Prevalence Study: Multiple Medication Impact**

<table>
<thead>
<tr>
<th>Number of Meds Taken</th>
<th>1</th>
<th>2</th>
<th>3</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>253</td>
<td>227</td>
<td>114</td>
</tr>
<tr>
<td>Average OSDI Score</td>
<td>12.9±13.1</td>
<td>16.7±17.0</td>
<td>19.4±18.1</td>
</tr>
</tbody>
</table>

P-Values

<table>
<thead>
<tr>
<th>1 Medication</th>
<th>2 Medications</th>
<th>3 Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.007</td>
<td>0.001</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Fechtner R, Budenz D, Godfrey D. Prevalence of ocular surface disease symptoms in glaucoma patients on IOP lowering medications. Poster presented at annual meeting of the American Glaucoma Society; March 8, 2008; Washington, DC.

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**Neuro-Protection in Glaucoma**
Are any of the following glaucoma medications neuroprotective?

- Beta blockers (timolol)
- Alpha agonists (brimonidine)
- Prostaglandins (travatan)
- Carbonic anhydride inhibitors (dorzolamide)

Four Criteria Required for a Medication to be Neuroprotective

- 1. Evidence of receptors on its target tissue
- 2. Adequate penetration into the vitreous and retina at pharmacologic levels
- 3. Evidence that supports a mechanism of action that enhances a neuron’s resistance to injury in animal studies
- 4. Demonstrated neuroprotective activity in human prospective randomized clinical trials

Retinal Receptors

- Brimonidine is a highly selective alpha 2 agonist
- Animal and human studies show alpha 2 receptors in the retinal ganglion cell

Brimonidine penetration into the Vitreous

- Brimonidine is absorbed into pigmented tissue after topical administration
- Vitreous concentrations with .2% brimonidine in monkey eyes was 82 +/- 45 nM
- Retina receptors activate with minimal concentrations of 2 nM
- Animal and human studies confirm that adequate amounts of brimonidine reach the posterior vitreous to activate ganglion cell receptors

Brimonidine Animal Studies

- Alpha2-adrenoreceptor agonists are neuroprotective in a rat model of optic nerve degeneration
- E Yoles, LA Wheeler and M Schwartz
  Department of Neurobiology, The Weizmann Institute of Science, Rehovot, Israel.

Brimonidine and Rats Part I

- Partial crush injury to optic nerves
- Treated with single doses of intraperitoneal brimonidine vs timolol
- Secondary degeneration of optic nerve was measured by electrophysiologically and counting ganglion cell axons
- Brimonidine treated rats had three times less loss of axons than timolol tx rats
Brimonidine Animal Studies

- **Neuroprotection of Retinal Ganglion Cells by Brimonidine in Rats with Laser-Induced Chronic Ocular Hypertension**
- Elizabeth WoldeMussie, Guadalupe Ruiz, Mercy Wijono and Larry A. Wheeler
- From the Department of Biological Sciences, Allergan Inc., Irvine, California.

Brimonidine and Rats Part II

- IOP was elevated in rat eyes by laser photocoagulation to episcleral and limbal veins
- Timolol, brimonidine or saline was injected subcutaneously after IOP elevation
- After 3 weeks of elevated IOP, GCA loss in control group was 33% loss, vs 26% and 15% loss for brimonidine (.5mg/kg and 1mg/kg) vs 33% loss for timolol
- Believed that brimonidine may reduce levels of intravitreal glutamate secondary to ischemia in rat models

Human Clinical Trials

- Phase I: Usually designed to evaluate safety, determine a safe dosage range, and identify side effects on a small group of patients.
- Phase II: If Phase I is successful, the trial is then repeated with a larger group to further evaluate its effect and safety.
- Phase III: Trials are conducted on an ever larger group and are compared with the best current treatment while gathering more information on effect and safety.
- Phase IV: These studies monitor long-term side effects after the treatment has been marketed.

Human Clinical Trials of Brimonidine Neuroprotection

- NAION
- Fazzone et al. retrospective study of 31 patients with NAION
- 14 patients received brimonidine up to qid after initial episode of AION compared with an age match group of NAION
- No benefit was seen in the brimonidine treated group and there was a trend towards worse visual fields, color vision and visual acuity

BRAION Study

- Wilhelm, et al. BRAION study
- Double blind randomized clinical trial comparing brimonidine and placebo for patients with acute AION
- No statistically significant benefit found

Other Human Clinical Trials

- No statistically sig benefit with brimonidine found in fellow eye of patients with Lebers hereditary optic neuropathy. Newman et al,
- No statistically sig benefit with brimonidine found in patients with retinal dystrophies Merin et al.
- Slight benefit found in reducing collateral damage caused by laser photocoagulation in pt with choroidal neovascularization Ferencz et al