

An Eye's Glance

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A Monthly Review of Important Clinical and Therapeutic Trends in Ophthalmology

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GLAUCOMA

Holló G, Thelen U, Teus MA, Quaranta L, Ferkova S, Babić N, Misiuk-Hojlo M, Mikropoulos DG, Kaluzny BJ, Kozobolis V, Januleviciene I, Kóthy P, Camara C, Russo A, Krzyzanowska-Berkowska P, Cieślińska I, Stewart JA, Kristoffersen MS, Nelson LA, Stewart WC. Long-term outcomes of prostaglandin analog versus timolol maleate in ocular hypertensive or primary open-angle glaucoma patients in Europe. *J Ocul Pharmacol Ther* 2011;27:493-498.

PURPOSE: To determine the direct costs of therapy over 5 years of a European monotherapy cohort begun on a prostaglandin (PTG) versus timolol in patients with primary open-angle glaucoma or ocular hypertension. **METHODS:** A retrospective, multicenter, active-controlled, observational study. Data were abstracted for European patients treated as initial monotherapy in 1996 or afterward, with 5 years of available records. **RESULTS:** This study included 271 patients (166 on a PTG and 105 on timolol at baseline). The average cost/month/patient over 5 years was \$45.47±12.61 for PTG and \$31.50±15.47 for timolol (P<0.001, based on German prices). After 5 years, although there was no difference in number of glaucoma medicines prescribed between groups (1.0 PTGs and 1.1 timolol, P=0.41), the timolol group demonstrated a higher intraocular pressure (17.7±2.9 vs. 16.5±3.0 mm Hg, P<0.001), more medication changes (P=0.01), greater incidence of glaucomatous progression (P=0.04), and less patients persistent on original monotherapy (P<0.001) than the PTG cohort. **CONCLUSIONS:** Patients originally on timolol monotherapy have a lower cost of care over 5 years than those started on a PTG. However, timolol patients during follow-up may demonstrate a higher intraocular pressure, more progression, more medication changes, and lower persistency of the original monotherapy.

Lieberman MF, Congdon NG, He M. The value of tests in the diagnosis and management of glaucoma. *Am J Ophthalmol* 2011;152:889-899.

PURPOSE: To assess the noneconomic value of tests used in the diagnosis and management of glaucoma, and explore the contexts and factors that determine such value. **DESIGN:** Perspective. **METHODS:** Selected articles from primary and secondary sources were reviewed and interpreted in the context of the authors' clinical and research experience, influenced by our perspectives on the tasks of reducing the global problem of irreversible blindness caused by glaucoma. The value of any test used in glaucoma is addressed by 3 questions regarding: its contexts, its kind of value, and its implicit or explicit benefits. **RESULTS:** Tonometry, slit-lamp gonioscopy, and optic disc evaluation remain the foundation of clinic-based case finding, whether in areas of more or less abundant resources. In resource-poor areas, there is urgency in identifying patients at risk for severe functional loss of vision; screening strategies have proven ineffective, and efforts are hindered by the inadequate allocation of support. In resource-abundant areas, the wider spectrum of glaucoma is addressed, with emphasis on early detection of structural changes of little functional consequence; these are increasingly the focus of new and expensive technologies whose clinical value has not been established in longitudinal and population-based studies. These contrasting realities in part reflect differences among the value ascribed, often implicitly, to the tests used in glaucoma. **CONCLUSIONS:** The value of any test is determined by 3 aspects: its context of usage; its comparative worth and to whom its benefit accrues; and how we define historically what we are testing. These multiple factors should be considered in the elaboration of priorities for the development and application of tests in glaucoma.

Bozkurt E, Kara N, Yazici AT, Yuksel K, Demirok A, Yilmaz OF, Demir S. Prophylactic selective laser trabeculoplasty in the prevention of intraocular pressure elevation after intravitreal triamcinolone acetonide injection. *Am J Ophthalmol* 2011;152:976-981.

PURPOSE: To evaluate the prophylactic efficacy of selective laser trabeculoplasty for preventing an increase in intraocular pressure (IOP) after intravitreal triamcinolone acetonide injection. **DESIGN:** Prospective, comparative,

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interventional case series. **METHODS:** We studied 31 eyes with a baseline IOP of 21 mm Hg or more of 31 patients for which intravitreal triamcinolone acetonide injection was planned for diabetic macular edema. The patients were divided into 2 groups, a study group and control group. The study group comprised 15 eyes of 15 patients that underwent selective laser trabeculoplasty a mean of 8.3 ± 4.1 days before intravitreal triamcinolone acetonide injection. The control group comprised 16 eyes of 16 patients who underwent only intravitreal triamcinolone acetonide injection. Main outcomes measures were mean IOP and number of patients requiring antiglaucomatous therapy. **RESULTS:** Mean baseline IOP was 21.6 ± 0.9 mm Hg in the study group and 21.5 ± 0.8 mm Hg in the control group ($P = .98$). Mean IOP at 1 day after injection was 17.0 ± 2.0 mm Hg in the study group and 19.5 ± 4.3 mm Hg in the control group ($P = .23$). Mean IOP at 1 week after injection was 16.9 ± 1.7 mm Hg and 18.4 ± 4.0 mm Hg, respectively ($P = .49$); mean IOP at 1 month after injection was 16.4 ± 1.5 mm Hg and 20.8 ± 5.6 mm Hg, respectively ($P = .003$); mean IOP at 3 months after injection was 15.8 ± 2.5 mm Hg and 18.3 ± 5.5 mm Hg, respectively ($P = .01$); and mean IOP at 6 months after injection was 15.7 ± 1.4 mm Hg and 17.1 ± 1.5 mm Hg, respectively ($P = .03$). The number of patients requiring antiglaucomatous therapy during follow-up was 0 of 15 eyes in the study group and 8 of 16 eyes in the control group ($P = .001$). **CONCLUSIONS:** The IOP elevation after intravitreal triamcinolone acetonide injection may be prevented by performing selective laser trabeculoplasty before intravitreal triamcinolone acetonide injection, especially in cases with a baseline IOP of 21 mm Hg or more.

RETINA

de Oliveira Dias JR, Rodrigues EB, Maia M, Magalhães O Jr, Penha FM, Farah ME. Cytokines in neovascular age-related macular degeneration: fundamentals of targeted combination therapy. Br J Ophthalmol 2011;95:1631-1637.

The neovascular form of age-related macular degeneration (AMD), called wet-AMD or choroidal neovascularisation, begins with damage to the outer retinal cells and retinal pigment epithelium (RPE), which elicits a cascade of inflammatory and angiogenic responses leading to neovascularisation under the macula. Studies showed that oxidative damage, chronic inflammation of the RPE and complement misregulation work at different steps of this disease. After established neovascularisation, several pro- and antiangiogenic agents start to play an important role. Vascular endothelial growth factors (VEGFs) are the most specific and potent regulators of angiogenesis, which are inhibited by intravitreal injections of ranibizumab, bevacizumab, VEGF Trap, pegaptanib sodium and other agents under investigation. Pigment epithelium-derived factor, on the other hand, shows neuroprotective and antiangiogenic activities. Hepatocyte growth factor (HGF) has a mitogenic effect on a wide range of epithelial and endothelial cells, and it is inhibited by an anti-HGF monoclonal antibody. Platelet-derived growth factor is a potent chemoattractant and mitogen for both fibroblasts and retinal RPE cells, which has been inhibited experimentally by VEGF Trap and human anti-platelet-derived growth factor-D monoclonal antibody. Fibroblast growth factor-2 has pleiotropic effects in different cell and organ systems, and it is blocked by anti-FGF antibodies, with a greater benefit regarding antiangiogenesis when combined treatment with anti-VEGF is performed. Tumour necrosis factor alpha is expressed in the retina and the choroid, and its blockade in choroidal neovascularisation includes the use of monoclonals such as infliximab. This paper reviews the most important cytokines involved in the pathogenesis of wet-AMD, with emphasis on potential combined therapies for disease control.

CATARACT

Fong CS, Mitchell P, Rochtchina E, de Loryn T, Hong T, Wang JJ. Sustainability of visual acuity in the first 2 years after cataract surgery. Br J Ophthalmol 2011;95:1652-1655.

PURPOSE: To assess whether improved visual acuity (VA) is sustained 2 years after the cataract surgery. **METHODS:** The Cataract Surgery and Age-Related Macular Degeneration (CSAMD) study followed 1936 patients aged ≥ 65 years undergoing phacoemulsification cataract surgery at Westmead Hospital (Sydney, Australia) between 2004 and 2007. Presenting and pinhole VA were assessed and retinal photography was performed annually. VA improvement or reduction was defined if VA differed by ≥ 2 lines between 1 and 24 months. **RESULTS:** VA data were available for 1809 patients at 1 month and 1294 at both postoperative visits (71.5% of 1809). At the 2-year visit, 930 patients (71.9%) maintained the same pinhole VA levels that they had at 1 month postoperatively, 199 (15.4%) had an improvement and 165 (12.7%) a reduction in pinhole VA. After adjusting for age and gender, pre-existing macular conditions (early AMD, macular hole or previous laser treatment) were associated with pinhole VA

reduction ($p=0.02$). At the 24-month visit, 58.1% of those with presenting VA improvement wore distance spectacles. **CONCLUSIONS:** One in eight cataract surgical patients lost at least two lines in pinhole VA over the 2-year postoperative period. Regular eye examinations of patients after cataract surgery may help to maximise the surgical benefits over the long term.

Schmoll C, Tendo C, Aspinall P, Dhillon B. Reaction time as a measure of enhanced blue-light mediated cognitive function following cataract surgery. *Br J Ophthalmol* 2011;95:1656-1659.

BACKGROUND/AIMS: Since 2002 the discovery of a novel population of intrinsically photosensitive retinal ganglion cells, expressing the photopigment melanopsin, has attracted broad interest in human blue-light mediated non-visual effects including circadian regulation and cognitive function. Ageing is associated with insomnia and cognitive decline. It has been postulated that reduced blue-light transmission through the formation of cataract impairs melanopsin dependant non-visual brain responses mediated by intrinsically photosensitive retinal ganglion cells. We aimed to establish if any objective improvement in cognition could be demonstrated using a reaction time task (RTT) following cataract surgery and intraocular lens implantation. **METHODS:** Following strict inclusion and exclusion criteria, 15 patients (age range 59-87, mean 75.4 years) with bilateral cataract performed the RTT before and after surgery on one eye. The mean and the SD of two modalities of reaction time, namely complex reaction time and simple reaction time, were measured and analysed. **RESULTS:** Responses became both quicker and more consistent following surgery, with statistically significant improvements in the complex reaction time ($p=0.016$) and the complex reaction time SD ($p=0.055$), which were not due to a learning effect or improved vision. **CONCLUSION:** The results suggest that improved blue-light transmission following cataract surgery has a beneficial effect on cognitive function. We advocate the RTT as an objective platform for exploring these benefits in large sample randomised controlled trials.

Hengerer FH, Dick HB, Conrad-Hengerer I. Clinical Evaluation of an Ultraviolet Light Adjustable Intraocular Lens Implanted after Cataract Removal Eighteen Months Follow-up. *Ophthalmology* 2011;118:2382-2388.

PURPOSE: To determine the effectiveness of a light-adjustable intraocular lens (LAL) that can be adjusted postoperatively using ultraviolet (UV) irradiation. **DESIGN:** A prospective, nonrandomized clinical trial was conducted at Center for Vision Science, Ruhr University Eye Clinic, in Bochum, Germany. **PARTICIPANTS:** We included 122 eyes of 91 patients with significant cataract. **METHODS:** All patients had a visually significant cataract and were willing to volunteer for the trial. Participants underwent small-incision phacoemulsification followed by implantation of a LAL and were treated with a spatially profiled UV light delivered by a digital light delivery device to induce a targeted spherical and cylindrical refractive change postoperatively. Once the desired correction was achieved, the LAL was treated again to lock in the lens power. Distance visual acuity and manifest refraction was determined with follow-up time to determine the achieved refractive corrections and their stability. **MAIN OUTCOME MEASURES:** We measured uncorrected visual acuity and best corrected visual acuity achieved versus targeted refractive outcome and refractive stability with a follow-up time of 18 months. **RESULTS:** Residual postoperative refractive errors of 0.96 ± 0.85 diopters (D) in sphere and -0.98 ± 0.50 D in cylinder were corrected and stable over a follow-up time of 18 months. Final refraction achieved was 0.03 ± 0.17 D in spherical equivalent refraction. **CONCLUSIONS:** Residual spherocylindrical errors up to 2.25 D in sphere and -2.75D in cylinder were successfully corrected with precision. The LAL technology has the potential individually to correct postoperative refractive errors precisely. The achieved refractive corrections are stable for up to 18 months.

McAlinden C, Gothwal VK, Khadka J, Wright TA, Lamoureux EL, Pesudovs K. A Head-to-Head Comparison of 16 Cataract Surgery Outcome Questionnaires. *Ophthalmology* 2011;118:2374-2381.

PURPOSE: To investigate the responsiveness of 16 questionnaires used in cataract surgery outcomes. **DESIGN:** Prospective, observational study. **PARTICIPANTS:** Patients at the Ophthalmology Eye Clinic, Flinders Medical Centre, Adelaide, Australia, and 1 matched eye clinic in Sweden. **METHODS:** Sixteen Rasch-scaled cataract surgery questionnaires were completed before and 6 months after surgery. These were: the Cataract Symptom Scale, 6 versions of the National Eye Institute Visual Function Questionnaire, the Quality of Life and Vision Function Questionnaire, the Cataract TyPE Specification, the Visual Activities Questionnaire, the Visual Disability Assessment (VDA), the Visual Function and Quality of Life questionnaire, the Visual Function Index, Catquest-9SF, the Visual Symptoms and Quality of Life questionnaire, and the Cataract Outcomes Questionnaire. Responsiveness was calculated with the effect size (ES) statistic (change in questionnaire score divided by pooled standard deviation of the preoperative and postoperative scores). **MAIN OUTCOME MEASURES:** Questionnaire responsiveness to cataract surgery (ability to detect clinically important change). **RESULTS:** All 16 questionnaires and their subscales were responsive to cataract surgery, with visual functioning scales being more responsive than socioemotional

scales and some subscales being less responsive. The largest ES was for the Catquest-9SF (1.45; 95% confidence interval [CI], 1.22-1.67), which was the only instrument with a mean and 95% CI of more than 1.0 (very large ES). Three measures had very large ESs and 95% CIs of more than 0.80 (large ES): the VDA (activity limitations and subscale) and the Cataract Outcomes Questionnaire, although their 95% CIs overlapped with a number of other instruments. CONCLUSIONS: The Catquest-9SF is short and highly responsive to cataract surgery, and so is ideal for measuring visual functioning outcomes. Other instruments may be preferred to measure different constructs.

DRY EYE

Pflugfelder SC. Tear Dysfunction and the Cornea: LXVIII Edward Jackson Memorial Lecture. Am J Ophthalmol 2011;152:900-909.

PURPOSE: To describe the cause and consequence of tear dysfunction-related corneal disease. DESIGN: Perspective on effects of tear dysfunction on the cornea. METHODS: Evidence is presented on the effects of tear dysfunction on corneal morphology, function, and health, as well as efficacy of therapies for tear dysfunction-related corneal disease. RESULTS: Tear dysfunction is a prevalent eye disease and the most frequent cause for superficial corneal epithelial disease that results in corneal barrier disruption, an irregular optical surface, light scattering, optical aberrations, and exposure and sensitization of pain-sensing nerve endings (nociceptors). Tear dysfunction-related corneal disease causes irritation and visual symptoms such as photophobia and blurred and fluctuating vision that may decrease quality of life. Dysfunction of 1 or more components of the lacrimal functional unit results in changes in tear composition, including elevated osmolarity and increased concentrations of matrix metalloproteinases, inflammatory cytokines, and chemokines. These tear compositional changes promote disruption of tight junctions, alter differentiation, and accelerate death of corneal epithelial cells. CONCLUSIONS: Corneal epithelial disease resulting from tear dysfunction causes eye irritation and decreases visual function. Clinical and basic research has improved understanding of the pathogenesis of tear dysfunction-related corneal epithelial disease, as well as treatment outcomes.

VISION

Shah N, Laidlaw DA, Shah SP, Sivasubramaniam S, Bunce C, Cousens S. Computerized Repeating and Averaging Improve the Test-Retest Variability of ETDRS Visual Acuity Measurements: Implications for Sensitivity and Specificity. Invest Ophthalmol Vis Sci 2011;52:9397-9402.

PURPOSE: The goals of this study were to investigate the effectiveness of computerized repeating and averaging of visual acuity measurements in reducing test-retest variability (TRV) and to estimate the increase in sensitivity and specificity that would be achieved in diagnosing visual acuity change. METHODS: Timed, paired ETDRS chart and computerized acuity mean measurement (CAMM) were performed in 100 subjects. CAMM(n) scores were the running mean of consecutive measurements. Bland-Altman methods were used to calculate 95% ranges for TRV. RESULTS: The 95% TRV range of ETDRS measurements and the CAMM score after 6 (CAMM6) measurements were, respectively, 8 and 5.7 ETDRS letters ($P = 0.02$). CAMM6 offered a pragmatically optimum tradeoff between reduced TRV and test time. A measured change of 5 letters or more in the absence of true change was observed in 13% (95% CI, 8%-21%) with the ETDRS chart and 4% (95% CI, 2%-10%) with CAMM6 measurements. To achieve $\geq 95\%$ test sensitivity (assuming 95% test specificity), change criteria of 15 and 11 letters must be set with an ETDRS chart and CAMM6, respectively. CAMM6 measurement times were longer (mean 234 seconds vs. 74 seconds) for the ETDRS chart. CONCLUSIONS: Compared with the current gold standard, computerized repeating and averaging of acuity measurements improve specificity and sensitivity when identifying true changes. The 160-second increase in test time should be set against the considerable economic and clinical benefits that may result.

Sun JK, Qin H, Aiello LP, Melia M, Beck RW, Andreoli CM, Edwards PA, Glassman AR, Pavlica MR; for the Diabetic Retinopathy Clinical Research Network. Evaluation of Visual Acuity Measurements After Autorefraction vs Manual Refraction in Eyes With and Without Diabetic Macular Edema. Arch Ophthalmol. 2011 Dec 12. [Epub ahead of print]

OBJECTIVE: To compare visual acuity (VA) scores after autorefraction vs manual refraction in eyes of patients with diabetes mellitus and a wide range of VAs. METHODS: The letter score from the Electronic Visual Acuity (EVA) test from the electronic Early Treatment Diabetic Retinopathy Study was measured after autorefraction (AR-EVA score)

and after manual refraction (MR-EVA score), which is the research protocol of the Diabetic Retinopathy Clinical Research Network. Testing order was randomized, study participants and VA examiners were masked to refraction source, and a second EVA test using an identical supplemental manual refraction (MR-EVAsuppl score) was performed to determine test-retest variability. RESULTS: In 878 eyes of 456 study participants, the median MR-EVA score was 74 (Snellen equivalent, approximately 20/32). The spherical equivalent was often similar for manual refraction and autorefraction (median difference, 0.00; 5th-95th percentile range, -1.75 to 1.13 diopters). However, on average, the MR-EVA scores were slightly better than the AR-EVA scores, across the entire VA range. Furthermore, the variability between the AR-EVA scores and the MR-EVA scores was substantially greater than the test-retest variability of the MR-EVA scores ($P < .001$). The variability of differences was highly dependent on the autorefractor model. CONCLUSIONS: Across a wide range of VAs at multiple sites using a variety of autorefractors, VA measurements tend to be worse with autorefraction than manual refraction. Differences between individual autorefractor models were identified. However, even among autorefractor models that compare most favorably with manual refraction, VA variability between autorefraction and manual refraction is higher than the test-retest variability of manual refraction. The results suggest that, with current instruments, autorefraction is not an acceptable substitute for manual refraction for most clinical trials with primary outcomes dependent on best-corrected VA.

CORNEA

Sankaridurg P, Holden B, Smith E 3rd, Naduvilath T, Chen X, de la Jara PL, Martinez A, Kwan J, Ho A, Frick K, Ge J. Decrease in rate of myopia progression with a contact lens designed to reduce relative peripheral hyperopia: one-year results. Invest Ophthalmol Vis Sci 2011;52:9362-9367.

PURPOSE: To determine whether a novel optical treatment using contact lenses to reduce relative peripheral hyperopia can slow the rate of progress of myopia. METHODS: Chinese children, aged 7 to 14 years, with baseline myopia from sphere -0.75 to -3.50 D and cylinder ≤ 1.00 D, were fitted with novel contact lenses ($n = 45$) and followed up for 12 months, and their progress was compared with that of a group ($n = 40$) matched for age, sex, refractive error, axial length, and parental myopia wearing normal, single-vision, spherocylindrical spectacles. RESULTS: On adjusting for parental myopia, sex, age, baseline spherical equivalent (SphE) values, and compliance, the estimated progression in SphE at 12 months was 34% less, at -0.57 D, with the novel contact lenses (95% confidence interval [CI], -0.45 -0.69 D) than at -0.86 D, with spectacle lenses (95% CI, -0.74 to -0.99 D). For an average baseline age of 11.2 years, baseline SphE of -2.10 D, a baseline axial length of 24.6 mm, and 320 days of compliant lens wear, the estimated increase in axial length (AL) was 33% less at 0.27 mm (95% CI, 0.22-0.32 mm) than at 0.40 mm (95% CI, 0.35-0.45 mm) for the contact lens and spectacle lens groups, respectively. CONCLUSIONS: The 12-month data support the hypothesis that reducing peripheral hyperopia can alter central refractive development and reduce the rate of progress of myopia.