Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

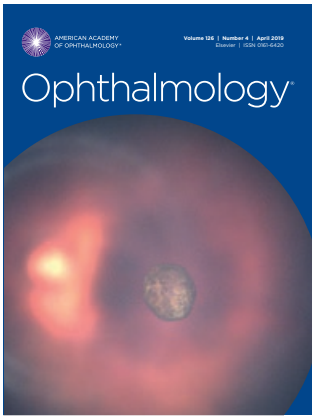
Ophthalmology

Selected by Stephen D. McLeod, MD

Cataract Surgery in Tamsulosin-Exposed Patients

April 2019

Tamsulosin has been linked to intraoperative floppy iris syndrome (IFIS), a risk factor for complications during cataract surgery. Despite many efforts to increase awareness of the risks related to tamsulosin, it is uncertain whether these efforts have been effective. In a population-based study, **Campbell et al.** looked at the rates of adverse events (AEs) over time among patients who did and did not have recent exposure to tamsulosin. Results showed that, over an 11-year period, both groups had a decline in the rate of AEs linked to cataract surgery complications.



Study participants were men aged 66 years and older (mean age, 78 years) who underwent cataract surgery from January 2003 through December 2013 in Ontario, Canada. The time frame included periods both before and after the initial reports of tamsulosin-associated IFIS. The authors used linked health care databases to compare the evolution of the risk of cataract surgery AEs between patients who did and did not receive tamsulosin, and they adjusted for patient-, surgeon-, and institution-level covariates. Outcome measures were the incidences of capsule rupture, dropped lens fragment, retinal detachment, and suspected endophthalmitis.

More than 400,000 cataract surgery cases were represented in the study. Of these, 39,144 had recent exposure to tamsulosin. Overall, the risk of surgical AEs declined over time for patients who had recent exposure to tamsulosin (odds ratio, 0.95/year), regardless of age group. Findings were similar for the patients who did not have recent exposure to tamsulosin (odds ratio, 0.96 per year). Incidence rates for the specific AEs were similar for the study arms, and ranged from 0.02% for retinal detachment (both groups) to 0.76% for posterior capsule rupture (tamsulosin group; vs. 0.58% no exposure group).

The authors suggested that the concurrent decline in adverse event rates for cataract patients with and without exposure to tamsulosin indicates that continuing medical education efforts that disseminate risk-modifying technical adjustments have been effective.

Nevertheless, they pointed out, as tamsulosin exposure remains a risk for AEs, these adjustments must be maintained and advanced.

Pneumatic Retinopexy or Vitrectomy for Primary RRD

April 2019

There are many clinical circumstances under which the best technique to repair rhegmatogenous retinal detachment (RRD) is not clear. **Hillier et al.** compared pneumatic retinopexy (PnR) and pars plana vitrectomy (PPV) for primary RRD considered amenable to both PnR and PPV. They found that PnR produced superior visual acuity (VA) and less vertical metamorphopsia.

In this prospective study, 176 patients with RRD and one or more breaks in the detached retina within 1 clock-hour above the 8- and 4-o'clock meridians were assigned randomly to receive PnR or PPV within 24 hours (macula on) or 72 hours (macula off) of detection. The primary outcome was VA at 12 months according to the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria. Other outcomes of interest were subjective visual function (25-item National Eye Institute Visual Function Questionnaire [NEI VFQ-25]), metamorphopsia score, and primary anatomic success.

Twelve-month assessments showed that mean ETDRS VA was better after PnR (79.9 ± 10.4 letters vs. 75.0 ± 15.2 letters after PPV; p = .024). Composite NEI VFQ-25 scores were better for PnR at three and six months, but similar at 12 months. At 12 months, vertical metamorphopsia scores were better for the PnR group (0.14 ± 0.29 vs. 0.28 ± 0.42; p = .026). Primary anatomic success was achieved by 12 months in

80.8% of patients who underwent PnR and in 93.2% of those who had PPV ($p = .045$). Secondary anatomic success was attained for 98.7% and 98.6%, respectively. Among phakic patients, 65% of those in the PPV arm and 16% of those in the PnR group underwent cataract surgery before month 12 ($p < .001$).

The authors concluded that PnR should be the first-line treatment for RRD in patients who fulfill the recruitment criteria of the PIVOT study. Despite the current global popularity of PPV, the relative simplicity and elegance of PnR remain attractive, said the authors.

Slowing Neurodegeneration in MacTel Type 2

April 2019

Chew et al. tested the effects of cell-based delivery of a neuroprotective agent on the progression of macular telangiectasia (MacTel) type 2. They found that retinal degeneration progressed more slowly in eyes that received the implanted device releasing ciliary neurotrophic factor (CNTF) into the vitreous cavity, and patients maintained monocular reading speed.

This single-masked trial included 11 retina centers in the United States and Australia. The researchers enrolled 67 patients (99 eyes); study eyes were required to have disruption in the ellipsoid zone layer (evidence of photoreceptor loss) ranging from 0.16 to 4.00 mm^2 and best-corrected visual acuity of 20/50 or better.

Participants were assigned randomly (1:1) to receive a sham operation or surgical implantation of an encapsulated system (NT-501, Neurotech) that provides sustained intravitreal delivery of human CNTF.

The main outcome was the change from baseline to 24 months in the area of neurodegeneration, measured by spectral-domain optical coherence tomography in the area of ellipsoid zone disruption or photoreceptor loss. Secondary outcomes included between-group differences in visual function changes.

Sixty-five of the 67 participants completed the trial; two died during the study period. The area of neurodegeneration progression was found to be 31% larger for sham-treated eyes. At 24 months, the difference in mean area of photoreceptor loss was 0.05 ± 0.03 mm^2 ($p = .04$). Retinal sensitivity changes, as measured by microperimetry, correlated strongly with changes in the area of photoreceptor loss ($r = 0.86$; $p < .0001$). The mean retinal sensitivity loss in the sham group was 45% greater than for patients with active treatment (decrease of 15.81 ± 8.93 dB; $p = .07$). Although reading speed deteriorated in the sham group (–13.9 words/minute), it was maintained in the active-treatment arm ($p = .02$). Adverse effects occurred in 4% of each study group.

Although the study results are promising, the authors encouraged more research to assess longer-term clinical outcomes and safety. They noted that their findings are not necessarily generalizable to all patients. Further study would be needed to understand the therapeutic effectiveness of the device in different patient populations.

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Quality of MIGS Trials

March/April 2019

Mathew et al. assessed the quality of published studies of minimally invasive glaucoma surgery (MIGS) devices. They found that a substantial proportion of MIGS trials do not adhere to the World Glaucoma Association (WGA) guidelines, thus limiting comparison between trials and hindering meaningful evaluation of these technologies.

For this study, the researchers searched five databases for comparative MIGS trials published from Jan. 1, 2000, to June 21, 2018. They then used the WGA guidelines—which cover the design, conduct, and reporting of glaucoma surgical trials—to evaluate the studies. Each study was assessed by two reviewers; differences were resolved by consensus.

The researchers identified 25 studies that met all eligibility criteria; of these, 10 were randomized controlled trials (RCTs). Overall, the RCTs were more likely to comply with the WGA guidelines than were the non-RCTs, with 52.8% of the RCTs complying, versus 40.8% of the non-RCTs. Problems with study design included the following:

- The WGA guidelines recommend a follow-up on a defined schedule up to three years. Only four (16%) of the 25 studies lasted three years or more. Nearly half of the studies had a follow-up of 12 months; two lasted only six months.
- With regard to intraocular pressure (IOP), the WGA guidelines consider two components mandatory for demonstrating surgical success: 1) an IOP-based survival curve with the number of patients at each time point and 2) an IOP scatterplot. None of the reviewed RCTs provided this information. Of the non-RCTs, two had a scatterplot, and seven included an IOP-based survival curve.
- In 16 studies (64%), at least one author reported an association with the industry. Furthermore, at least one author was a shareholder in 32% of the studies, and 24% of studies had an industry employee as an author. The WGA guidelines suggest several tools that can be used to manage potential conflicts, including masked study design and funding from sources unrelated to the innovation.

The researchers urged authors and journals to follow the WGA guidelines. As they pointed out, the development and use of standardized methodology and outcomes supports transparency of study results, facilitates comparisons between trials, and allows readers to accurately evaluate study results and assess new technologies such as MIGS.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Treatment Patterns for Diabetic Macular Edema

April 2019

Using a large national database, **Moulin et al.** evaluated the treatment patterns

and the predictors of different treatment standards in patients who were recently diagnosed with diabetic macular edema (DME). They found that intravitreal injections of anti-VEGF medications have become a mainstay of DME treatment—and that patients covered by private insurance received more injections than those covered by Medicaid or Medicare.

For this retrospective cohort study, the researchers used claims data on more than 8 million diabetic patients who had commercial or government-provided health insurance and were treated between Jan. 1, 2007, and March 31, 2015.

When exclusion criteria were applied, the final sample comprised 96,316 patients. These patients were then divided into yearly cohorts and followed for a full year after their index date (defined as the date of their first insurance claim with a diagnosis of DME).

In 2009, anti-VEGF injections accounted for 11.6% of all DME treatments; this percentage rose to 61.9% in 2014. In contrast, corticosteroids dropped from 6.1% of all treatments in 2009 to 2.8% in 2014, and focal laser procedures dropped from 75.3% in 2009 to 24% in 2014. The share of patients diagnosed with DME and left untreated declined from 55.8% to 50.1%.

The researchers also found that those patients covered entirely by third-party insurance had 45%, 31%, and 12% more anti-VEGF injections than those in Managed Medicare, Medicaid, and Medicare plans, respectively.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Predictors of Falls for Patients With Glaucoma

April 2019

Falls are particularly problematic for the visually impaired, and many experts recommend including vision screening in fall-prevention programs. **Ramulu et al.** evaluated whether falls are more common at home or away from home. They also assessed how damage to the integrated visual field (VF) affects fall rates at both locations. They found that most falls occurred at home and that the risk of any step resulting in a fall was highest at home. In addition, they found that those patients with more severe VF damage were at particular risk of falling, regardless of the location.

This three-year observational study included 225 patients with confirmed or suspected glaucoma (average age, 70.4 years). Patients with neovascular or uveitic glaucoma were excluded. Fall-related data were documented on calendars, and follow-up questionnaires were used to determine fall location (home or away). The number of steps taken was estimated by integrating tracking data from accelerometers and global positioning systems. Main outcome measures were the association of integrated VF sensitivity with fall rates, both per year and per step, stratified by location.

During the study period, participants accrued more steps away from their homes (2,366 outside vs. 1,524 steps at home; $p < .001$). Steps taken at home and away did not differ with respect to integrated VF sensitivity ($p = .22$). Fifty-seven percent of falls occurred at home, with each step taken at home being twice as likely to result in a fall (rate ratio [RR] = 2.02 vs. away steps; $p < .001$). Worse integrated VF sensitivity was not associated with a higher annual rate of home falls or away falls. In contrast, it was linked to more home falls per step (RR = 1.34/5 dB worse sensitivity, $p = .03$) and more away falls per step (RR = 1.47/5 dB worse sensitivity; $p = .003$).

In light of their findings, the authors stressed the importance of considering environmental modifications for visually impaired people. They recommend incorporating the delivery of modification services into the routine care of patients with moderate or advanced glaucoma.

Risk of Stroke After NAION

April 2019

Does an association exist between stroke and nonarteritic anterior ischemic optic neuropathy (NAION)? Study findings have been conflicting. **Park et al.** looked at a national database to better understand whether NAION could be a precursor to stroke. Among their Korean study population, NAION itself was not linked to greater risk of stroke.

This population-based retrospective study included more than 400,000 beneficiaries listed in the National Health Insurance Service–National Sample Cohort database (NHIS–NSC) from 2002 to 2013. Time-varying covariate Cox regression models were used to assess the relationship between incident NAION and the likelihood of subsequent stroke. Model 1 included only incident NAION as a time-varying covariate; model 2 included model 1 and demographic data; and model 3 included model 2 as well as comorbidity, comedication, and Charlson Comorbidity Index score. Results were expressed as the effect (hazard ratio [HR]) of NAION on the subsequent development of stroke.

The researchers found that NAION occurred in 1,125 patients, and stroke occurred in 16,998. In model 1, NAION was not associated with greater risk of subsequent stroke (HR, 1.31). For models 2 and 3, findings were similar after adjustment for demographic and confounding factors (HR, 1.19 and 1.10, respectively).

The authors acknowledged that the NHIS–NSC database does not include details on metabolic profiles, physical activity, body mass index, alcohol consumption, or smoking—all of which affect stroke risk. Even so, the study sample is large and population-based,

which minimized selection bias. The results of sensitivity analyses were consistent with those of the main analyses, as were results of matching based on propensity score. Thus, the authors concluded, the etiologic mechanisms of NAION and stroke appear to differ.

—Summaries by Lynda Seminara

JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

OCT Assessment of Retinal Changes With Retinal Prosthesis

March 2019

Little is known about postoperative retinal changes at the juncture of an implant electrode array and the retina—or whether the potential alterations could affect visual performance. To address these gaps, **Rizzo et al.** looked at morphologic changes in recipients of a retinal prosthesis and found that 50% had fibrosis-like hyperreflective tissue at the interface between the array and retina. Although this often led to retinal schisis, visual performance was not impaired.

The study was a noncomparative consecutive case series that involved review of pre- and postoperative findings of optical coherence tomography (OCT) for 33 eyes (33 patients) that received the Argus II Retinal Prosthesis System. This is the first—and, currently, the only—epiretinal device with commercial approval in Europe and North America for use in patients with blindness due to retinitis pigmentosa.

All procedures were performed by the same surgeon, at one of two centers in Italy. Participants received comprehensive exams before surgery, on postoperative day 1, and at months 1, 3, 6, 12, and 24. Yearly follow-up continued thereafter. Only the patients who completed at least six months of follow-up were included in the analysis.

Of the 20 patients eligible for analysis, all were white, and 12 (60%) were male. The mean age was 57.4 years. OCT findings showed fibrosis-like hyperreflective tissue, limited to the interface between the array and the retina, in 10 eyes (50%). In nine of these eyes, the fibrosis progressed to retinal schisis. Despite this, there was no deterioration of visual performance, which was assessed prospectively with visual function tests (square localization and direction of motion).

These results show that OCT can be used to detect retinal anatomic changes after implantation of the Argus II. The authors acknowledged that more research is needed to thoroughly investigate the morphologic features and pathogenesis of these changes. *(Also see related commentary by Julia A. Haller, MD, in the same issue.)*

Effect of Medication Change on Eyes With Macular Edema Due to Retinal Vein Occlusion

March 2019

What happens when patients who respond poorly to one anti-VEGF medication are switched to another? In evaluating patients with macular edema, **Ip et al.** found that patients with an inadequate response to bevacizumab may benefit from a switch to aflibercept, but the small sample and lack of control group do not allow for definitive conclusions.

This secondary analysis of SCORE2 data was performed at 66 centers in the United States (private practice or academic). Participants were required to have edema caused by central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO). Outcomes of interest were changes in visual acuity and central subfield thickness (CST) from month 6 (treatment switch) to month 12 for eyes that responded poorly to aflibercept or bevacizumab in SCORE2. Eyes that had received aflibercept monthly were switched to treatment with a dexamethasone implant at month 6 and, if needed, at months 9, 10, or 11. Eyes treated initially with bevacizumab were switched to aflibercept at months 6, 7, and 8, followed by a treat-and-extend regimen of aflibercept until month 12.

Forty-nine patients (49 eyes) were included in the study; aflibercept failed in 14, and bevacizumab failed in 35. Among the 14 eyes that were switched from aflibercept to dexamethasone, the mean change from months 6 to 12 in visual acuity letter score (VALS) was 2.63 ($p = .37$), and the mean change in CST was 46.0 μm ($p = .46$). For the 35 eyes that were switched from bevacizumab to aflibercept, the mean changes from months 6 to 12 were 10.27 in VALS ($p < .001$) and −125.4 μm in CST ($p < .001$).

This research suggests that eyes with CRVO or HRVO that do not respond well to bevacizumab may benefit from a switch to aflibercept. The authors recommended caution when interpreting the study findings, particularly because so few eyes had a poor initial response to aflibercept. The small sample and the lack of controls, randomization, and masking preclude determining whether a switching strategy is superior, similar, or inferior to continuing the original treatment.

Oculomotor Response to Cumulative Subconcussive Trauma in Football Players

March 2019

Repetitive subconcussive injury in athletes has become a major public health concern. Although most head injuries appear asymptomatic, they can have serious neurologic effects if sustained continually. The near point of convergence (NPC), denoting the closest point of focus before diplopia occurrence, has been shown to detect subclinical neuronal damage. Yet the longitudinal pattern of NPC changes due to subconcussive injury is unclear. **Zonner et al.** studied the NPC response to recurring subconcussive impact and found that initial disruption eventually led to adaptation of the oculomotor system to the subclinical brain injury.

The authors' study included 12 U.S. varsity football players (mean age, 16.4 years) from a single high school, who were followed throughout a season. NPC assessments were made prior to the season, before and after six games, and when the season concluded. An embedded accelerometer mouth guard measured the frequency of impact to the head and the magnitude of impact from practices and games.

During the games, players wore

chest-strap heart monitors to record heart rate and to estimate excess postexercise oxygen consumption, accounting for possible physical-exertion effects on NPC values. The players participated in practices and games with no restrictions.

During the football season, there were 8,009 head impacts, 177,907 g of peak linear acceleration, and 16,123,371 radians per second squared (rad/s^2) of peak rotational acceleration. NPC rose significantly until midseason (5.25 cm at baseline vs. 6.42 cm before game 3; $p = .01$), which correlated highly with the frequency and magnitude of impact. However, NPC began normalizing toward baseline after midseason (5.75 cm before game 6; $p = .32$), despite the continuation of such injuries. A significant quadratic trend also was observed ($\beta = -0.002$ cm/d; $p = .003$).

These results indicate that although NPC can be perturbed for an initial period of repetitive subconcussive trauma, it may normalize over time, even with additional injury.

The authors acknowledged that the mechanism by which this apparent "tolerance" develops is uncertain and warrants exploration. *(Also see related commentary by Ann C. McKee, MD, and Michael L. Alosco, PhD, in the same issue.)*

—Summaries by Lynda Seminara

Other Journals

Selected by Deepak P. Edward, MD

Toxic Posterior Segment Syndrome After Dropless Cataract Surgery

Retina
Published online Jan. 24, 2019

Patel et al. described seven cases of toxic posterior segment syndrome (TPSS) secondary to intracameral use of compounded triamcinolone-moxifloxacin during cataract surgery. The toxicity was attributed to high levels of the binding agent, poloxamer 407. The authors emphasized that clinicians need to be aware of this potential problem with compounded drugs.

All seven patients had undergone uneventful "dropless" cataract surgery and were given compounded triamcinolone-moxifloxacin from the same preparation. When postoperative complications arose, the patients were evaluated at the University of Texas Southwestern Medical Center. Immediately after the surgery, best-corrected visual acuity in the study eye ranged from 20/40 to counting fingers at 4 feet (average, 20/220).

The presenting symptoms of toxicity included flashes, floaters, glare, halos, photophobia, and problems assessing colors. In three patients, changes in foveal retinal pigment epithelium were detected by dilated fundus exams. In five patients, ellipsoid zone loss was observed with optical coherence tomography. Electrophysiology testing was performed in five eyes, all of which demonstrated similar findings of reduction in full-field electroretinogram (ERG), oscillatory potentials, pattern ERG, multifocal ERG, and visual evoked potential. One patient received a dexamethasone implant, but visual acuity did not improve.

To the authors' knowledge, this is the first case series of TPSS linked to intracameral use of compounded triamcinolone-moxifloxacin in cataract surgery. The FDA has attributed the toxicity to abnormally high levels of poloxamer 407, the agent used for binding the medications. For topical administration, the maximum concentration for poloxamer 407 set by the FDA is 0.1% to 0.2%; the concentration of poloxamer 407 in these cases was 12%.

The authors also noted that minimal research has been conducted on interactions between poloxamer 407 and retinal tissue. Until ample information exists, the authors advise against intraocular use of this binding agent.

More Evidence That Diabetes Is Linked to Greater CCT

JAMA Network Open
2019;2(1):e186647

High intraocular pressure (IOP) is the most treatable risk factor for glaucoma, but the degree of central corneal thickness (CCT) may impede accurate estimation of IOP. Research on links between diabetes and CCT has produced conflicting results, and few studies have addressed the effect of serum glucose or hemoglobin A_{1c} (HbA_{1c}) on the cornea. In a cross-sectional analysis of the Singapore Epidemiology of Eye Diseases (SEED) study, **Luo et al.** observed a correlation between thicker CCT and the presence of diabetes or hyperglycemia.

This study included 8,846 adults aged 40 years or older (mean, 58 years), who were of Chinese, Malay, or Indian ethnicity. The researchers also performed a meta-analysis—which included 12 previous clinical and population-based studies—to estimate the overall association of diabetes with CCT. Standardized clinical exams were conducted, and questionnaires were administered to collect demographic, systemic, and ocular information. The main outcome was CCT, measured using ultrasound pachymetry.

The CCT profile of participants with and without diabetes was similar (mean CCT, 545.3 vs. 544.8 µm, respectively; $p = .39$). After adjusting for age, sex, ethnicity, corneal curvature, axial length, and body mass index, the mean CCT was 4.9 µm greater for patients with diabetes. According to the meta-analysis, CCT was 12.8 µm greater in patients with diabetes. Multivariable analyses showed that greater CCT also was associated with higher levels of random glucose readings (per 10 mg/dL, $\beta = 0.3$; $p < .001$) and higher HbA_{1c} (per percentage, $\beta = 1.5$; $p < .001$). These associations were significant for patients with diabetes but not for those without diabetes.

Findings of this study may be useful for estimating CCT more accurately. Strengths of this research include the large sample size and use of standardized assessments, enabling adjustment for potential confounders and substantiating the validity of findings. Study limitations include the lack of fasting glucose measurements.

As a result, the authors recommended caution when interpreting the findings, and they acknowledged that further research is needed to explore causal factors for the associations.

—Summaries by Lynda Seminara