Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

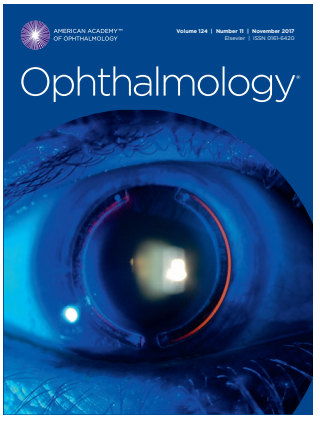
Ophthalmology

Selected by Stephen D. McLeod, MD

Selective Serotonin Reuptake Inhibitors and Cataract Risk

November 2017

Do the class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs) raise cataract risk? While recent population-based studies from Canada and the United States suggest that they do, **Becker et al.** quantified the risk of cataract among patients exposed to SSRIs and found mixed results, with a slight increase in risk observed only among those between the ages of 40 and 64.



The researchers drew their study population from the U.K.–based Clinical Practice Research Datalink (CPRD) and included 206,931 adults with first-time cataract (≥ 40 years of age) and an equal number of cataract-free controls matched for age, sex, date of cataract recording (index date), and number of prior years in the CPRD. The mean age at index date was 73.7 years. Those with a previous diagnosis of glaucoma were excluded from sensitivity analyses.

The number of prescriptions for SSRIs and other antidepressant drugs was noted, as was the exclusive use of a single SSRI. The researchers performed logistic regression analyses, adjusting for body mass index, smoking status, presence of diabetes or hypertension, and use of systemic steroids. For sensitivity analyses, they shifted the index date backward 2 years to account for latency of cataract recording and to ensure that the antidepressant exposure occurred before the cataract.

Overall, current long-term use of SSRIs (≥ 20 prescriptions [courses of treatment]) was not associated with elevated risk of cataract, and results for men and women were similar. However, among those in the 40-64 age group, cataract risk was slightly higher for long-term SSRI users than for nonusers. Although diabetes or cardiovascular disease increased cataract risk, smoking and obesity did not. No increase in cataract risk was found for patients who used a single type of SSRI exclusively.

Microstent or Trabeculectomy: Comparing Efficacy, Safety, and Risk of Failure

November 2017

Implanted ab interno gelatin microstents are perceived as safer and less invasive than trabeculectomy for treating progressive glaucoma, but comparison studies are lacking. **Schlenker et al.** conducted a retrospective study of the standalone treatments (each done with mitomycin C) and noted similar safety profiles and failure rates.

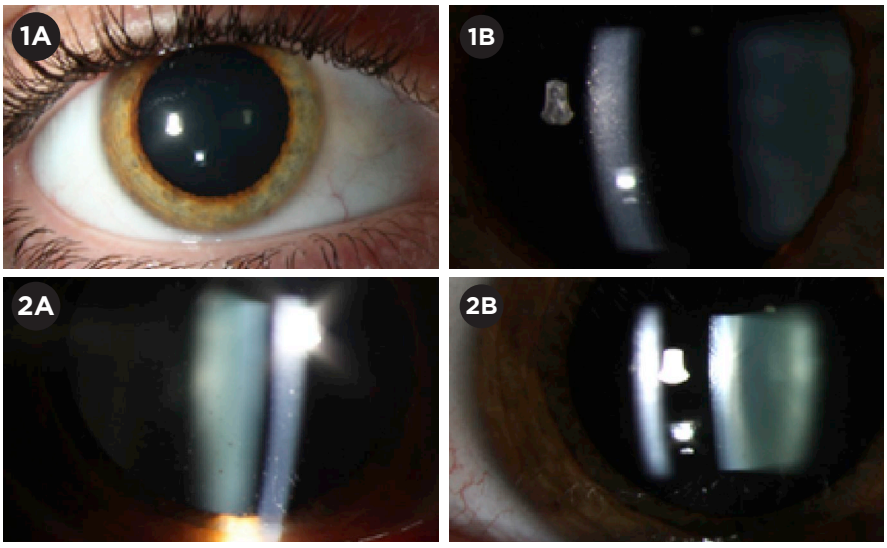
For this study, the authors reviewed medical records to identify adults with glaucoma who underwent either procedure at 1 of 4 academic ophthalmology centers located in different countries. The primary outcome was hazard ratio (HR) of failure. Failure was defined as 2 consecutive readings of intraocular pressure (IOP; < 6 mm Hg with vision loss or > 17 mm Hg without medications, which they defined as "complete success") at least 1 month after surgery despite in-clinic interventions. Secondary outcomes included IOP thresholds of 6-14 mm Hg and 6-21 mm Hg, and the same thresholds allowing for medications (defined as "qualified success").

Of the patients identified, 159 (185 eyes) received a microstent and 139 (169 eyes) had trabeculectomy. Preoperatively, those scheduled for microstent had better visual acuity, were younger, and more often were male. Other baseline characteristics were comparable.

For the primary outcome threshold of 6-17 mm Hg, adjusted HRs of failure for microstent relative to trabeculectomy were 1.2 for complete success and 1.3 for qualified success. Times to 25% failure were 11.2 and 10.6 months for complete success and 30.3 and 33.3 months for qualified success, respectively. White race was linked to lower risk of failure (adjusted HR, 0.49; more pronounced with trabeculectomy), and diabetes was associated with higher failure risk (adjusted HR, 4.21).

Overall, microstent and trabeculectomy recipients underwent 114 and 165 postoperative interventions, respectively, and 43% and 31% underwent needling. Fifty percent of those with trabeculectomy had laser suture lysis. There were 22 complications with microstent and 30 with trabeculectomy. Most were transient.

Although these findings indicate similar rates of complete and qualified success, the authors urged clinicians to weigh the pitfalls of each procedure, including the potential for needling and reoperation with microstent and the greater likelihood of interventions and complications after trabeculectomy. *(Also see related commentary by Dale K. Heuer, MD, in the same issue.)*



LHON OUTCOMES. *Two patients experienced asymptomatic transient mild anterior uveitis. The eye of a patient treated with low-dose gene therapy (1A) shows fine keratic precipitates (1B). Keratic precipitates in a second patient who was treated with medium-dose gene therapy (2A) resolved 1 month later (2B).*

Gene Therapy for Leber Hereditary Optic Neuropathy

November 2017

Guy et al. expanded their research on gene therapy for Leber hereditary optic neuropathy (LHON) and found that their collective results affirm the benefits of low and moderate doses.

In this open-label trial, 9 patients with visual loss and mutated G11778A mitochondrial DNA received a unilateral single-dose intravitreal injection of corrected DNA borne by the adenoassociated vector AAV2(Y444,500,730F)-P1ND4v2, which had also been administered previously to 5 other patients. Six of the 14 patients had bilateral visual loss lasting > 12 months (group 1), 6 had bilateral loss for < 12 months (group 2), and 2 had unilateral loss (group 3).

Eight patients received the low dose ($5 \times e^9$ vg), and 6 received the medium dose ($2.46 \times e^{10}$ vg). Nine patients had follow-up for ≥ 12 months.

Testing included visual acuity (VA), visual field, optical coherence tomography, and pattern electroretinography (PERG). Generalized estimating equations were used in longitudinal analyses. The main outcome was change in VA.

Because the study was not randomized or controlled, results were compared with data from the authors' previous natural history cohort, with inclusion limited to those who would have qualified for the gene therapy at baseline. The worse eye of natural history patients served as a surrogate for treated eyes in the current study; better eyes served as fellow eyes.

For groups 1 and 2 combined, the average improvement over 12 months was 0.24 logMAR in treated eyes and 0.09 logMAR in fellow eyes. The difference in improvement between study and fellow eyes was greater in group 2 than in the natural history cohort at month 12 (0.53 vs. 0.21 logMAR; $p = .053$) and month 18 (0.96 vs. 0.17 logMAR; $p < .001$).

The average thickness of the temporal retinal nerve fiber layer (RNFL) was 54 µm before injection and 55 µm at month 12. The respective values for fellow eyes were 56 µm and 50 µm. Estimating-equation analysis showed that PERG amplitudes worsened more in treated eyes. No between-eye differences were detected by other visual function measures. Two patients exhibited uveitis, which was asymptomatic and resolved (Figs. 1A-2B).

In conclusion, low and medium doses of allotopic gene therapy appear safe for treating LHON and do not damage the temporal RNFL. These findings warrant testing of higher doses.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Decreased Fundus Autofluorescence and Visual Acuity in Stargardt Disease

November/December 2017

Kong et al. set out to investigate the association between visual acuity (VA) and areas of decreased fundus autofluorescence (AF) in patients with recent-onset Stargardt disease. They found a small rate of VA loss per year, dependent on the level of VA at first visit and the location of lesion growth and not significantly associated with the rate of increase in areas of decreased AF.

For this study, the researchers evaluated 64 patients (124 eyes) drawn from the ProgStar (Progression of atrophy secondary to Stargardt disease) study. All were ≥ 6 years of age (median, 22.5 years) and had experienced symptom onset ≤ 2 years before the first study visit.

VA was measured as best-corrected or presenting VA; more than half the eyes had a VA worse than 20/70 at baseline, and 14.5% were > 20/200. In addition, 94% already had areas of decreased AF (DAF) in their images.

The overall VA change rate was

0.054 per year; faster rates of loss were observed in patients who were 20/30 to 20/70 at baseline as well as in those who were younger when symptoms first occurred. While the rate of VA loss was not significantly associated with the rate of increase in areas of definitely decreased AF (DDAF), questionably decreased AF (QDAF), or DAF, it was significantly associated with DAF in the fovea at baseline.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

iPad App Detects VF Loss

November 2017

Many cases of glaucoma are undetected, particularly in developing nations. Cost-effective practical methods are needed for detecting glaucoma, diabetic retinopathy, and other vision-threatening conditions. **Johnson et al.** tested the accuracy and efficiency of a free iPad app for suprathreshold perimetric screening. The tool proved fast and accurate for detecting both moderate and severe visual field (VF) loss.

This prospective cross-sectional validation study was conducted at Tilganga Institute of Ophthalmology in Nepal. Screening tests were performed using a calibrated iPad 2 containing the Visual Fields Easy (VFE) app. Of 411 eyes evaluated (206 subjects), 183 had glaucoma, 18 had diabetic retinopathy, and 210 were normal. Results were compared with those obtained by a Humphrey Field Analyzer for 373 of these eyes (glaucoma, 160; diabetic retinopathy, 15; normal, 198).

The VFE iPad app was able to detect most VF deficits of moderate loss (mean deviation [MD] of –6 to –12 dB) and advanced loss (MD worse than –12 dB). It was not as sensitive for detecting early loss (MD better than –6 dB), due mostly to the high rate of false-positive responses. The average time to perform the VFE test on each eye was 3 minutes, 18 seconds (standard deviation, 16.88 seconds).

The authors concluded that the VFE iPad app is a portable, quick, and effective method to identify moderate and advanced VF loss. Improvements are underway to enhance performance, reduce test time, monitor head and eye movement, and eliminate the need to touch the screen.

Medicare Reimbursement to Ophthalmologists

November 2017

In a recent public report on Medicare Part B spending for 2012 and 2013, ophthalmologists (who account for 2% of the physician workforce) were identified as having a disproportionate share of disbursements (7.7% in 2013). **Han et al.** reviewed data for the same period and determined that, unlike trends noted in other specialties, a substantial number of ophthalmology reimbursements were related to medication use, primarily injections of anti–vascular endothelial growth factor (VEGF) drugs.

For this retrospective cross-sectional study, the authors reviewed Medicare Physician and Other Supplier data (both aggregate and private use) to determine ophthalmic beneficiary demographics, Medicare Part B payments, and medical services provided. Codes were used to categorize each service as a procedure, drug, or office visit. The data set was limited to ophthalmologists in office or ambulatory surgical settings; optometrists were excluded.

Ophthalmology patients represented 3.7% and 3.6% of Medicare beneficiaries in 2012 and 2013, respectively. The mean age was 75 years; 61% were female. Aggregate ophthalmology payments totaled $5.6 billion in 2012 and $5.8 billion in 2013, for an increase of 3.6%. Although the quantity of reimbursed ophthalmic services rose 2% from 2012 to 2013, the mean dollar amount per service decreased by 5.4%.

According to gross reimbursements, 5 services accounted for 85% of payments to ophthalmologists in 2013, an increase of 11% from 2012. Cataract surgery topped the list, followed closely by injection of anti-VEGF drugs.

Drug-related reimbursement accounted for 32.8% of Medicare payments ($1.9 billion) to ophthalmologists in 2013; ranibizumab and aflibercept represented 95% of these payments. The only specialty that received higher reimbursement for drugs was hematology-oncology. Overall, the mean reimbursement per ophthalmologist was higher for procedures than for drugs or office visits.

The authors concluded that, although Medicare disbursements for drugs are high for ophthalmology as a specialty, this is not surprising given the growing demand for anti-VEGF agents as the population ages. In addition, they said, findings should be interpreted with caution because data sources did not include either Medicare members with private insurance or patients on Medicaid. *—Summaries by Lynda Seminara*

JAMA Ophthalmology

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

Retinal Emboli: Prevalence and Systemic Associations

October 2017

Population-based data on retinal emboli in Asia are limited. In the Singapore Epidemiology of Eye Disease Study,

AAO 2017 New Orleans

MORE AT THE MEETING

***Ophthalmology* and *Ophthalmology Retina* Meet and Greet.** Authors and peer reviewers are invited to meet members of the journals' editorial review boards. **When:** Sunday, Nov. 12, 1:00-3:00 p.m. **Where:** Academy Resource Center, Hall G, Booth 3140. **Access:** Free.

***Ophthalmology Retina* Launch Celebration.** If you are an early subscriber to—or have been published in—*Ophthalmology Retina,* you are invited to meet editor-in-chief Andrew P. Schachat, MD, and the editorial board. Refreshments will be served. **When:** Monday, Nov. 13, 10:00-11:00 a.m. **Where:** Museum of Vision, Hall G, Booth 3047. **Access:** By invitation.

Cheung et al. examined prevalence and risk factors among a large group of Chinese, Malay, and Indian patients. They found that retinal emboli were most common among the Indian individuals and were associated with chronic kidney disease as well as classic cardiovascular factors.

This cross-sectional study included 9,978 patients (40-80 years of age) with gradable retinal photographs. Of these, 88 exhibited retinal emboli, which were identified using a standardized protocol. Age-standardized prevalence of retinal emboli was calculated from the 2010 Singapore adult population. Interviews, lab tests, and comprehensive systemic and ophthalmic exams were performed to determine risk factors associated with retinal emboli.

The overall person-specific, age-standardized prevalence of retinal emboli was 0.75%. Prevalence rates in the Indian, Chinese, and Malay cohorts were 0.98%, 0.73%, and 0.44%, respectively. According to multivariable-adjusted analysis, common risk factors for retinal emboli were older age, Indian ethnicity, hypertension, chronic kidney disease, and history of stroke.

Elevated creatinine levels and low glomerular filtration rates were consistently linked to retinal emboli, independent of age, smoking status, concomitant hypertension, and other risk factors. Stratified analyses showed a similar correlation between retinal emboli and reduced renal function, even for participants without hypertension or diabetes. The odds of developing chronic kidney disease were twice as great among individuals with retinal emboli.

Of note, some of these relationships had not been identified in previous population-based studies.

The authors concluded that the presence of retinal emboli may signal vascular embolic damage to the brain as well as the kidneys. If their findings are confirmed by longitudinal studies, it would be prudent to ensure that patients with retinal emboli receive both a renal evaluation and a cardiovascular assessment. *(Also see related commentary by Robert N. Frank, MD, in the same issue.)*

No Relationship Between Eyelid Laxity and Obstructive Sleep Apnea

October 2017

Although studies have indicated a correlation between floppy eyelid syndrome and obstructive sleep apnea (OSA), the diagnostic criteria for eyelid laxity often are vague and subjective. **Fox et al.** employed quantitative markers to assess eyelid laxity and found no correlation between OSA and floppy eyelid syndrome.

For this cross-sectional observation study, the researchers evaluated 201 patients (402 eyes; mean age, 53 years), all of whom underwent overnight polysomnography at a sleep center in the United States. Eyelid laxity and ocular surface disease were evaluated through detailed bedside ophthalmologic examination, and severity scores for these markers were assigned to each eye. Bedside exams entailed measuring eyelid laxity (including horizontal eyelid distraction, upper eyelid traction, and presence of eyelash ptosis), determining ocular surface disease (including palpebral conjunctival reaction), and performing other objective assessments.

The presence and severity of OSA were established from polysomnographic findings. The initial correlation between OSA and ocular surface and eyelid markers was calculated from bivariate linear regression analysis. Associations between ocular symptoms were obtained through bivariate ordered logistic regression. Adjustments were made for known associations between OSA and sex, age, body mass index, and concomitant medical conditions.

After adjustments, no association was observed between OSA severity and eyelid laxity score or ocular surface score. Subset analyses showed a correlation between male gender and higher ocular surface score. Older age and the presence of diabetes were linked to greater eyelid laxity. Only 1 patient exhibited classic signs of floppy eyelid syndrome.

The authors concluded that, according to their method for measuring eyelid laxity, no significant relationship exists between OSA presence or severity and markers of laxity or ocular surface disease. Findings of their subset analysis suggest that earlier studies may have been hampered by confounding variables or the techniques used to determine eyelid laxity.

Incidence of Strabismus in a Danish Pediatric Population

October 2017

Population-based research on the incidence of strabismus is limited. **Torp-Pedersen et al.** examined data for young Danish children (≤ 7 years of age) and attained results comparable to those of smaller European and U.S. studies, but the ratio of esotropia to exotropia was higher in their study.

The authors reviewed records for 96,842 children enrolled in the Danish National Birth Cohort. Primary outcomes were age-specific incidence of strabismus, cumulative incidence of strabismus, and median age at detection (overall and by subtype).

All told, the researchers identified 1,309 cases of strabismus. The overall cumulative incidence of strabismus was 2.56% at age 7, and it was similar for boys and girls. The most common subtypes identified were congenital esotropia (16.5%, n = 216), fully accommodative esotropia (13.5%, n = 177), partially accommodative esotropia (19.3%, n = 252), and exotropia (13.8%, n = 181). The ratio of esotropia to exotropia was 5.4:1, which is higher than that observed in smaller studies. Other differences from previous findings were a lower incidence of central nerve system–associated strabismus and a greater incidence of congenital esotropia.

Age-specific incidence curves for congenital esotropia, fully accommodative esotropia, partially accommodative esotropia, and all exotropia suggested that the various subtypes have different age-specific incidence patterns ($p < .001$ for all pairwise comparisons of curves). The median age at detection of these 4 common subtypes was 0, 32.0, 26.1, and 16.6 months, respectively. Gender differences, which were nominal, were observed for only 3 subtypes (accommodative esotro-

pia; microesotropia; and intermittent esotropia). *(Also see related commentary by Scott R. Lambert, MD, in the same issue.)* —*Summaries by Lynda Seminara*

OTHER JOURNALS

Selected by Deepak P. Edward, MD

OCT-A Measurement of Retinal Vessel Density: Key Factors Influencing Repeatability

British Journal of Ophthalmology
Published online Aug. 16, 2017

Optical coherence tomography angiography (OCT-A) may permit rapid quantification of retinal capillary plexus density in various disease states. Although studies have indicated that OCT-A has potential for excellent reproducibility and repeatability, methods of appraising scan quality have not been clearly defined. **Fenner et al.** set out to identify key factors affecting the repeatability of OCT-A measurements and noted the importance of ensuring visibility of fine vasculature while minimizing motion artifact.

For this study, the researchers obtained OCT-A images of 44 healthy eyes (44 subjects; mean age, 70 years) during 2 separate clinic visits. Each eye was examined using the Topcon DRI OCT Triton imaging system. Parafoveal vessel density within a 1.5-mm radius centered over the fovea was determined with the built-in tool for assessing superficial and deep retinal plexuses. Repeatability of vessel density was ascertained by intraclass correlation (ICC) and mean variation. Several image-quality parameters were evaluated to determine their influence on the repeatability of vessel density measurements in each capillary plexus.

The repeatability of measurements was better for the superficial plexus, a finding that has been reported by other investigators. For the superficial plexus, mean parafoveal vessel density measurements for the first and second visits were 53.3 ± 11.1 and 53.3 ± 10.3, respectively; for the deep plexus, those measurements were 27.3 ± 8.59 and 27.0 ± 8.78, respectively. According to ICC analyses, clear visibility of fine vessels, absence of motion artifact, and a software-derived image-quality score of at least 60 were necessary to obtain good (ICC > 0.6) or excellent (ICC > 0.75) repeatability. Variations in centration and image tilt did not affect measurement repeatability for either plexus.

Fallout From the Opioid Crisis: IV Drug Abuse and Endogenous Fungal Endophthalmitis

JAMA Ophthalmology
2017;135:534-540

Abuse of intravenous (IV) drugs is a risk factor for endogenous fungal endophthalmitis (EFE), a severe vision-threatening intraocular infection. **Tirpack et al.** updated the characteristics, management, and visual outcomes among patients with EFE and found that this infection signals severe end-organ damage and poor visual outcomes.

For this study, the authors reviewed records for all patients with EFE referred to New England Eye Center at Tufts Medical Center from May 2014 to May 2016. Patients with a history of IV drug abuse and clinical evidence or culture proof of fungal endophthalmitis were included. Patient data were collected, including demographics, comorbidities, presenting symptoms, vitreoretinal findings, treatment regimens, culture results, and visual acuity (before and after treatment).

Ten patients with EFE related to IV drug abuse were identified during the study window period. Their mean age was 34 years (range, 24-60 years), and 50% were female. Presenting visual acuity ranged from 20/25 to hand motion. All patients were ambulatory at presentation, and 90% had isolated ocular symptoms but no systemic sign of infection. The most common presenting symptoms were floaters (n = 8), reduced vision (n = 6), and pain (n = 5). Initial treatment included systemic antifungals (all patients) and intravitreal antifungals (9 eyes). Pars plana vitrectomy was performed in 5 patients because of worsening vitritis. The most commonly isolated pathogen was *Candida albicans.* After treatment, visual acuity ranged from 20/40 to 20/300.

As the opioid crisis continues in the United States, clinicians should maintain a high degree of suspicion for EFE, the authors noted, as patients are ambulatory at presentation and may not have systemic signs of infection.

—*Summaries by Lynda Seminara*

Global Look at Visual Impairment

Lancet Global Health
2017;5(9):e888-e897

Bourne et al. set out to provide worldwide estimates, trends, and projections of vision impairment and visual loss. They found mixed results: On one hand, the age-standardized prevalence of visual impairment and loss continue to decline. On the other, however, the overall growth in population—and the aging of that population—is contributing to a substantial increase in the number of people affected.

For this meta-analysis, the researchers updated an earlier report, for a total of 288 population-based studies contributing data from 98 countries. Of the 7.33 billion people alive in 2015, an estimated 36 million (crude prevalence 0.48%) were blind (defined as visual acuity [VA] worse than 20/400), 216 million had moderately and severe impaired VA (between 20/400 and 20/60), and 188 million had mildly impaired VA (between 20/60 and 20/40).

For the first time, there was enough information on presbyopia for the researchers to complete a meaningful analysis of the condition. They estimate that 666.7 million people ≥ 50 years of age and 1.09 billion people ≥ 35 years of age are affected by uncorrected presbyopia.

Most of those who had the poorest VA resided in south Asia, east Asia, and Southeast Asia; and the age-standardized prevalence of blindness was highest in south Asia, western sub-Saharan Africa, and eastern sub-Saharan Africa. In addition, more women than men were visually impaired.

The findings highlight the need to scale up current efforts to improve vision, the researchers said, given the impact that visual acuity has on quality of life and economic security.

—*Summary by Jean Shaw*