

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Dig Rush Binocular Game for Children With Amblyopia

March 2019

Studies of binocular games in children with amblyopia have been hampered by noncompliance, perhaps due to the mundane nature of the games. Holmes et al. prescribed treatment with the dichoptic binocular Dig Rush game, which appeared engaging in a pilot study. They also compared visual outcomes between amblyopic children who played the Dig Rush game and those who continued with spectacle correction only. They found that the game did not result in better visual acuity (VA) or stereoacuity within four or eight weeks of treatment.

This multicenter randomized study included 138 children between the ages of 7 and 12 with amblyopia (resulting from strabismus, anisometropia, or both). Participants were required to have at least 16 weeks of optical treatment in spectacles, if needed, or to exhibit no improvement in the VA of the amblyopic eye for at least eight weeks leading up to enrollment.

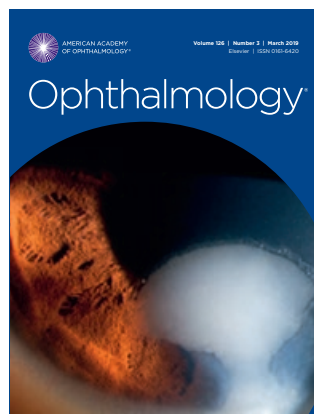
The children were assigned randomly either to receive eight weeks of treatment with the game and, if needed, spectacle wear ($n = 69$) or to continue with spectacle correction alone ($n = 69$). The

game, which was played on an iPad, was prescribed for one hour each day, five days per week.

The main outcome measure was VA change in the amblyopic eye from baseline through week 4, assessed by a masked examiner. Secondary outcomes included changes from baseline through eight weeks.

By the four-week mark, the mean VA letter score of amblyopic eyes had improved by 1.3 with binocular game treatment and by 1.7 with spectacle correction alone. After adjusting for baseline VA, the difference in letter score between the groups (binocular minus control) was -0.3 . After eight weeks of treatment, there was no difference in letter scores. Among the binocular group, adherence data obtained from the iPad indicated that just over half of the participants completed more than 75% of prescribed treatment (58% for four weeks; 56% for eight weeks).

Although the authors found no VA benefit from the binocular game, there is evidence that such treatment may help some younger children, particularly those who have not been treated previously. The issue is being evaluated in an ongoing study of children between the ages of 4 and 6.



Uncorrected Myopia's Impact on Productivity

March 2019

Naidoo et al. aimed to estimate the loss of productivity associated with the global burden of myopia. They found that, even by conservative estimation, the potential loss in productivity linked to uncorrected myopia outweighs the cost of correction.

For their study, the authors performed a systematic review and meta-analysis to estimate the number of people with myopia and myopic macular degeneration (MMD), stratified by visual acuity thresholds. The percentages of myopes who had spectacle correction were compared with country-level variables for the year of data collection (2015). Variation in spectacle correction was represented by a model based on the human development index, with adjustment for age and urbanization.

The authors combined data for spectacle correction with myopia data, from which they estimated the number of people with each predefined visual-impairment level of uncorrected myopia (from mild myopia to blindness). They applied disability weights, employment rates, labor-force participation rates, and gross domestic product per capita to estimate the degree of productivity loss among individuals with each level and type of myopia-related visual impairment in 2015, expressed in U.S. dollars.

Their analyses showed that adequate correction of myopia is less common for older people who live in rural areas

of less-developed countries. In 2015, the estimated global productivity loss associated with visual impairment was \$244 billion for uncorrected myopia (95% confidence interval [CI], \$49 billion to \$697 billion) and \$6 billion for MMD (95% CI, \$2 billion to \$17 billion). The regions with the greatest burden as a proportion of their economic activity were Southeast Asia, South Asia, and East Asia. The region with the greatest absolute burden was East Asia.

Understanding the economic burden of uncorrected visual impairment is crucial for addressing public health problems such as myopia. The authors emphasized that the productivity effects of myopia should be considered in a broader framework by policymakers. Findings of their study highlight the economic value of interventions.

When Diabetic Eyes Are Lost to Follow-Up

March 2019

Although panretinal photocoagulation (PRP) greatly reduces the risk of severe vision loss from proliferative diabetic retinopathy (PDR), it has side effects that might be avoided by using anti-VEGF treatment. Studies of intravitreal injection of anti-VEGF agents have shown that this treatment produces similar (and possibly superior) outcomes, but strict adherence to the follow-up schedule is crucial. Little information exists on eyes that are lost to follow-up after either treatment. Obeid et al. compared anatomic and functional outcomes for eyes with PDR that were lost to follow-up for more than six months after treatment. They observed better outcomes for eyes treated with PRP than for those that received anti-VEGF injections.

For their study, the authors identified 59 patients (76 eyes) who were lost to follow-up immediately after treatment and returned more than six months later. Documented data included visual acuity (VA) and anatomic outcomes at the last visit before the patients were lost to follow-up, at their return visit, six months later, 12 months later, and at the final visit. The

authors compared outcomes for the treatments, including functional changes that occurred between visits.

Of the 76 treated eyes, 46 underwent PRP, and 30 received anti-VEGF treatment. Results were as follows:

- In the PRP group, mean VA worsened significantly between the last visit before patients were lost to follow-up and when they returned (0.42 ± 0.34 vs. 0.62 ± 0.64 logMAR; $p = .03$). However, the difference in mean VA from the visit before being lost to follow-up to the final visit was not significant (0.46 ± 0.47 logMAR; $p = .38$).
- For the anti-VEGF group, the decline in mean VA was significant from the visit before being lost to follow-up to the return visit (0.43 ± 0.38 vs. 0.97 ± 0.80 logMAR; $p = .001$) and to the final visit (0.92 ± 0.94 logMAR; $p = .01$).
- At the final visit, the incidence of tractional retinal detachment and of iris neovascularization was higher in the anti-VEGF group. Four anti-VEGF eyes experienced iris neovascularization, and 10 experienced retinal detachment—versus none and one, respectively, of the PRP eyes.

These findings suggest that when patients are lost to follow-up, anatomic outcomes are better for PRP than for anti-VEGF treatment. Although the difference in functional outcomes also appears to favor PRP, the study

lacked randomization. The authors recommend considering the sequelae related to follow-up noncompliance when selecting a treatment for PDR. They encourage studies of noncompliance predictors, which may help guide personalized treatment strategies. (Also see related commentary by Andrew P. Schachat, MD, in the same issue. For another study on this topic, see page 19.)

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

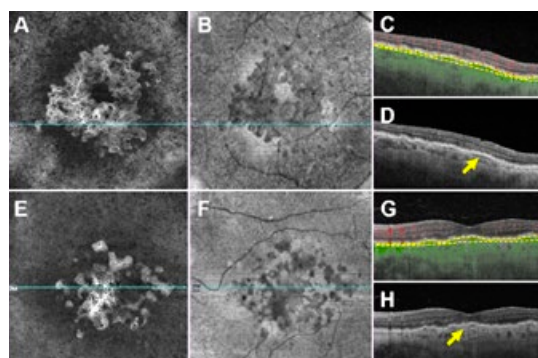
Using the Double-Layer Sign to Predict Subclinical Macular Neovascularization

March 2019

Can the double-layer sign on optical coherence tomography (OCT) images be used to predict the presence of subclinical macular neovascularization (MNV) in cases of dry age-related macular degeneration (AMD)? Shi et al. found that the sign on OCT B-scans was associated with subclinical type 1 MNV and can be used to identify these lesions with good predictive values.

For this prospective observational study, the researchers evaluated 100 eyes from 94 patients. Of these, 64 eyes had intermediate AMD (iAMD) and 36 eyes had late AMD. Thirty-three eyes had subclinical MNV (20 of the 64 eyes with iAMD and 13 of the 36 eyes with late AMD). All eyes were initially scanned with swept-source OCT angiography (SS-OCTA), using a 6×6 mm scan pattern centered on the fovea. All eyes included in the study had no evidence of exudation. Eyes with geographic atrophy (GA) that was not fully contained within the scan area were excluded.

Two groups of graders—including junior graders who had no prior knowledge of the cases—evaluated the B-scans for the presence of the double-layer sign. The senior and junior graders



AGREEMENT. Graders agreed on the presence of the double-layer sign (yellow arrows) in these two eyes with iAMD and MNV. En face angiographic (A, E) and structural (B, F) images show the CNV pattern. Structural B-scans through the MNV (C, G) are color-coded for flow (red = retinal microvasculature; green = flow under the retinal pigment epithelium [RPE]). The yellow dashed lines represent the slab boundaries from the RPE to Bruch membrane.

agreed on the presence of a double-layer sign in 24 of the 33 eyes with subclinical MNV and on the absence of the sign in 52 of the 67 eyes without subclinical MNV. For junior graders, the sensitivity, specificity, positive predictive value, and negative predictive value were 73%, 84%, 69%, and 86%, respectively; and for the senior grader, 88%, 87%, 76%, and 94%, respectively. The two gradings also showed that the double-layer sign was a better predictor of subclinical MNV in eyes with drusen than in eyes with GA.

The authors note that the development of a machine-learning algorithm to identify subclinical MNV based on structural OCT is under way. This would be of particular benefit to clinical practices that do not have SS-OCTA capabilities. —*Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Glaucoma Study Results and Masked Adjudication of Endpoints

March 2019

The commingling of glaucomatous and nonglaucomatous endpoints in clinical trials can lead to overestimation of glaucoma incidence or progression, underestimation of treatment effect, or reduction in statistical power. The FDA and the European Medicines Agency recommend centralized adjudication if treatment assignment is unmasked or if endpoints are subjective or involve complex definitions. **Gordon et al.** evaluated the effect of a masked Endpoint Committee on estimates of the incidence of primary open-angle glaucoma (POAG), treatment efficacy, and statistical power in the Ocular Hypertension Treatment Study–Phase 1, an unmasked randomized trial of the safety and efficacy of ocular hypotensive medication for preventing or delaying POAG onset. Their new research showed that masked adjudication of endpoints improved POAG incidence estimates, increased statistical power, and increased the calculated treatment effect by 23%.

The Endpoint Committee comprised

three practicing clinicians who decided independently whether an endpoint was “most probably due to POAG” or “most probably not due to POAG.” For optic disc deterioration, each member specified whether the change was clinically significant. The Committee reviewed 267 first endpoints from 1,636 participants and attributed 155 (58%) of them to POAG. The incidence of all-cause endpoints versus POAG endpoints was 19.5% versus 13.2% (respectively) for the observation group and 13.1% versus 5.8% (respectively) for the medication group. Treatment effect for all-cause endpoints was a 33% reduction in risk (relative risk, 0.67) and a 56% reduction in risk for POAG endpoints (relative risk, 0.44). Post-hoc statistical power for detecting treatment effect was 0.94 for all-cause endpoints and 0.99 for POAG endpoints.

The authors advocate endpoint adjudication for clinical trials in which common ocular or systemic comorbidities could compromise the results. Given the strong treatment effect in this trial, the increased power was not crucial. However, it could be important in studies of interventions that have less robust effects.

Kalman Filtering Can Forecast NTG Disease Trajectory

March 2019

Unlike most types of open-angle glaucoma, normal-tension glaucoma (NTG) often includes dense visual field (VF) loss, which may occur close to central fixation and early in the disease. Because common activities such as reading and driving can be difficult for patients with central or paracentral VF loss, it would help to personalize the forecasting of disease trajectory, allowing identification of patients at high risk for progression before the damage occurs. The Kalman filtering (KF) algorithm, which has been used for decades by the aerospace industry to guide planes and shuttles, recently has been applied to the trajectory of chronic diseases. The KF model accounts for underlying disease dynamics among patient populations, as well as unique patient-specific characteristics. Personalized forecasts are derived,

which can be updated whenever the patient has additional testing. **Garcia et al.** previously tested the model in patients with high-tension open-angle glaucoma and found it effective in forecasting disease progression. In a new study, they established its utility for patients with NTG.

Initially, the authors validated a KF model, named KF-NTG, to forecast mean deviation (MD) and other parameters. The algorithm was used for 263 eyes (263 Japanese patients) with NTG. The proportion of patients with MD forecasts within 0.5, 1.0, and 2.5 dB of the actual values was determined, and the root mean squared error (RMSE) was calculated for each forecast. Results of KF-NTG were compared with those of the KF model used for patients with high-tension OAG. Of this group, 242 eyes had enough data to forecast two years into the future.

Twenty-four months in advance, KF-NTG was able to forecast MD values that fell within 0.5, 1.0, or 2.5 dB of actual values for 78 eyes (32.2%), 122 eyes (50.4%), and 211 eyes (87.2%), respectively. The percentage of eyes with forecasted MD values within 2.5 dB of actual values (87.2%) was similar to that with the model for high-tension OAG (86.0%) and with the null model (86.4%), and much better than data from two linear regression models (72.7%-74.0%). KF-NTG achieved a lower RMSE than the other models in this study, denoting the superiority of its performance.

These findings suggest that KF holds promise for personalizing disease trajectory forecasts. The authors continue to refine their KF models by incorporating additional variables and validation studies.

—*Summaries by Lynda Seminara*

JAMA Ophthalmology

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

Endothelial Cell Loss: Donor, Recipient, and Operative Factors

February 2019

For the Cornea Preservation Time Study (CPTS), researchers looked at the effect

of donor preservation time (PT) on graft survival and endothelial cell loss after Descemet stripping automated endothelial keratoplasty (DSAEK). Results showed a small difference in endothelial cell loss at 3 years. In a secondary analysis of data from this prospective trial, **Lass et al.** found that donor diabetes, recipient diagnosis of pseudophakic/aphakic corneal edema (PACE), lower screening endothelial cell density, and operative complications were associated with lower endothelial cell density three years after DSAEK, potentially affecting long-term graft success.

In CPTS, 1,330 eyes (1,090 participants; median age, 70 years) underwent DSAEK for Fuchs dystrophy or PACE. Of these, 913 eyes (749 patients) with a functioning graft and analyzable preoperative and endothelial images at the three-year mark were included in the secondary analysis. Preoperative endothelial cell density was used as the baseline. Recipient and donor characteristics were similar to those of the full CPTS population.

In the final multivariable model, the following factors were associated with lower endothelial cell density at three years: donors with diabetes (-103 cells/mm²), lower screening endothelial cell density (-234 per 500 cells/mm²), PACE diagnosis (-257 cells/mm²), and operative complications (-324 cells/mm²). Mean endothelial cell loss from baseline to year 3 was 47% in participants with tissue from donors with diabetes versus 43% without; 53% in recipients with PACE versus 44% with Fuchs dystrophy; and 55% with surgical complications versus 44% without.

Among the factors linked to lower endothelial cell density in this study, surgical complications are the most modifiable.

The authors urged additional study of the effects of diabetes on long-term DSAEK outcome, coupled with improved characterization of diabetes in donors and recipients by means of multiple methodologies. Although findings of this study do not prove causation, they may help to optimize donor selection, minimize surgical trauma, and improve outcomes.

Effects of Low Self-Perception in Children With Amblyopia

February 2019

The self-esteem of school-aged children is affected by their scholastic, social, and athletic competence. Limitations caused by amblyopia may impede children's ability to demonstrate their knowledge and participate in physical activities, which in turn may reduce self-esteem.

In a cross-sectional study, **Birch et al.** explored this matter further and found that low self-perception among children with amblyopia is associated with slower reading speed and poorer motor skills than their peers.

For this study, which was conducted in 2016 and 2017, the researchers enrolled 68 healthy participants in grades 3 through 8. Of these, 50 had amblyopia and 18 served as controls. Self-perception was assessed using the Self-Perception Profile for Children, which includes five domains (behavioral conduct, physical appearance, and scholastic, social, and athletic competence) and a separate scale for global self-worth. In addition, reading speed, eye-hand task performance, visual acuity, and stereoacuity were evaluated.

Compared with controls, children with amblyopia scored much lower scholastically (mean, 2.93 vs. 3.58; $p = .004$), socially (mean, 2.95 vs. 3.62; $p < .001$), and athletically (mean, 2.61 vs. 3.43; $p = .001$). Among children with amblyopia, lower self-perception of scholastic competence was associated with slower reading speed ($r = 0.49$; $p = .002$), and lower self-perception of scholastic, social, and athletic competence was linked to poorer catching and aiming skills (scholastic: $r = 0.48$; $p = .007$; social: $r = 0.63$; $p < .001$; athletic: $r = 0.53$; $p = .003$). There were no meaningful differences between the control and amblyopia groups in regard to conduct, self-perception of physical appearance, or global self-worth.

It is noteworthy that most of the participants with amblyopia wore eyeglasses, versus none of the healthy controls. Therefore, it is possible that the stigma of wearing glasses may contribute to the lower social and ath-

letic self-perceptions of children with amblyopia.

Findings of this study suggest that the impaired visual development related to amblyopia may have wide-ranging negative consequences for affected children. (*Also see related commentary by Joseph L. Demer, MD, PhD, in the same issue.*)

Do Glaucoma Staging Systems Underestimate the Severity of Macular Damage?

February 2019

Although recent studies have found that loss of macular function is more common in early glaucoma than originally thought, 24-2 and 30-2 standard automated perimetry (SAP) tests may routinely miss macular damage in the central 10 degrees of the visual field. This can lead to underestimation of glaucoma severity. In a cross-sectional study, **de Moraes et al.** demonstrated that most participants with glaucoma and 24-2 mean deviation (MD) better than -6 dB were classified by 24-2 and 30-2 SAP as having no or early-stage defects despite matching evidence of macular damage. The research was conducted at a New York glaucoma referral center and included 57 eyes of 57 participants with confirmed glaucoma (mean age, 57 years; 57% women). Macular damage was defined by 10-2 SAP and spectral-domain optical coherence tomography (SD-OCT) evidence of retinal ganglion cells plus inner plexiform layer probability maps.

Findings of glaucoma staging according to Hodapp-Parrish-Anderson (HPA) criteria, visual field index (VFI), and the Brusini Glaucoma Staging System 2 were then compared with visual field and SD-OCT results.

Forty-eight (84%) of the 57 eyes were confirmed to have macular damage. For the affected eyes, the mean (standard deviation [SD]) of the 24-2 MD was -2.5 (1.8); the mean (SD) of the 10-2 MD was -3.0 (2.4) dB; and the mean (SD) of the VFI was 94.2% (4.5%). In contrast, according to the HPA criteria, VFI, and Brusini systems, early defects were apparent in 70%, 81%, and 68% of the eyes that had

macular damage, respectively.

The authors' observations suggest that glaucoma staging systems based exclusively on 24-2 or 30-2 visual fields risk underestimating disease presence, location, and extent; moreover, they also may result in suboptimal care that ultimately may affect patients' visual-related quality of life. If these results are confirmed and found to be generalizable to other patients, the authors would advocate using at least a 10-2 visual field and high-resolution macular SD-OCT scans in the classification of glaucoma.

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Causes and Outcomes of Misdiagnosed Optic Nerve Sheath Meningioma

JAMA Neurology

Published online Dec. 17, 2018

Kahraman-Koytak et al. documented the reasons for initial misdiagnosis of optic nerve sheath meningioma (ONSM). They found that misdiagnosis occurs often, with optic neuritis being the most common erroneous label. Factors contributing to misdiagnosis were inaccurate funduscopy exams, biased pre-established diagnoses, failure to order correct tests, and incorrect interpretation of magnetic resonance imaging (MRI) results.

For this retrospective study, the authors reviewed records of 35 patients (mean age, 45 years) with unilateral ONSM who were seen at Emory University's neuro-ophthalmology practice during a 15-year period. To ascertain causes of diagnostic errors, the Diagnosis Error Evaluation and Research taxonomy tool was applied to cases of missed or delayed diagnosis.

Of the 35 patients, 25 (71%) had a delayed or initially missed diagnosis, the mean of which was 63 months. The most common diagnostic error (n = 19) was clinician assessment failure (errors in hypothesis generation and weighing), followed by errors in diagnostic testing (n = 15). The most common initial misdiagnosis was optic neuritis

(n = 12). Another common contributor to diagnostic delay or inaccuracy was failure to recognize optic neuropathy in patients with ocular disorders. Sixteen (64%) of the 25 patients had poor visual outcomes.

Of the 16 patients with a missed diagnosis, five had unnecessary lumbar puncture, 12 received inappropriate lab tests, and six had unwarranted steroid treatment. Eleven of the 16 had previous MRI results that were considered healthy: Five showed ONSM but were misread by a clinician other than a neuroradiologist, and six were performed improperly (without orbital sequence or contrast).

Compressive optic neuropathy should be considered in the differential diagnosis of monocular vision loss that is painless and progressive. Diagnostic delays and errors are costly and often lead to suboptimal visual outcomes in patients with ONSM.

The authors emphasized that various efforts can minimize diagnostic difficulty, including effective neuroimaging education, better diagnostic strategies, and easier access to neuro-ophthalmologists.

Refractive Outcomes: IOL Formulas for Patients With Previous PPV

Journal of Cataract & Refractive Surgery

Published online Dec. 21, 2018

Although refractive surprises after phacoemulsification have become less common with newer formulas for calculating the power of IOLs, estimates can be inaccurate for some patients, including those with previous ocular surgery. Lamson et al. looked at refractive outcomes of cataract surgery in previously vitrectomized eyes and compared the accuracy of various formulas for calculating IOL power. They found that, regardless of the calculation method, refractive outcomes after cataract extraction in vitrectomized eyes were more variable and hyperopic than the predicted outcomes. Of the formulas used in their study, Holladay 2 provided the best estimates.

This retrospective study involved a record review of phacoemulsifications performed from 2013 to 2017 (61 eyes of 57 patients; mean age, 60 years). Patients with previous pars plana vitrectomy (PPV) in the same eye were included. However, patients with a history of refractive surgery or silicone oil in the eye—or with any other factor that could preclude accurate calculation of IOL power—were excluded from the study.

The mean postoperative spherical equivalent was -0.16 D. Mean prediction errors were as follows: 0.30 ± 0.82 D for Holladay 1; -0.09 ± 0.76 D for Wang/Koch adjusted (WKA) Holladay 1; 0.23 ± 0.76 D for Holladay 2; 0.25 ± 0.81 D for SRK/T; 0.04 ± 0.85 D for WKA SRK/T; 0.33 ± 0.80 D for Hill-Radial Basis Function; 0.45 ± 0.80 D for Ladas; and 0.30 ± 0.82 D for Barrett.

The formula with the highest percentage of predictions within ± 0.50 D of the postoperative outcome was Holladay 2 (60.42%). Significant differences between the predicted and actual refractive outcomes were found with all methods ($p < .05$) except WKA Holladay and WKA SRK/T. Intraclass correlation showed low repeatability (<0.50) for all formulas.

The authors acknowledged that the study is limited by its retrospective nature and small size, which did not allow for subgroup analyses by axial length or other parameters.

Moreover, the indications for vitrectomy varied widely, and differences in retinal pathology may have resulted in anatomic differences that affected formula performance.

Predicting refractive outcomes for this population is challenging, and patients should be counseled accordingly. Larger studies are needed to determine the best methods for choosing IOLs for patients who have previously undergone eye surgery.

—Summaries by Lynda Seminara

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