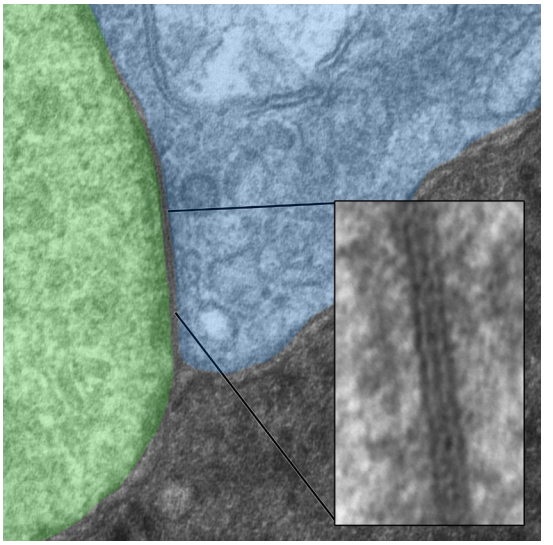
News in Review

COMMENTARY AND PERSPECTIVE



GAP JUNCTION. *This image shows a gap junction in a transmission electron micrograph between an Aii glycinergic amacrine cell (green) and a rod bipolar cell (blue). The gap junction between them (inset) is shown magnified to 25,000×.*

RETINA

Early Retinal Rewiring in RP Visualized

A MASSIVE NEW STUDY OF RETINAL degeneration has concluded that, long before retinitis pigmentosa (RP) has progressed to complete blindness, deterioration of rod photoreceptors leads to rewiring events within the retina—a process that previously was thought to commence much later in the disease.[1]

"RP in many ways is a black box mystery," said lead author Rebecca L. Pfeiffer, PhD, at the University of Utah's Moran Eye Center in Salt Lake City. "We know these changes in retinal circuitry occur as photoreceptors die, leading to blindness. But our research points to much smaller-scale processes before that, which could be important to developing therapeutics in the future," she said.

The scientists' painstaking examination of thousands of transmission electron microscope images revealed that rod photoreceptor postsynaptic target cells begin making new neural/synaptic connections to cone photoreceptors prior to complete loss of rod photoreceptors. These results, and evidence of other kinds of neural rewiring, were found by an ambitious project to construct a "pathoconnectome" for RP retinas.[1]

3-D visualization. The researchers detected the structural changes in retinal neural networks by stacking serial images from transmission electron microscopy into a 3-D visualization of a retinal segment. The visualization showed not only the cells present but also the synaptic connections between them (a "connectome"), Dr. Pfeiffer said. (Molecular probes helped the researchers identify phenotypes of the visualized cells.)

This study builds upon earlier research: In 2011, the researchers assembled the first-ever retinal connectome, built with images from a normal rabbit's retina.[2] In the current study, they followed up by building a pathoconnectome that shows neural network alterations in a rabbit model of retinal degeneration demonstrating a form of early, cone-sparing RP.

At this stage, some rods had already died, but many others remained morphologically intact. "The remaining rod photoreceptors, along with the inner retinal cell population, allowed for connectomics-based evaluation of early stage RP rewiring, corresponding to a clinical point where human patients would still have vision," the researchers wrote. However, the patients "would likely be suffering from scotopic deficits as well as adaptation deficits."[1]

Mixed signaling. Examination of the rod synaptic network showed that rod bipolar cells, which normally synapse with rod photoreceptors, react to the partial loss of the rods by sprouting neurites to connect with cone photoreceptors while maintaining contact with the remaining rods, Dr. Pfeiffer said. Simultaneously, rod bipolar cells form gap junctions with other cell types, including Aii amacrine cells (a common synaptic partner in the inner retina), although the rod bipolar cells never make gap junctions in the healthy retina, she said.

"While they're maintaining some input from the rod photoreceptors that are still in place, they're also getting input from the cone photoreceptors as well. There is mixed signaling going on," Dr. Pfeiffer said. "You have a bleeding of signals between the day and night vision pathways that doesn't exist in a healthy retina."

How the pathoconnectome was built. The studies are being performed in an NIH-funded connectomics research laboratory headed by Bryan William Jones, PhD, at the University of Utah's Brain Institute and Moran Eye Center. "We are taking apart and reconstructing the retina at nanometer scale—and exploring how those con-

Rebecca L. Pfeiffer, PhD, and Bryan W. Jones, PhD

nections are broken in retinal disease," he said.

The lab constructed the pathoconnectome by studying 946 tissue sections, just 70 nm thick, obtained with two transmission electron microscopes.

What's next? The researchers have already gathered images and data for two other retinal pathoconnectomes, reflecting later stages of RP, but these must be further studied before publication, Dr. Jones said.

The analyses likely will be helpful for understanding not only retinal neurodegeneration but also other degenerative conditions, such as Parkinson and Alzheimer diseases, he said.

—Linda Roach

1 Pfeiffer RL et al. *Exp Eye Res.* 2020;199:108196.
2 Anderson JR et al. *Mol Vis.* 2011;17:355-379.
Relevant financial disclosures—Dr. Pfeiffer: None; Dr. Jones: University of Utah Research Foundation: P.

GLAUCOMA

Marijuana as Tx: What Are Your Patients Thinking?

RESEARCHERS IN COLORADO, WHERE recreational and medical marijuana both are legal, report that glaucoma patients are receiving conflicting information regarding the therapeutic use of medical marijuana.[1] Few glaucoma specialists in the state recommend marijuana, in keeping with a statement from the American Glaucoma Society (AGS) advising against its therapeutic use.[2] Yet most marijuana vendors endorse its use, without supporting scientific evidence.

Perspectives from three populations. In a cross-sectional study, Leonard K. Seibold, MD, and his colleagues at the University of Colorado surveyed three groups: AGS members, patients at the university's glaucoma clinic, and vendors at marijuana dispensaries.

SURVEY RESULTS. *Many Colorado dispensaries routinely recommend marijuana to glaucoma patients, despite lack of supporting evidence.*

Physicians. Of the nearly 300 AGS members who responded, only 22 had recommended marijuana for glaucoma —and done so rarely. Their decisions typically were influenced by patient re-

CORNEA

Statins, Dyslipidemia, and Dry Eye

STATIN USE AND DYSLIPIDEMIA APPEAR TO BE BROAD-ly associated with dry eye disease (DED), according to a large retrospective study of patients treated at the University of North Carolina (UNC) ophthalmic clinics.

In a cohort of 39,336 people, the odds of being diagnosed with DED were approximately 40% greater in people taking statins and 60% greater for those with a total cholesterol greater than 200 mg/dL. As for lipid fractions, the odds of being diagnosed with DED were 40% to 50% greater in patients with low high-density lipoprotein (<40 mg/dL), elevated low-density lipoprotein (>130 mg/dL), and high triglycerides (>150 mg/dL).[1] The intensity of the statin therapy did not appear to have any impact on the DED incidence.

Previous findings on a potential association between DED risk and dyslipidemia or lipid therapy have been mixed. "Although previous studies of smaller, select populations support an association between dyslipidemia and MGD [meibomian gland dysfunction] or DED, none of those studies have specifically evaluated the association of statin use/intensity and a clinical diagnosis of DED," the UNC researchers wrote.[1]

Lack of clarity. The researchers eliminated patients with confounding factors, such as autoimmune diseases or concomitant use of antihistamines and other medications, from the original cohort of 72,931 patients seen over a 10-year period. However, it is possible that other potential confounding factors might have affected the odd ratios, they wrote.

Commenting on the study, Bennie H. Jeng, MD, agreed, noting that other issues make it difficult to draw definitive conclusions based on the study. These factors include classification of the subjects as having DED based solely on coding and not on objective tests or assessments for dry eye or MGD. In addition, the older ICD-9 coding was used for most subjects in the study, so the MGD diagnosis code (found in ICD-10 coding) was not used.

"The authors [of this study] could not confirm the diagnosis, and there are many confounders that they couldn't control for," said Dr. Jeng, at the University of Maryland School of Medicine in Baltimore.

"Furthermore, some of the patients diagnosed with dyslipidemia may have been seen at eye care providers outside of the UNC system, and this could skew the results," he noted.

Need for prospective research. Despite these concerns, the study's results suggest that prospective studies of this topic—with more diagnostic rigor and adjustment for all confounding factors—are warranted, Dr. Jeng said.

—Linda Roach

1 Aldaas KM et al. *Am J Ophthalmol.* 2020;218:54-58.
Relevant financial disclosures—Dr. Jeng: EyeGate Pharmaceuticals: O; GlaxoSmithKline: C; Merck: C.

quests or failed prior treatments. Those who had not recommended marijuana cited lack of research, followed by concerns regarding safety and legality.

Patients. Of the 231 patients surveyed, 58% had heard of marijuana's use for treating glaucoma and 36.9% had used it recreationally, yet only 2.6% had used it therapeutically.

Patients who knew of marijuana's purported therapeutic use or had used it recreationally were more willing to try it as a glaucoma treatment, and younger patients were more likely to regard it as effective. In addition, those with moderate glaucoma were more likely to be interested in marijuana therapy than those with mild disease.

Vendors. Callers assuming the role of glaucoma patients contacted 203 randomly selected dispensaries to ask whether they recommended marijuana to treat glaucoma and whether it was safe and effective. While 49% of vendors deferred answering or said that they were unsure, 51% of dispensary employees recommended marijuana to the callers. Of these, 91% agreed it was a safe alternative treatment for glaucoma. The 16% who stated that scientific evidence existed to support marijuana's efficacy could not cite any evidence.

A need for research. An early study suggested that marijuana could lower intraocular pressure (IOP) by as much as 30%.[3] But given the dearth of research, "We still do not fully understand which component of marijuana is responsible for an IOP reduction, which method of consumption works best, and duration of effect from each [method]," said Dr. Seibold.

For now, he advised physicians to be aware of the information that patients may be receiving—and to tell patients that our current knowledge does not support its regular use for glaucoma. "My favorite line to patients who ask me about marijuana for glaucoma is, 'The most likely thing it will do is make you forget to take the medications that we know *will* help you.'"

—Miriam Karmel

PREVALENCE. *In China, the prevalence of myopia reaches 5.25% of children by age 6 and exceeds 80% among university students.*

humphery/Shutterstock.com

1 Weldy EW et al. *Ophthalmol Glaucoma.* 2020; 3(6):3(6):453-459.

2 Jampel H. *J Glaucoma.* 2010;19(2):75-76.

3 Helper RS, Frank IR. *JAMA.* 1971;217:1392.

Relevant financial disclosures—Dr. Seibold: None.

PEDIATRICS

Low-Dose Atropine for Myopia in China

IN THE FIRST YEAR OF A TWO-YEAR study, a once-nightly dose of atropine 0.01% eyedrops slowed the progression of myopia and axial elongation in Chinese children with low and moderate myopia.[1] However, given a relatively high rate of loss to follow-up (nearly 30%), additional research is necessary, the researchers cautioned.

First in China. This is the first randomized, double-masked, placebo-controlled trial of low-dose atropine in mainland China.

Researchers at Beijing Tongren Hospital enrolled 220 children (age range, 6-12 years) with myopia of –1.00 D to –6.00 D in both eyes. The children were randomized in a 1:1 ratio to receive either 0.01% atropine eyedrops or placebo once each night in both eyes for one year. Refraction and axial length were measured at baseline and at six and 12 months. At the beginning of the second year, the groups were crossed over.

At baseline, mean refractive error was –2.58 D and axial length was 24.59 mm. At one year, myopia progression in the atropine group had declined by a mean of 0.26 D (34.2% reduction) and axial elongation declined by 0.09 mm (22.0%) compared with placebo. No serious adverse events occurred.

Respectable but weak. Ningli Wang, MD, PhD, and his coauthors noted that a 34.2% difference in myopia between atropine and placebo groups was smaller than that observed in a European study.[2]

In an accompanying commentary, Michael X. Repka, MD, MBA, called the 34% reduction "respectable," but he noted that the results were less than the 50% reduction hoped for.[3] "The best concentration of low-dose atropine eyedrops remains to be determined, but this study suggests to me that a stronger formulation should be considered for a more substantial effect," said Dr. Repka, at Wilmer Eye Institute in Baltimore.

Dr. Wang agreed. "A reasonable strategy may be to treat initially with atropine 0.01%, then change to a higher concentration if myopia progression continues."

Dr. Repka also questioned the study's crossover design, which eliminates the ability to detect multiyear evidence of effectiveness in treating a progressive condition. Dr. Wang, who designed the study, hoped the crossover data might reveal a rebound of myopia after cessation of eyedrops.

Going forward. Trial results from Europe and North America are not expected for at least two years, Dr. Repka said. For now, he advises families interested in atropine treatment to expect to treat for at least two years, with three or four years more likely to achieve a meaningful reduction in myopia progression. He also noted that, in the United States, low-dose atropine is prescribed off-label, requires compounding by a pharmacy, and is not covered by insurance.

—Miriam Karmel

1 Wei S et al. *JAMA Ophthalmol.* Published online Oct. 1, 2020.

2 Sacchi M et al. *Acta Ophthalmol.* 2019;97(8): e1136-e1140.

3 Repka MX. *JAMA Ophthalmol.* Published online Oct. 1, 2020.

Relevant financial disclosures—Dr. Repka: NEI: S; Dr. Wang: None.

See the financial disclosure key, page 8. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.