GLAUCOMA

Oral Supplements May Promote Neurorecovery

COULD OPHTHALMOLOGISTS EVEN-tually be able to protect glaucoma patients' vision by giving them nutritional supplements that rev up the mitochondria in retinal ganglion cells (RGCs)? Results of a small phase 2 dosing and safety trial suggest that the answer might be yes.[1]

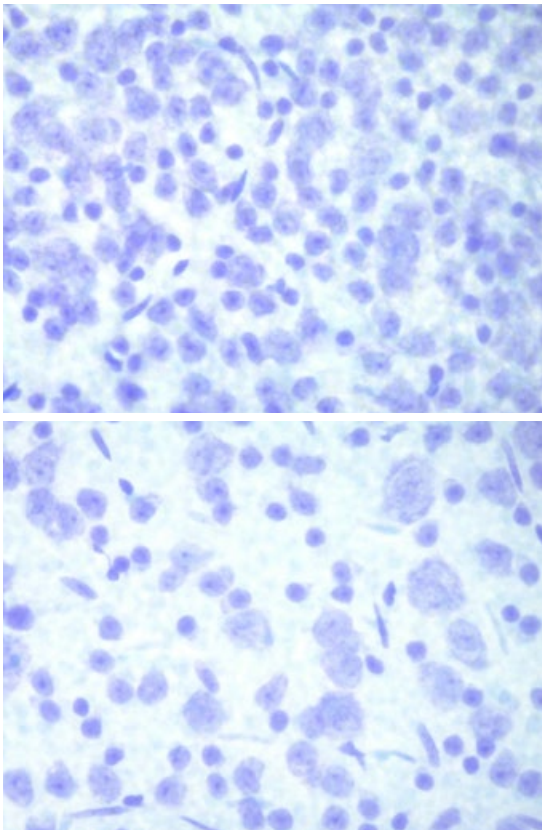
"This our first attempt at proof-of-concept in humans for this type of intervention in glaucoma," said study leader Jeffrey M. Liebmann, MD, at Columbia University Medical Center in New York City. "So far, it looks like there's a potential role for vitamin and nutritional supplementation as a treatment to help protect nerve cells."

With this neurorecovery strategy, "you postulate that some RGCs are sick—and that if you provide them with neuroenhancing compounds, the cells will function a little bit better, and we'll see a small uptick in visual function," Dr. Liebmann added.

Two compounds tested together. In the study, 32 participants with treated open-angle glaucoma and moderate visual field loss were randomized to placebo or to oral doses of two compounds:

Nicotinomide is a vitamin B3 amide that is a precursor for nicotinamide adenine dinucleotide (NAD+). NAD+ is a key intracellular molecule involved in mitochondrial production of energy and in redox metabolism. As nicotinamide levels in sera decline with age, the investigators hypothesized that increasing the availability of nicotinamide (and, as a result, NAD+) might prevent flagging RGCs from progressing further toward apoptosis, Dr. Liebmann said.

Pyruvate is a compound that can overcome ocular deficits in glycolysis. It also acts as an antioxidant in the retina and aids oxidation and adenosine triphosphate production in RGCs and other cells. Animal studies have shown that levels of retinal pyruvate fall in response to high IOP and that this decrease occurs before detectable optic nerve degeneration.



Jeffrey M. Liebmann, MD

RGC LOSS. *RGCs are plentiful in a healthy mouse (top). In comparison, the mouse with glaucoma (bottom) has experienced substantial RGC loss.*

Results. The participants were followed for a median of 2.2 months. Visual field tests performed during this time showed that the number of improving test locations was higher in the treatment group than in those who received placebo ($p = .005$).

Looking ahead. Buoyed by the early hints of efficacy, the investigators are planning to follow up with a larger, longer-term clinical trial to gauge the effectiveness of this strategy.

Dr. Liebmann noted that his patients, who often follow the glaucoma literature, have begun asking him about taking nicotinomide and pyruvate. "They want to know how much to take. But I try not to encourage too many people to use it, as our data are very limited. We will know much more in the next two years." If pressed, Dr. Liebmann recommends nicotinamide 1,000 mg daily, divided into two equal doses. Although participants in the dosing trial received up to 3,000 mg daily with no serious adverse events, longer studies are needed to rule out downstream adverse effects with larger doses, he said.

—Linda Roach

1 De Moraes CG et al. *JAMA Ophthalmol.* Published online Nov 18, 2021.

Relevant financial disclosures: Dr. Liebmann—Allergan: C; Diopsys: O; Galimedix Therapeutics: C,O; Thea Pharmaceuticals: C.

CORNEA

Nasal Spray for Dry Eye Comes to Market

THE FIRST NASAL SPRAY DEVELOPED to treat dry eye disease (DED) is now available. In the phase 3 trial known as ONSET-2, researchers found that varenicline (Tyrvaya; Oyster Point Pharma) promoted tear film production and significantly improved the signs and symptoms of DED.[1]

The medication was developed to pharmacologically activate the trigeminal nerve in the nasal cavity, noted lead author David Wirta, MD, at the Eye Research Foundation in Newport Beach, California. And the delivery method provides a new option for patients, particularly those who may have difficulty administering eyedrops.

Study design. ONSET-2 included 758 patients who were randomized 1:1:1 to a nasal spray containing either placebo (n = 252), varenicline .6 mg/mL (n = 260), or varenicline 1.2 mg/mL (n = 246). All participants were 22 years of age or older and had an Ocular Surface Disease Index score of 23 or more and a Schirmer test score of 10 mm or less.

Participants self-administered the spray twice daily in each nostril for four weeks. They assessed their symptoms using the Eye Dryness Score (EDS) at clinic visits and in a controlled adverse environment (CAE) chamber that simulates everyday situations known to exacerbate dry eye symptoms.

Results. At week 4, the percentage of patients who achieved a 10-mm improvement or more in their Schirmer score was 47.3% of those who received varenicline .6 mg/mL, 49.2% of those in the 1.2 mg/mL varenicline cohort, and 27.8% of those who received placebo.

The EDS improved with varenicline, as measured during clinic visits, although the improvement had limited clinical significance. In addition, the advent of the COVID-19 pandemic restricted the use of the CAE chamber. In a subgroup analysis, tear film production improved regardless of baseline anesthetized Schirmer score tear production or baseline EDS severity.

Adverse events. The most common adverse event was sneezing: Nearly all patients on varenicline sneezed at least once during treatment, particularly during the first minute following administration.

With regard to potential safety issues, Dr. Wirta noted that since 2006, varenicline has been used at much higher doses by over 20 million patients worldwide as an aid for smoking cessation. "It's rare to have as much safety

RESEARCH ON AGING

Red Light Improves Vision of Aging Eye

OVER THE LAST DECADE, NEUROSCIENCE RESEARCH has revealed that slowly progressing vision deficits can occur in otherwise normal eyes because of age-related declines in the number and functionality of photoreceptor mitochondria. In a recent study, researchers found that this phenomenon can be temporarily reversed by a single three-minute exposure to deep red (670 nm) light.[1]

"The retina has more mitochondria than any other part of your body, and they have distinct optical characteristics," said study leader Glen Jeffery, PhD, at University College London's Institute of Ophthalmology. "Short wavelengths—deep blues—reduce the amount of energy that mitochondria produce. But long wavelengths, like the deep red we used in our study, improve mitochondrial function."

Study specifics. Dr. Jeffery's group used a specially modified LED flashlight to deliver a single three-minute dose of the deep red light unilaterally to the retinas of 20 subjects (age range, 38-70 years).

The researchers found that cone-mediated color contrast thresholds in the treated eyes improved to acuity levels normally found in younger adults—and that the improvements persisted for one week. The thresholds significantly improved by mean levels of 17% (blue-yellow axis) and 12% (red-green axis; both $p < .0001$). However, the visual gains from the treatment only occurred if the light exposure was provided in the morning.

The research group hypothesizes that exposure to the deep red wavelength increases the impaired mitochondria's energy production by reducing the viscosity of water surrounding the rotating mitochondrial pumps that generate adenosine triphosphate, thus improving their efficiency.

It is possible that the pumps gain greater momentum and that this is sustained for a period, Dr. Jeffery said. "But as with a lot of mitochondrial research, there is much we do not know," he said.

Next steps. The researchers are planning further clinical studies aimed at understanding the temporal difference that emerged in the results. They also are seeking to optimize the treatment parameters to achieve longer-lasting effects while maintaining the safety of the light exposures.

Dr. Jeffery said he hopes his studies will help address important quality-of-life issues posed by mitochondrial dysfunction as retinas age. With further research, it might become apparent, for instance, that the virtual nonexistence of long wavelengths in much of today's indoor lighting is preventing optimal vision in the elderly, he said. *—Linda Roach*

1 Shinhmar H et al. *Sci Rep.* 2021;11(1):22872.

Relevant financial disclosures: Dr. Jeffery—None.

data available for a medication at the time of approval," he said.

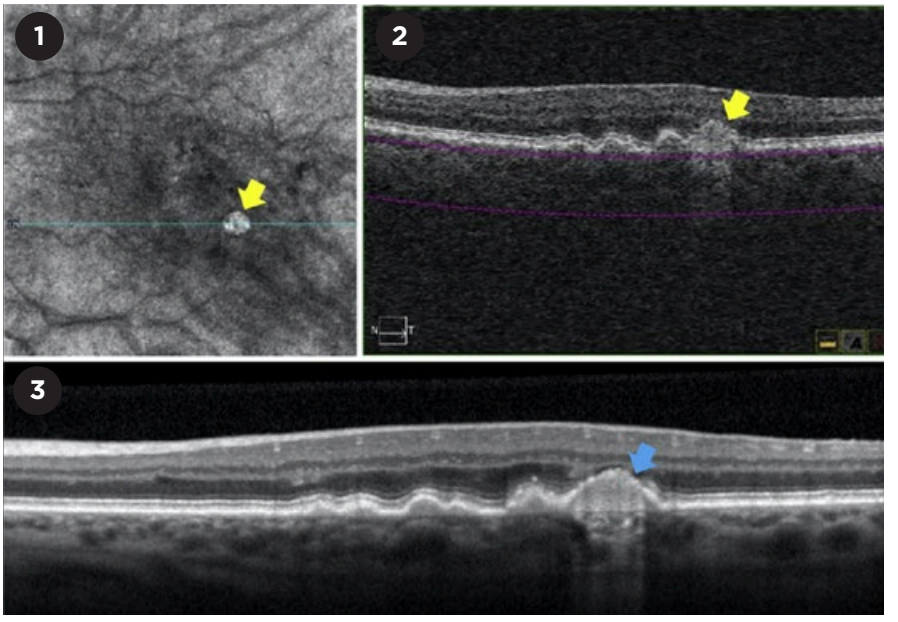
Clinical implications. Treatment duration will depend upon the individual patient, Dr. Wirta said. He added, "As dry eye disease is a chronic multifactorial disease, we expect that patients will take the medication for the duration of their disease." —*Miriam Karmel*

1 Wirta D et al. *Ophthalmology.* Published online Nov. 10, 2021.

Relevant financial disclosures—Dr. Wirta: Oyster Point Pharma: C,S.

RETINA

Hypertransmission Defects Predict GA Formation



EVIDENCE. *(1) A hyperTD shows as a bright lesion on en face OCT (yellow arrow). (2) Corresponding OCT B-scan shows the increased choroidal hypertransmission (yellow arrow). (3) Nascent GA (blue arrow), identified on OCT B-scan.*

IN A PAIR OF STUDIES, RESEARCHERS at the Bascom Palmer Eye Institute in Miami have confirmed that persistent hypertransmission defects (hyperTDs) —defined as those with a greatest linear dimension of 250 µm or more—can serve as an independent risk factor for the progression of drusen to geographic atrophy (GA) in dry age-related macular degeneration (AMD).[1,2]

On OCT, hyperTDs appear as bright regions due to increased light transmission into the choroid where the retinal pigment epithelium (RPE) is attenuated or absent. Previous research has found that hyperTDs could be seen during the progression from intermediate AMD to late-stage AMD.

En face SD-OCT. Using en face spectral-domain OCT, the researchers evaluated 81 patients (157 eyes). Thirty-nine hyperTDs were documented in 22 patients (27 eyes) and classified as either persistent (26 lesions) or transient (13 lesions) over a three-year period. The presence of the lesions was confirmed on corresponding OCT B-scans.[1]

The hyperTDs (≥250 µm) were associated with nascent GA, the analysis found. Because of the high negative predictive value (≥94%), the researchers concluded that these persistent hyperTDs could be used as a standalone precursor for the progression from intermediate AMD to GA.

En face SS-OCT. In a larger study, the researchers found that a persistent hyperTD significantly increases the risk of developing GA in eyes with intermediate AMD.[2]

For this study, the researchers used en face swept-source OCT to assess 134 patients (190 eyes). All told, 73 eyes had at least one hyperTD at baseline or follow-up. However, those with hyperTDs >250 µm (n = 31) were more likely to progress to GA than were those with smaller lesions (n = 42). Overall, the researchers estimated, the risk of developing GA increased by 80-fold once a hyperTD >250 µm appeared.

Next steps. The Bascom Palmer researchers are planning a treatment trial to slow disease progression in eyes with intermediate AMD, using the appearance of persistent hyperTDs as the clinical trial endpoint, said Philip J. Rosenfeld, MD, PhD, coauthor of both studies. They've also developed and trained a machine learning algorithm that can detect hyperTDs on en face images.

High praise for en face OCT. Dr. Rosenfeld credits the Classification of Atrophy Meeting (CAM) group, an international team of AMD and retinal imaging experts, for emphasizing the importance of OCT over autofluorescence imaging for diagnosing GA.

"I love the simplicity of the method," Dr. Rosenfeld said. "En face OCT imaging is the most accurate and efficient way to diagnose and monitor disease progression in dry AMD when compared with other imaging modalities. There's no need to use color fundus imaging, autofluorescence imaging, or infrared reflectance imaging to detect the earliest formation and subsequent growth of GA. We can do it all with a single OCT raster scan." —*Miriam Karmel*

1 Shi et al. *Ophthalmol Retina.* 2021;5(12):1214-1225.

2 Laiginhas R et al. *Am J Ophthalmol.* Published online Nov. 13, 2021.

Relevant financial disclosures: Dr. Rosenfeld—Apellis: C,O; Bayer: C; Carl Zeiss: C,S; Boehringer Ingelheim: C; Chengdu Kanghong Biotech: C; Gyroscope Therapeutics: S; OcuDyne: C,O; Ocunexus (inflammX): C; Regeneron: C; Stealth BioTherapeutics: S; Unity Biotechnology: C; Valitor: O; Verana Health: O.

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