

# News in Review

COMMENTARY AND PERSPECTIVE

## RETINA

### Metabolic Link to MacTel Confirmed

#### AN INTERNATIONAL RESEARCH

collaboration has discovered that a deficiency of the amino acid serine is associated with the accumulation of certain toxic lipids in the blood and retina, causing photoreceptor apoptosis in macular telangiectasia (MacTel) type 2.<sup>1</sup>

The new finding about this orphan disease points researchers toward a possible molecular road map for slowing or preventing retinal degeneration in MacTel, said Martin Friedlander, MD, PhD, at Lowy Medical Research Institute in La Jolla, California. “Through this highly collaborative project, we now have an understanding of macular telangiectasia. If you see a patient with MacTel, you should tell them that new research has revealed a cause of the disease and that we might have a treatment in the next few years,” said Dr. Friedlander, also at Scripps Research and Scripps Clinic in La Jolla.

**Building the case.** In 2017, the MacTel research group first reported on the suspected retinal role of serine,<sup>2</sup> which is used in many pathways in the body but was not previously known to affect macular health.

In the current study, the researchers confirmed the link, and they determined that low serine levels lead to the same lipid-associated degenerative process that occurs in a rare genetic disease called hereditary sensory and autonomic neuropathy 1 (HSAN1).<sup>1</sup> Moreover,



**COMPLEX INTERACTION.** *The researchers cautioned against prescribing fenofibrate or serine supplements to patients with MacTel type 2, “given the complex genetic etiology of the condition and the genetic diversity in the patient population.”*

they identified the gene common to both MacTel and HSAN1, although this genetic variant is found in only a small number of MacTel patients, Dr. Friedlander said.

**Tracking toxicity.** Through a painstaking combination of genetic analysis, metabolomics, animal studies, and in vitro tests in human retinal organoids grown from stem cells, the scientists determined that insufficient serine leads to the formation of toxic deoxysphingolipids in the retina. These toxic molecules form instead of normal sphingolipids when serine is lacking, Dr. Friedlander said.

When the researchers examined 13 HSAN1 patients who had not previously had ophthalmic testing, nine had undiagnosed MacTel, and two more had early signs of the disease. Furthermore, blood tests in 125 MacTel patients showed levels of deoxysphingolipids 84.2% higher than those found in unaffected controls.

**A new disease class?** “In this case, a single biochemical mechanism causes

disease in both the eye and the peripheral nervous system,” Dr. Friedlander said. “We think this is an example of a new class of neurodegenerative disease that we are calling ‘serineopathies.’” He added that the finding may have application to more common metabolic and neurological disorders. For instance, he noted, elevated blood levels of deoxysphingolipids have been reported in people with diabetic retinopathy.<sup>3</sup>

**Patient management.** The MacTel researchers found that cell damage was prevented if the scientists either supplemented with serine or used a drug that regulates lipid metabolism to block the toxic lipids from forming, Dr. Friedlander said. (For this study, they used fenofibrate.)

Already, some physicians are treating HSAN1 patients with oral serine supplements, Dr. Friedlander said. But it is too early to recommend this for patients who have MacTel or are at genetic risk for it, he said. For now, he recommended that patients whose neuropathy has been diagnosed as HSAN1

be examined for signs of macular telangiectasia. —*Linda Roach*

1 Ganter ML et al. *N Engl J Med.* 2019;381(15):1422-1433.

2 Scerri TS et al. *Nat Genet.* 2017;49(4):559-567.

3 Zuellig RA et al. *Diabetes.* 2014;63(4):1326-1329.

Relevant financial disclosures—Dr. Friedlander: None.

## GLAUCOMA

# Gabapentin Raises Risk of Acute Angle Closure

**THE GABAPENTINOIDS GABAPENTIN** and pregabalin are among the most commonly prescribed drugs in North America. Now, researchers have found an association between gabapentin and the incidence of acute angle-closure glaucoma (AAG).<sup>1</sup> A similar association was not found for pregabalin.

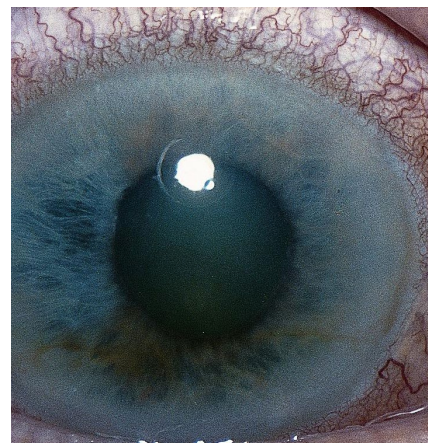
Both drugs are approved to treat

epilepsy and selected chronic pain conditions and are widely used off-label for mood disorders and pain.<sup>2</sup> “We were surprised that this commonly prescribed psychotropic agent might increase the risk of AAG,” said coauthor Mahyar Etminan, PharmD, MSc, at the University of British Columbia Eye Care Center in Vancouver, British Columbia, Canada.

The bottom line, he said: “If you see patients with acute angle-closure glaucoma and they are on gabapentin, this drug might be the culprit.”

**Study rationale.** Previously, gabapentin has been linked to AAG, but only in case reports citing complaints of blurred vision, nystagmus, diplopia, and visual defects. These reports, plus the wide use of the drug, factored into the decision to conduct a large epidemiological study, Dr. Etminan said.

**Study specifics.** Researchers evaluated a random sample of 1,307 patients who developed AAG after gabapentin and pregabalin exposure in the year



**RX LINK.** Additional evidence has emerged of a link between acute angle-closure glaucoma (shown here) and gabapentin use.

before diagnosis. The sample, drawn from a medical and pharmaceutical claims database over a 10-year period ending Dec. 31, 2016, also included 13,070 controls.

**Who's at risk?** Gabapentin use in the year before AAG diagnosis was associ-

## COMPREHENSIVE

# RVO Risk: CVD and Hypertension

**RETINAL VEIN OCCLUSION (RVO) IS ASSOCIATED WITH** increased risks for stroke, myocardial infarction (MI), and other cardiovascular events, conferring levels of risk beyond traditional factors, a meta-analysis of 15 longitudinal cohort studies has concluded.<sup>1</sup>

Meanwhile, a separate meta-analysis has found that hypertension doubles the risk of RVO, making it the strongest risk factor for development of an occluded retinal vein.<sup>2</sup>

**CVD in general.** Researchers in New York and Hawaii evaluated observational data on 474,466 subjects, 60,069 of whom (12.7%) had RVO. The results showed that the patients with RVO were at greater risk of cardiovascular disease (CVD) and all-cause mortality than their healthy counterparts. Specifically, they had a 45% increased risk of stroke, 26% increased risk of MI, 53% increased risk of heart failure, 26% increased risk of peripheral arterial disease, and 36% increased risk of all-cause mortality.<sup>1</sup>

The added risks were statistically significant despite adjustment for confounding factors such as age, gender, hypertension, diabetes, and other medical comorbidities,

said coauthor Avnish Deobhakta, MD, at the New York Eye and Ear Infirmary of Mount Sinai in New York City.

Previous case series and longitudinal cohort studies that examined the association of RVO with stroke or MI produced inconsistent conclusions, Dr. Deobhakta said. He said he believes the current study settles the issue. “I think the evidence is pretty compelling that RVO is a sentinel event for cardiovascular risks,” Dr. Deobhakta said. “I look at it now as a canary in the coal mine for these other systemic kinds of morbidity-inducing or even life-threatening health risks.”

**Hypertension in particular.** Researchers in the United Kingdom and China assessed the impact of nine risk factors on the development of any type of RVO. Hypertension proved to be the strongest risk factor, followed by heart attack history, stroke history, and elevated levels of total cholesterol and creatinine.<sup>2</sup>

Overall, the researchers estimated, the global prevalence of any type of RVO was 0.77% in 2015, equivalent to 23.38 million cases of branch RVO and 6.7 million cases of CRVO. That was up from 16.4 million total cases worldwide of any type of RVO in 2008.

**Urgent issue.** Once RVO is diagnosed, Dr. Deobhakta suggested, the ophthalmologist should consider urgently referring the patient to a primary care physician for intensive medical management of the person's cardiovascular risks—and, possibly, should add a strong recom-

ated with a 42% increase of AAG, the researchers found. However, no association was found for current use of either gabapentin or pregabalin.

In addition, the incidence of AAG was associated with moderate drug exposure (3-5 prescriptions in the year before diagnosis). In contrast, neither limited exposure (1-2 prescriptions) nor significant exposure (6 or more) yielded an association with AAG. The small number of cases identified for significant exposure may have affected results, the researchers noted.

**Method of action?** The authors theorized that the mechanism of AAG associated with gabapentin use is similar to that of topiramate with regard to forward displacement of the ciliary body.

**Clinical implications.** While the findings need to be validated by other studies, Dr. Etminan suggested that ophthalmologists closely evaluate patients diagnosed with AAG who are on gabapentin. He added that it's possible

recommendation for prompt evaluation and follow-up by a cardiologist or neurologist.

"A retinal vein occlusion, by definition, is when a really small vessel in the eye is blocked or there's some kind of pathology with it. Well, if a really small vessel in the eye is showing that it can be affected in this way, then other vessels can have that kind of problem" as well, Dr. Deobhakta said. "And if we can prevent a stroke or other cardiovascular complication by sending these patients to the right specialists, or getting the right imaging tests, then that would be recommended." —Linda Roach

1 Wu CY et al. *Retina*. 2019;39(9):1635-1645.

2 Song P et al. *J Glob Health*. 2019;9(1):010427.

**Relevant financial disclosures—**Dr. Deobhakta: Alimera Sciences: C; Allergan: C.

that patients with a previous history of AAG might be able to safely take pregabalin instead. —Miriam Karmel

1 Browne MJ et al. *J Glaucoma*. 2019;28(9):777-779.

2 Goodman CW, Brett AS. *JAMA Intern Med*. 2019;179(5):695-701.

**Relevant financial disclosures—**Dr. Etminan: None.

## PUBLIC HEALTH

# Opioid Rx After Eye Surgery

**HOW OFTEN DO PATIENTS WHO** undergo incisional ocular surgery fill a prescription for an opioid medication? Despite increased awareness of the opioid crisis in the United States, researchers at the University of Pennsylvania found that the odds of having an opioid prescription filled after ocular surgery was more than 3 times higher in 2014-2016 than in 2000-2001.<sup>1</sup>

"Though opioid abuse has been declared a public health emergency, until now little has been known about the association between opioids and ocular surgery," said coauthor Brian L. VanderBeek, MD, MPH, MSCE, at the Scheie Eye Institute in Philadelphia. "The findings of our study provide a basis for discussing the role of opioids in post-ophthalmic surgical management."

**Study specifics.** The researchers used medical claims data from a U.S. insurer's database for the period of January 2000 through December 2016. For the primary analysis, the researchers looked at the rate of filled opioid prescriptions for each ophthalmic subspecialty surgery over time.

**Results.** A total of 2,407,962 incisional ocular surgeries were included; of these, 45,776 (1.90%) were associated with a filled opioid prescription. The lowest number of filled prescriptions was in 2000-2001, in which 671 prescriptions were filled for 53,912 surgeries (1.24%). In contrast, in 2016, 5,851 prescriptions were filled for 282,106 surgeries (2.07%). Multivariate logistic

regression showed that year of surgery was significantly associated with filling an opioid prescription, with the highest odds in 2014 (odds ratio [OR] 3.71), 2015 (OR, 3.33), and 2016 (OR, 3.27).

The highest prescription fill rates were associated with strabismus surgery, trauma, and retina surgery.

**Bottom line.** These findings suggest the rate of filled prescriptions for opioid medications are increasing for all types of incisional ocular surgery over time, the researchers said. They concluded, "Given the ongoing national opioid epidemic, we hope the trends of increased prescription use we have described will motivate clinicians to evaluate their opioid prescribing practices to help in reversing the epidemic."

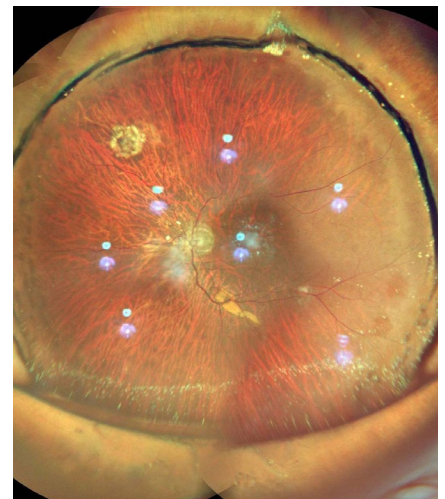
To help reduce unnecessary opioid prescribing, the CDC has published guidelines that cover such topics as risk assessment, drug selection, dosing regimens, and appropriate follow-up.<sup>2</sup>

—Arthur Stone

1 Kolomeyer A et al. *JAMA Ophthalmol*. Published online Sept. 19, 2019.

2 Dowell D et al. *MMWR Recomm Rep*. 2016;65(1):1-49.

**Relevant financial disclosures—**Dr. VanderBeek: NEI/NIH: S; Paul and Evanina MacKall Foundation: S; Research to Prevent Blindness: S.



**TYPICAL RECIPIENT.** Scleral buckling surgery is one of the top three ocular surgeries for which patients are likely to be prescribed an opioid medication.

See the financial disclosure key, page 8. For full disclosures, including category descriptions, view this News in Review at [aao.org/eyenet](http://aao.org/eyenet).