

## Pregnancy and glaucoma

Medications, dosage and trimester

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#### References:

1. ILEVRO<sup>®</sup> Approved Product Information, 25 May 2016.
2. Modi SS *et al.* *J Cataract Refract Surg* 2014;40(2):203–11.

**NSAID:** non-steroidal anti-inflammatory drug.

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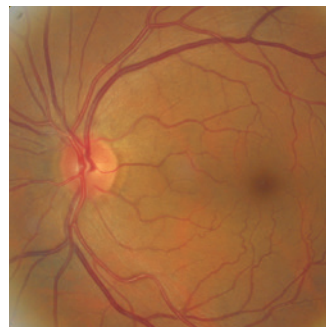
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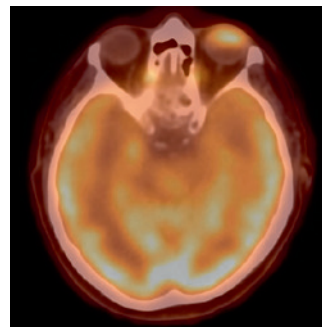
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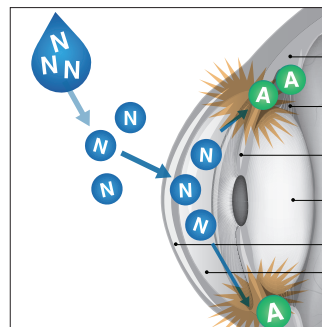
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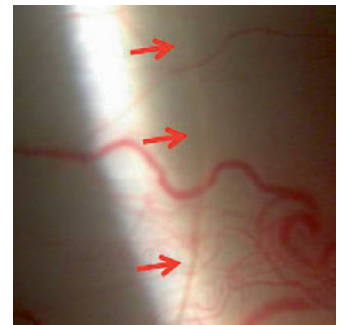


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# Glaucoma medications and pregnancy

## Which agent, dose and trimester?

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IN THE MAJORITY of cases, glaucoma in pregnant women is managed with topical anti-glaucoma medications. Unfortunately, there is currently a lack of a strong evidence base to provide guidance on the best course of action for clinicians when managing glaucoma in these patients.

Glaucoma in women of child-bearing age also tends to be due to disorders acquired early in life, such as congenital malformations, anterior segment dysgenesis and cataracts, or secondary to coexisting conditions such as uveitis or diabetes rather than the primary open angle glaucoma more prevalent in older age groups.<sup>1,2</sup> These types of glaucoma usually require aggressive intraocular pressure (IOP) interventions to preserve vision and therefore treatment discontinuation is not an option during the pregnancy and lactating period.<sup>3</sup>

### Topical glaucoma therapy options in pregnancy

One frequent comment regarding medical therapy in pregnancy is that there is 'no clinical data specifically for humans available,' so most recommendations are based on animal or laboratory studies where the applicability to use in humans is questionable.<sup>1,3,4</sup>

The recommendations of the *Australian Medicines Handbook (AMH)*, which is looked on as a reliable source of information by clinicians for prescribing in Australia, attempts to synthesise information based on human data as well as clinical experience when prescribing for special populations such as those who are pregnant or breastfeeding, although it is quick to note that absence of data and information does not necessarily suggest medicines or other products are safe.

The *AMH* also does not currently list the pregnancy categories for medications as deemed by the Australian Therapeutic Goods Administration (TGA) or American Food and Drug Administration (FDA), due to shortfalls of both systems regarding perceived staging of risk and safety ('higher' letter codes do not necessarily imply better safety), the inability of these codes to change over time as new data emerge, the lack of reflection of which stage of foetal development specifically is potentially affected by the drug and overall, a lack of specific utility to aid clinical decision-making regarding a balance of risks and benefits to prescribing.<sup>5</sup>

The FDA is in the process of eliminating pregnancy categories in a gradual process to improve

drug labelling with more relevant and useful information.<sup>6</sup> The *AMH* recommendations for use of topical glaucoma medications during pregnancy and/or while breastfeeding, based on the best available evidence at the time of publication, are summarised in Table 1.<sup>5</sup>

### Prostaglandin analogues (PGAs)

While the PGAs are considered the first-line form of medical treatment for the majority of glaucomas, they are currently not the first choice to manage the condition in pregnant patients for a number of reasons. There are concerns regarding abortion and induction of labour with these molecules, especially with their activity on the F2-alpha receptor which is intimately involved in the parturition (birthing) process.<sup>7</sup> Indeed, other prostaglandin analogues such as misoprostol are used in practice to induce labour or abortions.<sup>8,9</sup> There are also concerns regarding teratogenesis, with oral use of prostaglandins being associated with birth defects.<sup>10</sup>

Considering their low dose and route of administration, the actual risk of PGA use for glaucoma during pregnancy has been debated. It has been argued that there is an insufficient drug quantity to induce effects on the foetus with

typical eye-drop administration, while others have suggested that the potential risks outweigh the benefits.<sup>11</sup> Case series have been published which suggest that it is mostly safe for use in the first trimester, with only one case of spontaneous abortion (miscarriage) noted in a 46-year-old patient.<sup>12</sup> Causation of this event due to concurrent latanoprost administration could not be established due to the presence of other risk factors in that particular patient; all other patients (90 per cent) within the series displayed no other adverse effects, with three women having continued treatment with latanoprost throughout pregnancy.

**Beta-blockers (BBs)**

As a class, beta-blockers have been reported to cause the following adverse effects during pregnancy and in the neonate: intrauterine growth retardation, maternal and foetal bradycardia, premature labour, delayed neonatal breathing, neonatal hypoglycaemia, and neonatal hyperbilirubinaemia.<sup>13</sup> Timolol specifically has been shown to cross the placental barrier and be secreted in breast milk.

Beta blockers are used not only in the management of glaucoma but also for the management of hypertension when administered systemically. Studies in pregnant patients with hypertension treated using systemic beta-blockers have demonstrated mixed results, with some studies demonstrating intrauterine growth retardation and lighter birth weight when oral atenolol was given from early pregnancy.<sup>14,15</sup> There are risks for the foetus of

developing permanent respiratory or cardiac disorders following delivery. In topical form, timolol, as a lipid-soluble formulation, reaches high concentration in the foetus, with isolated case reports in support and against timolol usage in pregnancy.<sup>16,17</sup> Thus, the typical recommendation is to avoid beta-blockers in early pregnancy, in late pregnancy and during lactation.

**Alpha2-agonists (AAs)**

Of the two alpha2-agonists available for glaucoma, brimonidine is routinely recommended over apraclonidine for use during pregnancy. Brimonidine is considered by the US FDA to be the safest anti-glaucoma medication based on animal studies demonstrating little to no risk to developing foetus (FDA Pregnancy Category B).<sup>4</sup> However, it should be noted that brimonidine readily penetrates the blood brain barrier and can cause central nervous system depression, including apnoea.<sup>18</sup> Because breast milk is produced in late pregnancy, it is typically recommended that brimonidine use be ceased before labour and during breastfeeding to reduce transmission to the infant. In contrast, apraclonidine use in high doses during gestation and lactation in animals can lead to poor weight gain and embryotoxicity.<sup>19</sup> With the availability of brimonidine this renders apraclonidine to be not routinely recommended for use during pregnancy.

**Carbonic anhydrase inhibitors (CAIs)**

The concerns with use of CAIs during pregnancy are teratogenesis and

electrolyte imbalances in the foetal bloodstream. Animal studies with systemic carbonic anhydrase inhibitors have shown potential teratogenesis at high doses. There have also been studies regarding potassium depletion and its effects on limb development in rats, which was readily treated with potassium replacement therapy.<sup>20</sup>

Teratogenesis with CAIs used in pregnancy has been observed only rarely in humans. A higher dose of oral acetazolamide used in the management of intracranial hypertension (1 g/day) compared to the typical dose in glaucoma (250-500 mg/day) led to no maternal or foetal complications in a group of 12 women.<sup>21</sup> However, other case reports have shown complications in the newborn following treatment with acetazolamide during pregnancy.<sup>22-24</sup> Notably, administration of oral acetazolamide in these cases were all throughout pregnancy, beginning from the first trimester.

Topical carbonic anhydrase inhibitors for glaucoma therapy, on the other hand, have not been demonstrated to lead to foetal complications, except for one reported case of low birth weight and reduced renal function.<sup>25</sup> In animals, high doses of dorzolamide and brinzolamide have been shown to lead to decreased weight gain in the newborns of lactating rats. Therefore, it is suggested that topical carbonic anhydrase inhibitors at the typical glaucoma dosage may be an appropriate option for pregnant patients.

**Continued page 4**

Specific concerns of glaucoma medications during pregnancy and lactation		
Drug class	Use in pregnancy	Use while breastfeeding
Prostaglandin analogues	Avoid use, no data available	Unlikely to be concern; latanoprost safe
Beta-blockers	May cause foetal bradycardia, no specific recommendation	Unlikely to have effects at usual doses
Alpha2-agonists	Apraclonidine: avoid use Brimonidine: suitable if necessary	No data available, unlikely to be concern
Carbonic anhydrase inhibitors (topical)	Avoid use, no human data available	No human data available
Acetazolamide (systemic)	Contact pregnancy drug information centres	Contact pregnancy drug information centres

▲ Table 1. Recommendations for use of anti-glaucoma medications during pregnancy and breastfeeding from the *Australian Medicines Handbook*.<sup>5</sup> Note that some medications do not have explicit recommendations under some conditions.

# Glaucoma and pregnancy

From page 3

## Parasympathomimetics

Parasympathomimetics have been shown to have teratogenic and adverse effects on the foetus in animal studies, particularly in early stages of development.<sup>26-28</sup> Pilocarpine is also a tertiary cholinergic amine with a weak base, which facilitates membrane penetration. Local side-effects of parasympathomimetics such as ciliary spasm and miosis are also poorly tolerated in a younger cohort. In combination, this precludes recommendation of pilocarpine for use in pregnant women.

## Current recommendations

The NHMRC guidelines for the management of patients with glaucoma suggest the following order

(most preferred to least preferred) for topical medications in the management of glaucoma in pregnant or lactating patients: beta-blockers, AAs, cholinergics, CAIs then PGAs.<sup>29</sup> However, based on the most recently available evidence, customising the selection of agent and dose based on the particular stage of pregnancy and foetal development<sup>3,11</sup> has been suggested:

- First trimester: brimonidine, PGAs; avoid BBs and CAIs
- Second trimester and early third trimester: brimonidine, CAIs, BBs; PGAs only with caution
- Late third trimester and during lactation: CAIs or a lower dose of BBs seem to be preferred; avoid brimonidine; PGAs may trigger premature labour.

## Summary

Overall, the recommendations would be to consult with the patient's entire medical team, including but not limited to: ophthalmologist, general

physician, obstetrician/gynaecologist, paediatrician and endocrinologist. Decisions on medication use during pregnancy and breastfeeding should be carefully considered and discussed based on the relative risks and benefits for the patient and developing foetus or child.

The clinician is reminded of the detailed advice which is available through Pregnancy Drug Information Centres which can be contacted to discuss specific recommendations based on particulars of a specific case. Clinicians are also advised to discuss with patients of childbearing age being treated for glaucoma the alternatives such as glaucoma surgery which can be initiated prior to becoming pregnant to avert concurrent medication use. If medications are used during pregnancy, the expectant mother should be informed to expect to have tests at regular intervals to monitor for drug-related adverse effects, and patients should be taught and reminded of punctal occlusion to minimise systemic absorption. ▲

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# Improving survival in uveal melanoma

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WITH ADVANCES in melanoma research in recent years, for the first time survival rates are skyrocketing. However, these promises of hope are not being seen in a rare form of melanoma, known as uveal melanoma, and researchers are desperately trying to uncover new ways to treat this disease.

Uveal melanoma is the most common form of cancer originating from the eye in adults. While there are effective treatments for early uveal melanoma, options are limited for patients who develop advanced (metastatic) disease.

It is a very different disease from skin melanoma; it is caused by different gene mutations, is not linked to sun exposure and responds differently to treatment. Unlike skin melanoma, the survival rate of patients with uveal melanoma, which is a form of ocular melanoma, has not changed over the past 35 years. It is an understudied cancer and further research is essential if survival rates are going to change.

Dr Matteo Carlino, medical oncologist at Melanoma Institute Australia (MIA) says the drugs that are proving effective in skin melanoma have only minimal activity in uveal melanoma. In skin melanoma, response rates to anti-PD1 treatment are greater than 40 per cent but when these same immunotherapy treatments are given to people with uveal melanoma, response rates are only three to four per cent.

‘A lot of doctors treat uveal melanoma with drugs usually used for advanced skin melanoma, mainly because of a lack of other options rather than evidence of success,’ Dr Carlino said. ‘We don’t know why, but there is a very small percentage of people with uveal

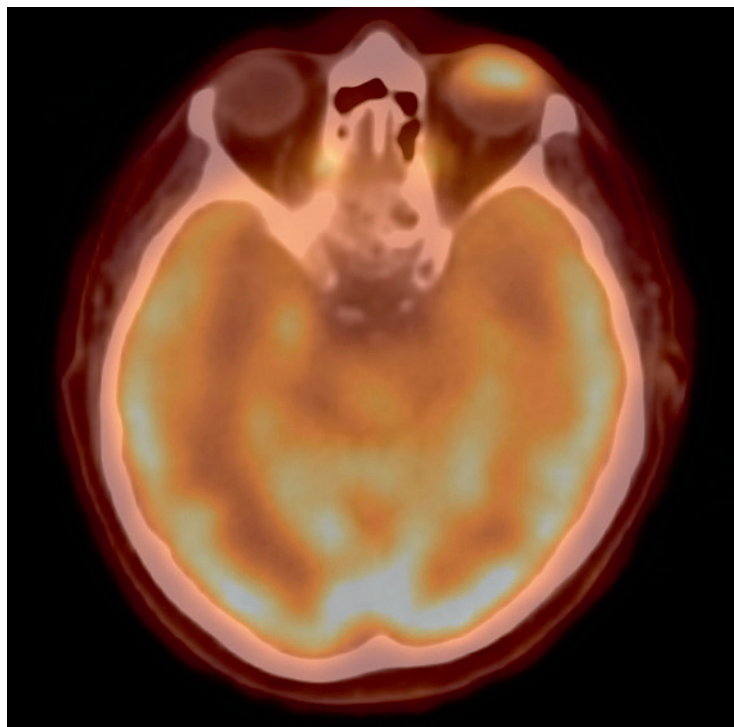
melanoma who do respond to those treatments, and we need to find out why.’

## Different disease

In addition to responding differently to treatment, uveal melanoma has different genetic mutations from those of skin melanoma. BRAF and NRAS gene mutations, which are commonly seen in skin melanoma, are not seen in uveal melanoma. However, uveal melanoma is commonly associated with mutations in two genes (GNAQ and GNA11), offering hope that specific drugs can be developed to target these mutations.

## Treating uveal melanoma

Following local treatment to the eye with surgery or radiotherapy, about one half of all people with uveal melanoma will suffer a recurrence of the disease.



▲ Figure 1. Head: PET-CT showing the primary melanoma (uveal) in the left eye Image: Lisa Tarlinton, St Vincent’s Clinic Medical Imaging and Nuclear Medicine

There is currently no standard treatment for advanced uveal melanoma and so there is variable care between doctors. Some oncologists treat patients with advanced uveal melanoma in the same way as a patient with advanced skin melanoma. In selected patients, treatment can be directed at the liver, the most common site of recurrence.

‘Ninety per cent of people with uveal melanoma will have liver metastases as their site of recurrence; often it is their only site of recurrence,’ Dr Carlino explained.

## Uveal melanoma clinical trials

‘More research and trials are desperately needed to elevate survival rates, as has been the case with skin melanoma,’ Dr Carlino said.

**Continued page 6**



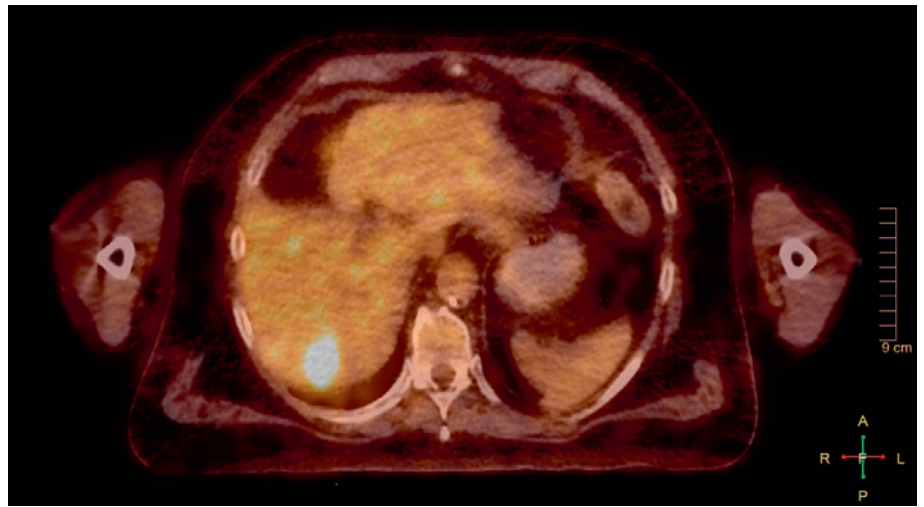
## Uveal melanoma

### From page 5

To address this need in patients with uveal melanoma, MIA is running two new clinical trials investigating novel treatments for patients with metastatic uveal melanoma.

The Phase 1 study of a new targeted treatment for uveal melanoma, led by Dr Carlino at Westmead Hospital in affiliation with MIA, is currently recruiting. The trial will test the safety, tolerability and efficacy of LXS196, an oral protein kinase C inhibitor, in patients with metastatic uveal melanoma. This drug has been specifically developed to target uveal melanoma mutations in the GNAQ and GNA11 genes.

There will also be a Phase 3 trial commencing at MIA this year to



▲ Figure 2. Liver: PET-CT showing liver metastases in a patient with uveal melanoma  
Image: Lisa Tarlinton, St Vincent's Clinic Medical Imaging and Nuclear Medicine

compare a new immunotherapy (called Immunocore) with chemotherapy (dacarbazine) in patients who have

not received any other treatments. This is being investigated by Associate Professor Alex Guminski at MIA.

## A PATIENT'S VIEW: participating with Stage 4 melanoma in



▲ Guy Winship

BEING DIAGNOSED with uveal melanoma at the age of 52 was not something Guy Winship could have imagined happening to him. Now facing a Stage 4 melanoma diagnosis, Guy's only hope of spending more time with his family is to participate in a new clinical trial at Melanoma Institute Australia.

'This whole experience has been somewhat surreal. I didn't even know there was such a thing as eye cancer; I'd never heard of it,' Guy said.

In September 2013, Guy presented to his GP with blurred vision in his left eye that had persisted, without pain, for a week. His GP thought his retina had detached and he was sent to the Sydney Eye Hospital. At the hospital, Guy was told that there was a mass behind his eye. He was referred to ophthalmologist Dr Michael Giblin and underwent enucleation under a local anaesthetic.

'I regret having a local anaesthetic. Although my physical recovery time was minimal, I've been emotionally scarred from the experience,' Guy said jokingly.

Living with one eye has been an adjustment but he's learned to adapt to the changes well, and has a good sense of humour about it.

'My car has scratches all over it,' he said. 'In the beginning, I found it really hard to pour water into a glass. It's such a simple task but I'd end up with water everywhere. But you learn to adapt. I move my head more now to get more information in and I've learned to touch the top of the glass when pouring water.'

A year after his enucleation, Guy

received from his oncologist, Professor Alex Guminski, the news that he had been dreading. The melanoma had metastasised. It presented in his liver, which is typical of uveal melanoma, and in his bones and joints.

'I was told to get my affairs in order and he gave me 12 months to live,' Guy recalled. 'Going home and telling my kids, then 15 and 11 years old, was incredibly hard. It's been hard on them and my wife too. Facing your own mortality is a very sobering experience. I'm a very positive person but you definitely have your dark periods.'

Guy has undergone a number of treatments to buy him time, including transarterial chemotherapy where a catheter delivers chemotherapy directly into the artery that feeds the liver. When this failed, his oncologist treated him with an immunotherapy, ipilimumab (Yervoy). After suffering severe side-effects, like losing the use of his pituitary and thyroid glands, he was put on another immunotherapy, pembrolizumab (Keytruda). Again, severe side-effects, this time pneumonitis, caused Guy to come off the treatment.

'Tumours in my liver over the past



In addition to these clinical trials, laboratory studies to understand the response to these and other novel treatments for uveal melanoma will occur in Professor Helen Rizos's MIA-affiliated research group at Macquarie University.

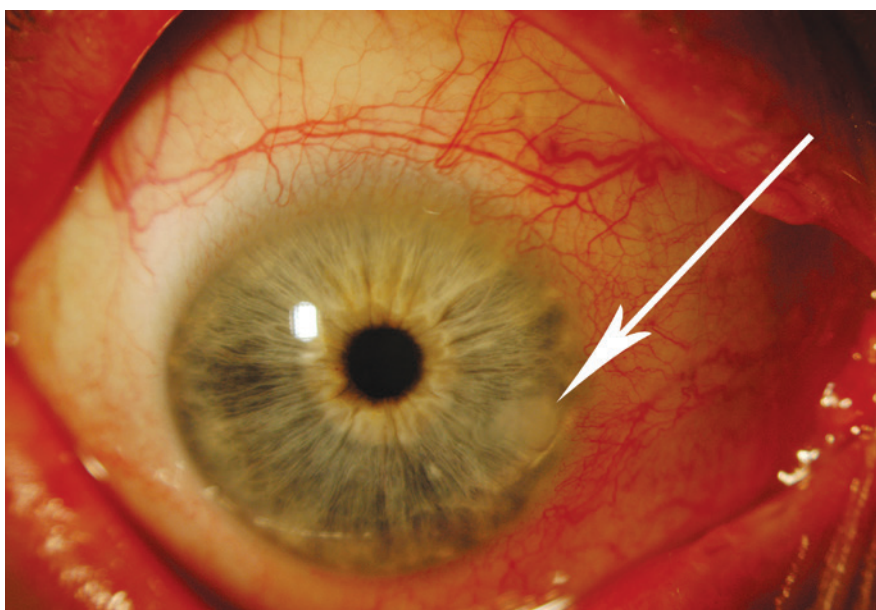
'The Phase 1 study will be the first time MIA has run a clinical trial in uveal melanoma and I'm excited to be part of it. This is a world-wide trend; uveal melanoma has historically been under-represented in clinical trials but I think the tide is finally turning,' Dr Carlino said.

Patients interested in participating in a clinical trial should have their oncologist contact Dr Carlino or Professor Guminski as strict eligibility criteria apply. ▲

## Clinical quiz

**Associate Professor  
Mark Roth**

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▲ Figure 1. Right anterior eye of 68-year-old Caucasian male. Image: Associate Professor Mark Roth

## MIA's Phase 1 trial

year have been largely stable, thanks to the immunotherapies, although there has been a spread to the lungs and peritoneum but I can't continue on the treatments because of the side-effects,' Guy said.

Running out of options, Guy's oncologist suggested that he participate in a new clinical trial being run at Melanoma Institute Australia. Guy has been on the Phase 1 trial testing the compound LXS196 since November. This is a new therapy that specifically targets gene mutations found in uveal melanoma.

It is still early days but Guy's tumours have stabilised. He does have a number of side-effects again, most notably a rash all over his body, but it is being managed.

'This research is a chance for me to live, to survive. It's as simple and straightforward as that. This is the only realistic option I have of beating this cancer and surviving longer so I'll do whatever it takes,' Guy said.

'It would be great if I could see my kids finish high-school. That would be really nice. I've got five years to go. If I can hang on, that'd be great.' ▲

A 68-YEAR-OLD Caucasian male presents, reporting symptoms of a gritty sensation, watery discharge and increasing photophobia in his right eye. Although he says he has been symptomatic for only the past seven months, the patient's wife reports that the eye has been red for 10 years.

There is conjunctival injection; however, it is not global but restricted to the nasal aspect. The key feature is a raised, yellow-white corneal lesion in the periphery at four o'clock. (Figure 1, arrow)

The shape of the raised lesion is oval and the approximate size is 1.5 mm x 2.0 mm. There is no significant staining of the lesion but there are signs of long-standing dry eye and ocular surface disease.

**What is your diagnosis? What is your management?**

**Answer: page 21**

# New NSAIDs take us into the

Associate Professors Mark Roth and  
non-steroidal anti-inflammatory



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**Roth:** Dr Lee, thanks for taking your time to cover this important topic that affects all our patients undergoing cataract surgery. Most optometrists have never found a great use for non-steroidal anti-inflammatory drugs (NSAIDs) in primary eye care but they are important in surgical eye care.

**Lee:** In Australia, we have had access to ketorolac 0.5% (Acular, Allergan) and diclofenac 0.1% (Voltaren Ophtha, Novartis Ophthalmics) for many years. I agree they have not been used in primary eye care widely and are contraindicated in cases of epithelial defects and keratitis or ulceration due to the risks of corneal melting. They may have a role as steroid-sparing agents in allergic conjunctivitis and episcleritis. Their most useful role is in the prevention of intra-operative miosis, reduction of post-operative inflammation and pain, and management of cystoid macular oedema (CME).

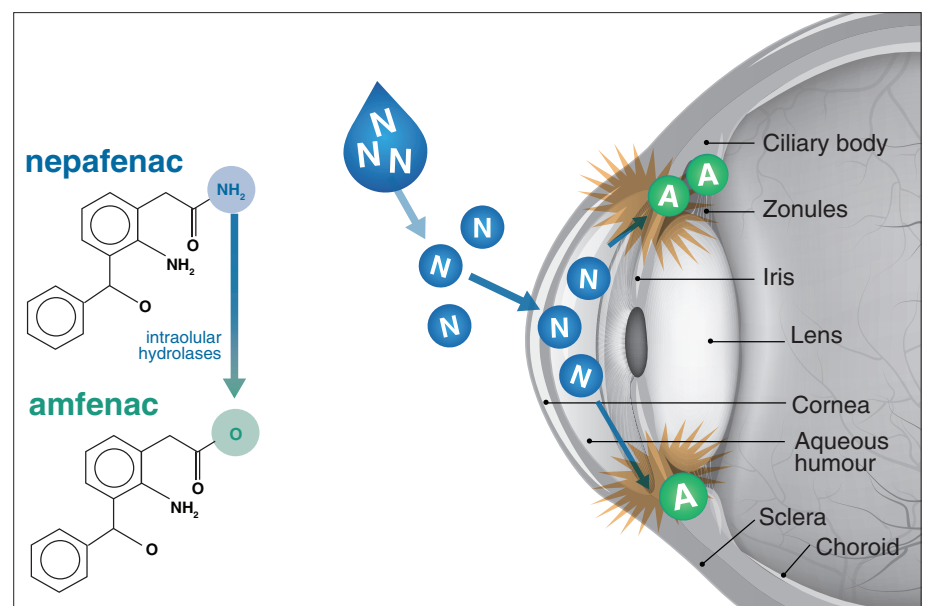
**Roth:** NSAIDs are never a true substitute for steroids when topical drugs are required to treat inflammation; in fact they don't

directly reduce inflammation but rather inhibit an enzyme along the synthetic pathway to the production of prostaglandins. What is the mechanism that makes them so potentially effective for surgical eye care, such as the prevention of CME?

**Lee:** NSAIDs block prostaglandin synthesis by inhibiting the cyclo-oxygenase (COX) pathway. Corticosteroids are more potent as they block prostaglandin synthesis by inhibiting both the COX and lipoxygenase (LOX) pathways of inflammation. By blocking prostaglandin synthesis, the inflammatory cascade is reduced, that is, leukocyte migration, vasodilatation, pain and vascular permeability. The topical NSAIDs have been proposed to have a synergistic effect with topical corticosteroids and this has been useful in treatment of CME.

**Roth:** I found the article by Kim et al in *Ophthalmology* 2015<sup>1</sup> to be a great review of NSAIDs and cataract surgery, but it left me wondering if there really is consensus for prophylactic use to reduce CME. Many people are debating the important points from this key review. What are your views?

**Lee:** The Kim et al article was a report from the American Academy of Ophthalmology. It was a review and meta-analysis of the literature on topical NSAIDs. The main messages I got from that study was the lack of Level 1 evidence for the long-term benefit of NSAID therapy in preventing vision loss from CME at three months or more after cataract surgery, but it did hasten visual recovery in the first three months. Therefore, it is more useful in the early post-operative period but doesn't provide superior outcomes. There is good collective evidence



▲ Figure 1. Inhibition of PG synthesis. Nepafenac inhibits all prostanoid production by the iris/ciliary body excised 60 minutes following dosing.

# future

Graham Lee discuss the next generation in agents, nepafenac 0.3% suspension (Ilevro).

that topical NSAIDs used three days prior to surgery reduces CME. This is not necessarily important for routine cataract patients; however, for those at greater risk of CME, such as a previous history of CME or an epiretinal membrane, this may be useful.

**Roth:** Is the evidence stronger for a combination of NSAIDs and topical steroid?

**Lee:** The Kim et al article reported the evidence for synergistic action of NSAIDs and corticosteroid is not supported by the literature; however, it is common practice to use both in conjunction and although the Level 1 evidence is lacking, clinically there appears to be an advantage in concurrent use.

**Roth:** Does the whole paradigm change when we split diabetic from non-diabetic patients?

**Lee:** For straightforward cases, topical NSAIDs are not necessary, although

some of my colleagues routinely use them in conjunction with topical corticosteroids. I consider their use for at-risk patients.

**Roth:** Glaucoma and cataract surgery is a huge topic on its own, but specifically: how do you manage glaucoma patients prior to cataract surgery if they are on a prostaglandin analogue for primary open angle glaucoma (POAG)? Exogenous prostaglandin analogue use has been linked to CME.

**Lee:** I tend to stop the prostaglandin analogue one day post cataract surgery to reduce the risk of CME. This gives patients a trial off the medication to see how much pressure-lowering effect was obtained from the cataract surgery and/or stent insertion. If needed, I will restart the prostaglandin analogue at three weeks post cataract surgery. This practice varies among different surgeons. Some cease a week prior to surgery and don't restart until one month post-surgery as required. Others



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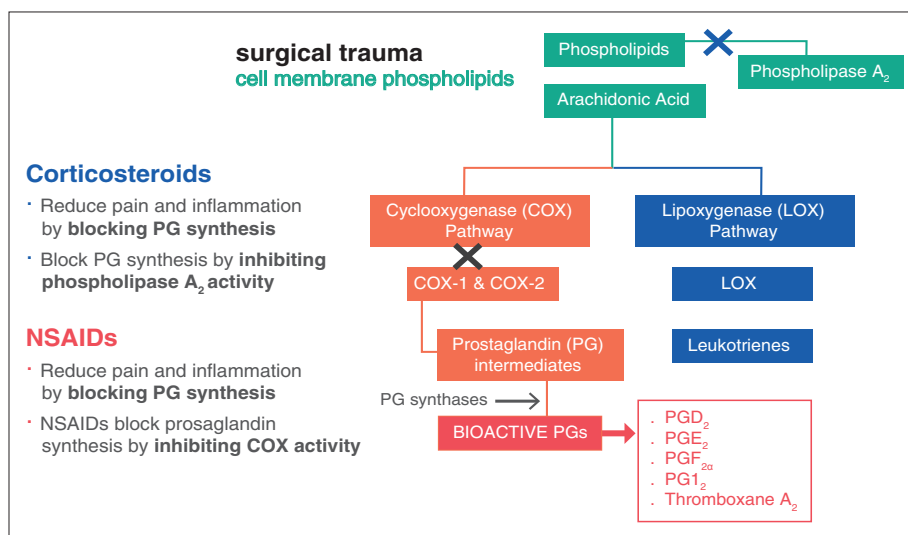
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continue the prostaglandin analogues as usual, without a period of cessation.

**Roth:** Nepafenac 0.3% (Ilevro, Novartis Ophthalmics) is the new non-steroidal anti-inflammatory agent for cataract surgery. What are its main features that differentiate it from the other NSAIDs available?

**Lee:** The advantages of nepafenac 0.3% suspension is that it is once-daily as opposed to ketorolac 0.5%, dosed at four times a day. It stings much less than the other NSAIDs drops. Ilevro uses pro-drug technology. It enters the cornea as nepafenac, and hydrolysis in various ocular tissues converts the molecule into amfenac, the more potent form of the molecule. This provides maximal efficacy at target sites including the iris and ciliary body.



▲ Figure 2. Inflammation cascade

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## New NSAIDs

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**Roth:** As a suspension there is greater contact time with the ocular surface. Is that how once-a-day dosing is achieved or are there other mechanisms in play?

**Lee:** The 0.3% suspension provides a higher concentration of active molecule (compared to the 0.1% solution; not available in Australia), reduced particle size, increasing surface area for dissolution and other additives including carboxymethylcellulose sodium (milling agent) and guar (retention agent).

**Roth:** Apart from a hypersensitivity to NSAIDs, including asthma, this drug is pretty well tolerated, including less stinging. Are there any other significant precautions?

**Lee:** As mentioned earlier, in cases of epithelial defects, keratitis or ulceration, there are risks of corneal melting. Diabetic patients, patients with rheumatoid arthritis and other collagen vascular diseases, rosacea, chemical or thermal burns, neuropathic corneas, graft vs host disease, dry eye, herpetic disease either zoster or simplex and a history of LASIK flaps are at higher risk of corneal and scleral complications. Any condition where the ocular surface is compromised is potentially at risk. It also should be avoided in patients with a bleeding tendency, pregnancy, breast-feeding, children and adolescents under 18 years, and not used with soft contact lenses.

**Roth:** Does hypersensitivity or allergy to oral NSAIDs necessarily translate to topical NSAIDs?

**Lee:** I would avoid due to the risk for potential systemic absorption.

**Roth:** Less stinging and less frequent dosing logically seem better for compliance, but has that actually been your experience? It's a big challenge.

**Lee:** Once-daily dosing is definitely better for compliance and the reduced stinging is also important. Patients have reported more blurring with initial instillation as it is yellow, opaque and thicker than the usual

NSAID	Chemical class	Formulation	Dosing	Lipophilic	Prodrug
Bromfenac <sup>1</sup>	Phenylacetic acid	0.09% solution	2x daily	Yes	No
Diclofenac <sup>2</sup>	Phenylacetic acid	0.1% solution	4x daily	No	No
Ketorolac <sup>3</sup>	Phenyllokanic acid	0.5% solution	4x daily	No	No
Nepafenac <sup>4</sup>	Arylacetic acid	0.1% or 0.3% suspension	3x daily (0.1%) 1x daily (0.3%)	Yes	Yes

1. Xibrom Summary of Product Characteristics, ISTA Pharmaceuticals 2006  
 2. Voltaren Ophthalmic Summary of Product Characteristics, Novartis Ophthalmics 2003  
 3. ACULAR Summary of Product Characteristics, Allergan 2002  
 4. Nevenac Summary of Product Characteristics, Alcon 2016

▲ Table 1. Overview of NSAID treatments

eye-drop solutions. If patients have reduced vision from CME, they will be motivated to take medications to hasten their recovery.

**Roth:** I think optometrists should play a greater role in helping with education and compliance pre- and post-surgically. What's your opinion?

**Lee:** Patients find access to their optometrist easier and often the first port of call, particularly if their ophthalmologist is not available. Optometrists need to be familiar with the appearance of the eye post-surgery to detect what is normal recovery versus a complication. If they know the how and why of post-operative management, they can reinforce what the ophthalmologist has instructed and overall this will be of benefit to patient outcomes.

**Roth:** My first two patients using this drug all came back with the same complaint: 'It's hard to get the drop out of the bottle.' I had no idea, so it was difficult for me to discuss the issue with them. I had to go away and try the bottle for myself. I must admit, it's more difficult to get the drop out compared to other topicals. If patients are informed beforehand, it's less of a surprise. Your views?

**Lee:** The drop is a 0.3% suspension so will be more viscous and harder to squeeze out of the bottle. Shaking the bottle to mix the contents thoroughly may be helpful before opening. It should be stored under 25 degrees, but if it is refrigerated, it may be more difficult to squeeze the bottle. Patients with weakness of their fingers, for example, those who have arthritis or carpal tunnel syndrome, may need to

have someone administer the drops for them.

**Roth:** Ilevro is approved and indicated for ocular pain and inflammation. The recommended regimen is one drop the day before cataract surgery, two drops on the day of surgery and once daily for 14 days, for a total of 17 drops. What would be your suggested regimen for cataract surgery including steroids?

**Lee:** For my routine cataract patients, the cost-benefit ratio for using NSAIDs is not warranted. For medium-risk patients, I would use it once a day from day one post-operation in conjunction with the topical corticosteroids and antibiotics for four weeks.

**Roth:** Are there circumstances in which you would vary that regimen? For example, a patient with recurrent uveitis or perhaps CME in the first cataract operated eye?

**Lee:** For higher risk patients, I would consider commencing three days pre-operatively and continue up to eight weeks post-operatively, depending on evidence of CME on OCT in the first eye. Of course, it's important to note that the use of topical NSAIDs for prevention or treatment of cystoid macular oedema is an off-label indication, despite their widespread use.

**Roth:** I'm going to take my eye physician hat off and put my well-informed, anxious patient hat on. Isn't all cataract surgery a risk factor for CME? If it were my eye having cataract surgery, I would be keen on the NSAIDs before, during and after surgery (LOL!).

**Lee:** For routine cataract surgery, I do not feel the risk/cost-benefit ratio is in favour of the use of topical NSAIDs. However, if there are no contraindications as outlined previously and the patient was concerned regarding CME, it would be reasonable to use NSAIDs.

**Roth:** We have focused on NSAIDs and the prevention of CME but if a patient post-operatively developed CME, then would an NSAID become an integral part of the treatment regimen together with corticosteroids?

**Lee:** Management of CME is whole topic in itself. It is most important to identify the cause and address the underlying factors. For example, there may be a vitreous strand causing retinal traction, an epiretinal membrane, prostaglandin analogue use and so on. Once causes of the CME are resolved, my pharmacological management of visually-significant CME is commencement of topical steroid such as prednisolone acetate 1% four times a day and an NSAID such as nepafenac 0.3% daily or ketorolac 0.5% four times a day. If after two months there is limited response, intravitreal triamcinolone (40 mg/ml) can be useful. Oral acetazolamide has also been used; however, side-effects limit its use.

**Roth:** Is a drop-less approach to cataract surgery with intracameral injection of antibiotic and anti-inflammatory the future?

**Lee:** 'No drops' post surgery would be a revolution. Whether it is a depot of medication variously intracameral, via a trabecular stent, intracorneal, subconjunctival, subtenons, punctal plug, forniceal and so on, it will take out the compliance factor. However, there is this issue: if the patient has an adverse reaction, a depot is difficult to remove. The Holy Grail will be maximally effective surgery, with minimal invasion resulting in no significant inflammation or risk of infection. Now that would be a grand future. ▲

1. Kim SJ, Schoenberger SD, Thorne JE, Ehlers JP, Yeh S, Bakri SJ. Topical nonsteroidal anti-inflammatory drugs and cataract surgery: A report by the American Academy of Ophthalmology. *Ophthalmology* 2015; 122: 11: 2159-2168. doi: 10.1016/j.ophtha.2015.05.014.

# Cataract in older Australians

## An investigation into falls and depressive symptoms

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CATARACT is a primary cause of vision impairment in older Australians.<sup>1</sup> An estimated one-third of the population aged 65 years and older has cataract-related vision loss, representing approximately 1.2 million people.<sup>2</sup> Cataract surgery is one of the most cost-effective health interventions<sup>3</sup> but patients with age-related cataract can wait up to three years for first eye surgery, comprising two years waiting for outpatient ophthalmology assessment and a further 12 months on the surgical waiting list.<sup>4</sup>

The consequences of waiting for surgery encompass physical, mental and social domains, compromising an older person's quality of life and limiting active ageing. Studies from the United Kingdom and Canada show that those who undergo cataract surgery sooner (six weeks to six months after referral) experience better vision<sup>5</sup> and quality of life,<sup>6,7</sup> improved physical activity levels,<sup>6</sup> and reduced levels of anxiety and depression<sup>6,8</sup> than

patients who wait longer than six months.

Patients receiving expedited first eye cataract surgery also experience fewer falls and fractures in the 12 months after surgery than those facing a routine waiting period of about 12 months.<sup>6</sup> However, data describing the impact of protracted waiting for surgery on older Australians with cataract have until now been scarce, hindering policy change to support timely care.

### The FOCUS study

The FOCUS study<sup>9</sup> (Falls in Older People with Cataract: A Longitudinal Evaluation of Impact and Risk) investigated fall risk in older adults undergoing cataract surgery in eight Australian public hospitals across Sydney, Melbourne and Perth. It is the first longitudinal evaluation of fall risk in older Australians with bilateral cataract, and it followed more than 320 adults aged 65 years and older for up to two years after recommendation for first eye surgery.

By examining falls in a real-world clinical setting, the FOCUS study makes an important contribution to understanding cataract-associated fall risk and injury. In addition, the study highlights the personal costs of cataract-related vision impairment, exploring the impact of cataract on psychological well being, physical function, mobility and quality of life.

### Fall risk and cataract

We found that one in three older adults with cataract experienced a fall while waiting for first eye cataract surgery.<sup>10</sup> Almost one half of these falls resulted

# Cataract in older Australians

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in an injury, including 15 head injuries and two fractures (Figures 1 and 2). Over a median pre-surgical observation time of 176 days (about five and a half months), the annual incidence of falls in our cohort was 1.2. This is two to three times higher than fall rates arising from studies of the general older community-dwelling population. An annual incidence of 0.4–0.6 falls per person in those aged ≥ 65 years in the United States has been recently reported.<sup>11</sup>

Compared to non-fallers, those who fell while waiting for surgery had a greater number of comorbidities, took more medications, had a lower quality of life and a higher fear of falling. Adults who experienced a fall also demonstrated poorer lower limb function on entry into the study than those who did not fall.

More frequent falls were evident in those who undertook greater walking activity while waiting for cataract surgery, and in those who had a history of falling in the previous 12 months. Interestingly, we found no link between

vision status (including high contrast visual acuity and contrast sensitivity) and fall risk. However, more than 70 per cent of adults had no to mild vision impairment (Snellen visual acuity better than 6/18 in the better eye) and it is feasible that a floor effect in visual acuity may explain its lack of association with falls in this patient group.

### Cataract and psychological well-being

Older people with vision loss are susceptible to depression;<sup>12,13</sup> however, few studies have evaluated rates and predictors of depression in those with age-related cataract. The FOCUS study demonstrated a high (28.6 per cent) prevalence of depressive symptoms in older Australians with cataract on surgical waiting lists.<sup>14</sup> This is about three times greater than rates of depressive symptoms found in recent studies of general community-dwelling older people.<sup>15</sup> We found a significant association between increasing patient-reported visual disability (assessed by the Catquest-9SF instrument) and depressive symptoms, and a 10 per cent greater likelihood of depressive symptoms for each additional comorbidity.

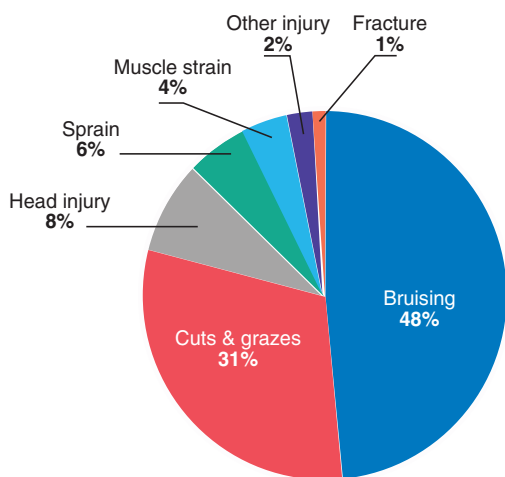
Our data predicted the onset of depressive symptoms at a Snellen visual acuity of 6/12 among older

adults awaiting cataract surgery in Australia (Figure 3 and 4). Previous studies exploring associations between ophthalmic disorders and depression have focused on the permanently vision impaired or blind. We have uniquely illustrated the presence of depressive symptoms at even modest levels of vision loss, suggesting that the psychological impact of cataract may manifest in its earliest stages.

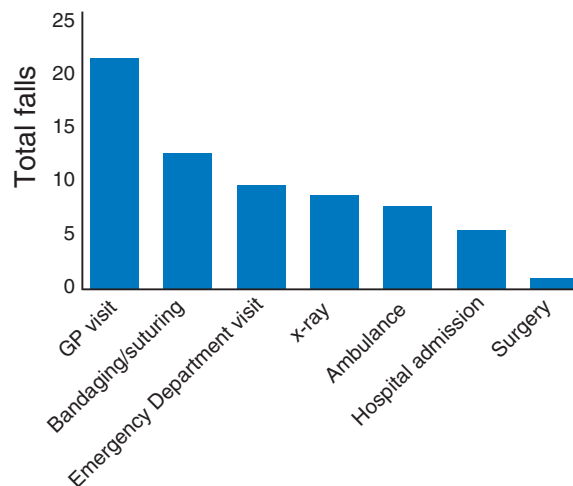
### Recommendations for policy and practice

Waiting time for public patients requiring first eye cataract surgery in Australia remains significant for many, and the contribution of surgical delays to fall risk and psychological well-being should not be overlooked. With a projected 3.5 per cent annual increase to the older Australian population anticipated in the coming decade,<sup>16</sup> the burden of age-related eye disease will continue to grow, bringing key challenges to the health system in terms of increased demand for health services and rising health costs.<sup>17</sup> In this context, a new policy direction is required to improve the efficiency of cataract surgery pathways and avert the costly impact of visual disability both for the health system and for older adults with cataract.

Understanding who is more likely to fall while waiting for cataract

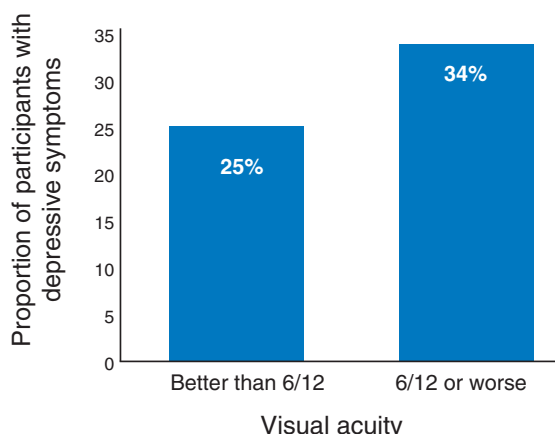


▲ Figure 1. Injuries sustained in falls (n = 267) experienced by 329 patients 65 years and older with bilateral cataract while waiting for first eye cataract surgery (median time of observation = 176 days [range 2-730 days])

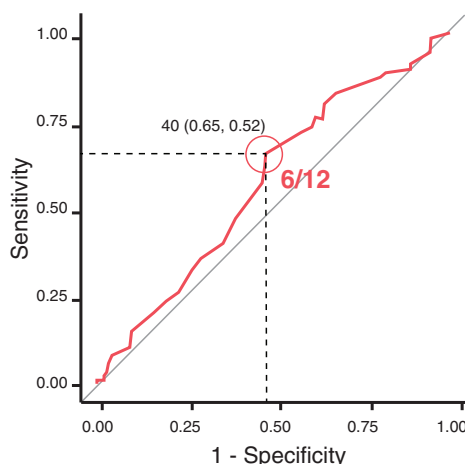


▲ Figure 2. Treatment received for injuries sustained in falls in Figure 1, (n = 267) experienced by 329 patients 65 years and older with bilateral cataract while waiting for first eye cataract surgery (median time of observation = 176 days [range 2-730 days])





▲ Figure 3. Thirty-four per cent of participants with binocular visual acuity of 6/12 or worse had depressive symptoms, compared to 25 per cent of those with visual acuity better than 6/12



▲ Figure 4. ROC curve analysis illustrates an optimal visual acuity cut-point of 40 ETDRS letters (6/12 Snellen acuity) for the onset of depressive symptoms (sensitivity 0.65, specificity 0.52)

surgery, and why they are likely to fall, will facilitate early recognition and management of those at highest risk and may reduce the negative physical and psychological outcomes associated with falls and fall injury. Our findings reinforce the need for clinicians to consider non-visual factors, including walking activity and falls history, when assessing fall risk during the surgical waiting period.

Recognition of the susceptibility of older people with cataract to depression, even in the earliest stages of vision impairment, is important. Efficient referral processes, more rapid surgical management and increased awareness of depressive signs while waiting for surgery may minimise the negative psychological effects of cataract-related vision loss in this already vulnerable population. ▲

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# Subconjunctival cilium following phacoemulsification cataract surgery

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COMPLICATIONS associated with phacoemulsification cataract surgery have been well documented.

Books dedicated to the subject highlight issues with capsulorrhexis execution, endothelial damage from phacoemulsification, intraocular lens implant malpositioning and so on.<sup>1,2</sup> Sections specific to wound construction and closure discuss the advantages of different sutureless incision techniques including clear cornea and scleral tunnelling.

One aspect not addressed is the rare possibility of a foreign body entering the eye through the incision which, by definition, is not closed with sutures. Our case highlights one such situation where the retained foreign body happened to be the patient's own cilium or eyelash.

Complications involving retained cilia occur very infrequently after cataract surgery. Only a handful of cases has been reported involving cilia found in the anterior chamber of patients following phacoemulsification cataract surgery.<sup>3-6</sup> These cilia can be completely inert prompting no treatment or cause severe endophthalmitis requiring immediate surgical removal.

The unique aspect of our patient's retained cilium was its location. In our case, the cilium was positioned under the temporal conjunctiva in the potential space between the episclera and Tenon's capsule. As such, we report the first case detailing diagnosis and excision of a subconjunctival cilium after phacoemulsification cataract surgery using the scleral tunnelling incision technique and conjunctival peritomy.

## CASE REPORT

A 77-year-old white female was referred back by her comanaging optometrist to the eye clinic for a conjunctival foreign body removal. The object was identified by her optometrist in the temporal conjunctiva of her left eye. The patient had complained that her left eye felt dry, irritated and gritty. She reported that the discomfort in her left eye started gradually about one day after she had undergone phacoemulsification cataract surgery in the same eye and it continued to bother her for the following two weeks. She denied any redness, pain, purulent discharge, photophobia or epiphora.

The patient had previously been diagnosed by the referring optometrist with nuclear sclerosis in both eyes and had recently undergone phacoemulsification with intraocular lens implant in both eyes. The left eye was done first and the right eye was done one week later. When she presented to her comanaging optometrist, it had been two weeks since the operation on her left eye. No complications were noted during either procedure or during any of the previous follow-up visits. When she was asked directly about any accidental rubbing of the left eye, the patient emphasised that she had been wearing the prescribed eye shield over her left eye while sleeping for one week following surgery and had not rubbed

the eye during the day when the shield was not worn.

The patient presented to our office for consultation about one month after surgery was performed in the left eye. Our patient's ocular medications included prednisone acetate 1%, instilled three times daily in the right eye and prednisone acetate 1%, instilled once daily in the left eye. There was no history of previous eye injuries or other eye surgeries. The family history was negative for any pertinent ocular conditions.

Systemically, the patient had previously been diagnosed with hepatitis B, depression, anxiety, rheumatoid arthritis, headaches, esophageal reflux, hyperlipidaemia and osteoarthritis of her hips, back and knees. Current oral medications include omeprazole 20 mg twice daily, gabapentin 600 mg three times a day, trazodone 50 mg once in the evening, citalopram 50 mg once in the evening, lovastatin 20 mg once daily, sumatriptan 100mg as needed, lorazepam 0.5 mg as needed and acetaminophen 1 gram as needed. She is allergic to hydrocodone, macrolide antibiotics and sulfa drugs.

Entering uncorrected distant acuities were 20/20- OD and 20/25 OS. Extraocular motilities were full for both eyes. Pupils were equal, round and reactive to light. Confrontation fields were full with no restrictions in both eyes. The anterior segment examination of the right eye revealed trace cells in the anterior chamber, due to the recent cataract surgery. The cornea, conjunctiva, iris, lids and lashes were all unremarkable in the right eye. The surgical incision was stable and Seidel's sign was negative. The intraocular lens implant was stable, centred and clear.

In the left eye, all findings were unremarkable except the presence of a slightly curved, tapered, cylindrical,

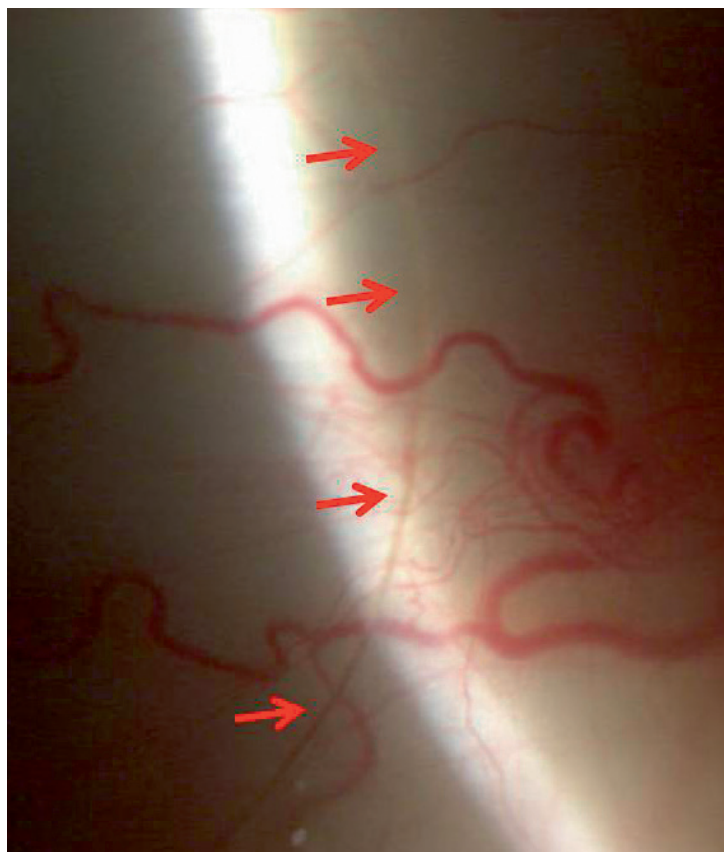
## A rare complication results when a scleral tunnelling technique provides an entry point for an eyelash

semi-translucent foreign body which was oriented vertically, in the temporal conjunctiva approximately 10 mm from the limbus (Figure 1). The cilia-like foreign body was measured to be 5.0 mm in length and less than 1.0 mm in diameter. Using optical section illumination, it was determined that the foreign body was located between Tenon's capsule and the episclera. Intraocular pressures were 15 mmHg OD and 17 mmHg OS measured with the iCare tonometer. A dilated fundus examination was not performed.

It was decided to excise the foreign body from beneath the conjunctiva due to the patient's ocular irritation symptoms. Consent was obtained and the patient was sterilely prepped for removal of the foreign body. Lidocaine hydrochloride ophthalmic gel 3.5% was applied to the temporal conjunctiva of the left eye and allowed to stay in contact with the site for 60 seconds.

The surgical procedure was performed behind the slitlamp. Westcott tenotomy surgical scissors were used to make a small 0.5 mm incision above the upper end of the foreign body. Using jeweller's forceps, the tip of the foreign body was engaged and it was removed through the small incision. The cilia was not attached to any conjunctival tissue and slid easily through the tunnel that the conjunctival tissue had formed around it. The specimen was placed in a sterile container with 10 percent formalin and sent to the pathology lab.

Bacitracin ophthalmic ointment was applied to the patient's left eye. The patient was prescribed the bacitracin ointment for use in the left eye twice daily for one week to provide prophylactic protection against infection of the incision site. The pathology report revealed that the specimen was a fine hair with some pigmentation (Figure 2).



▲ Figure 1. Foreign body under the temporal conjunctiva of the patient's left eye

### Discussion

The mechanism by which the cilium entered the subconjunctival space is still unknown but we suspect the cataract surgical incision site may have provided a point of entry. The scleral tunnelling technique was used in the phacoemulsification surgery in both of the patient's eyes. To gain entry into the globe using this particular technique, a conjunctival peritomy needs to be performed. A 3 mm wide conjunctival flap was made using Westcott tenotomy surgical scissors 1 mm posterior to the limbus at the 12 o'clock position in order to expose the sclera. A partial thickness incision was made into the sclera using a crescent knife and the

sclera and peripheral cornea were dissected using the same instrument. A keratome was then used to enter the anterior chamber via the dissection channel. This forms a self-sealing incision. Following the surgery, the conjunctival flap was laid back down and allowed to heal without sutures.

Nearly all of these conjunctival flaps are sealed when patients present for their one-week post-operative examination. As a result, we believe that an eyelash entered under the conjunctival flap soon after the cataract surgery. It then must have migrated through the potential space between



# Subconjunctival cilium

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Tenon's capsule and the episclera to its position under the temporal conjunctiva.

To our knowledge, this is only the fourth case of subconjunctival cilia entrapment in a patient with history of intraocular surgery and only the



▲ Figure 2. Histopathology of cilia specimen; note the interrupted medullary pigmentation pattern

second following a conjunctival peritomy reported in the literature.<sup>7-9</sup> The first case occurred in a patient after he had undergone surgery to repair a retinal detachment, while ours was after scleral tunnel cataract surgery. In a standard retinal detachment repair with peritomy, the entire conjunctiva is detached for 360 degrees. Our standard scleral tunnel cataract surgery peritomy is only 3 mm in width. Our case indicates that a foreign body can enter the subconjunctival space through a very small breach in the conjunctiva.

Subconjunctival cilia not entering through surgical incisions have been reported as early as 1921; however, the point of entry in that particular case was caused by another foreign body lacerating the bulbar conjunctiva.<sup>10</sup> In another case, the eyelash entered after a subtenon injection was administered.<sup>11</sup>

Cicatricial conditions including ocular pemphigoid and symblepharon have also resulted in entrapment of lashes in the bulbar conjunctiva.<sup>9</sup> Generally,

removal is the treatment of choice regardless of cause but in cases where the patient was asymptomatic, no treatment was initiated.<sup>12</sup>

Our case highlights the fact that different incision techniques present unique complications. In the cases where clear corneal incision technique was used, cilia were retained in the anterior chamber.<sup>13,14</sup> Because clear corneal incisions involve entering the anterior chamber via a corneal incision anterior to the limbus, there is little to no risk for a lash to become entrapped under the conjunctiva. When a scleral tunnel technique is used, it is more

difficult for the eyelash to work its way into the anterior chamber but the peritomy may provide an entry point for a cilium or other foreign body to become trapped under the conjunctiva.

Our patient's symptoms were mild but scleral ulceration and granuloma formation have occurred in cases of conjunctival entrapped cilia.<sup>11,15</sup> It is important to do a thorough anterior segment examination following cataract surgery, not only of the incision site and anterior chamber, but of the entire globe. Knowledge of the surgical technique used may prove helpful when performing the post-operative examination. This information may prevent a benign problem from becoming a sight-threatening emergency.

## Disclosure

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# Raised IOP with plateau iris

## Understand the benefits and limitations of tonometry techniques

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DETECTION of early glaucoma can be difficult even when the eye pressure is relatively high. Visual symptoms that can accompany early chronic and even acute glaucoma are many and varied but in general, are completely absent. Patients may say that their vision is blurred or haloed. There are many reasons why this may be the case, one of which could be acutely increased eye pressure and it is important for optometrists to exclude the possibility of high IOP when presented with these symptoms.

Most patients have little or only basic understanding of a glaucoma check and many regard it as simply an eye pressure check. The detection of glaucomatous optic neuropathy in primary care optometry requires a clinician to introduce a multimodal narrative to the patient. Among other benefits, this narrative helps to educate patients that a comprehensive glaucoma assessment requires many diagnostic tests apart from eye pressure. For example, gonioscopy, which gives a dynamic assessment of the angle, and other advanced optical diagnostic instruments such as OCT should be used to achieve optimum information to help confirm the diagnosis.

### CASE REPORT

LL is 63 years old and has a long history of elevated eye pressure. She reports that she often ‘calls into’ various optometry practices, including this one, to have her pressures checked. She also reports that she has had her eyes checked regularly and comprehensively by her ophthalmologist and that to date no sign of glaucoma has been detected.

Her corrected vision is normal and she has had lifelong hyperopia: RE +3.00/-1.25x80 6/6 LE +3.00/-0.75x90 6/6.

Her IOPs at this practice in August 2015 were RE 25 and LE 27 with her cornea slightly thicker than normal at RE 0.573 mm and LE 0.571 mm with non-contact pachymetry. Recently,

she has had red and sore eyes but this was diagnosed as presumed viral conjunctivitis. Because her eyes were feeling better, on presenting to our practice she requested an eye pressure recheck. Perkins tonometry showed elevated IOP of RE 34 mmHg, LE 38 mmHg with a large amount of variability in each eye reading due to pressure pulsation. Nonetheless, she had no pulsatile tinnitus, proptosis, hypertension or history suggestive of carotico-cavernous fistula.

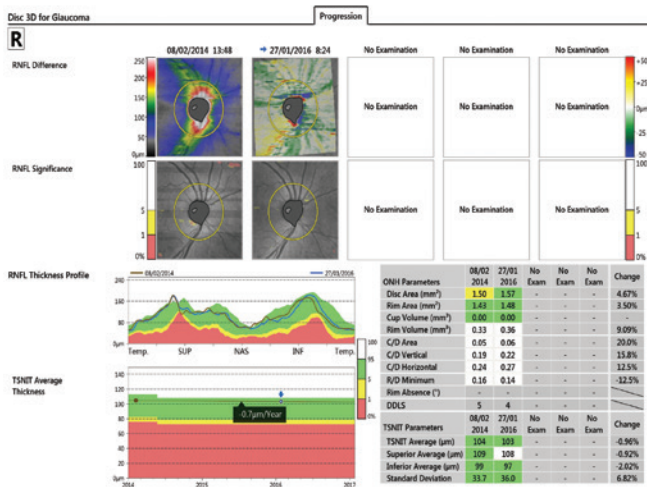
Her eyes had intact optic nerves (Figure 1), confirmed with OCT results (Figures 2A and 2B), and she reported that visual field threshold tests had been full in the recent past. Slitlamp and anterior OCT showed an iris that was bowed forward (Figure 3). After explaining, with the aid of the anterior eye OCT, that her angle is where the

**Continued page 18**

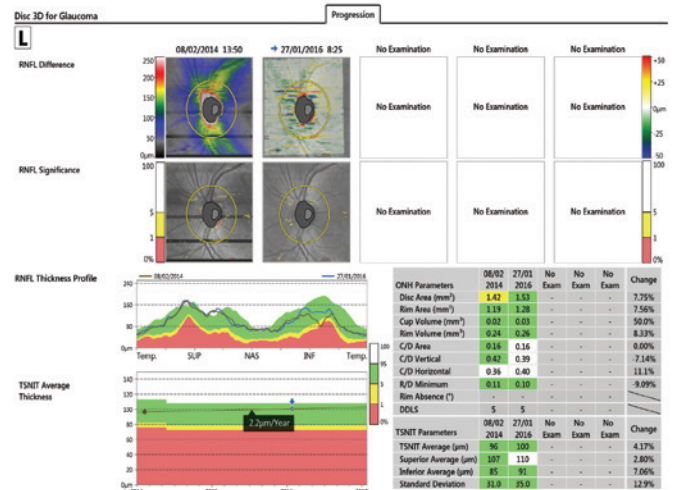


▲ Figure 1. Retinal photo, left eye





▲ Figure 2A. Right eye, unchanged for two years



▲ Figure 2B. Left eye, unchanged for two years

## Raised IOP with plateau iris

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pressure is drained from her eye, gonioscopy was used to confirm the angle as open but somewhat pigmented if not difficult to assess as it was over the horizon of her plateau-shaped iris. Compression gonioscopy showed no peripheral anterior synechiae and the characteristic sine wave, or double hump, of a plateau iris configuration.

Given her case presentation, it was thought that she might require multiple treatment options to control her IOPs and was referred to an ophthalmologist to evaluate treatment options. Initial therapy was commenced with Xalatan and Simbrinza, with a view to additionally performing bilateral selective laser trabeculotomy.

Eventually, she may require peripheral laser iridoplasty to treat her plateau iris configuration if her angle becomes threatened. Therefore, close monitoring by the optometrist and ophthalmologist is key to optimum management.

### DISCUSSION

This glaucoma case illustrates that applanation tonometry and gonioscopy are key examination techniques to be performed on glaucoma suspects.

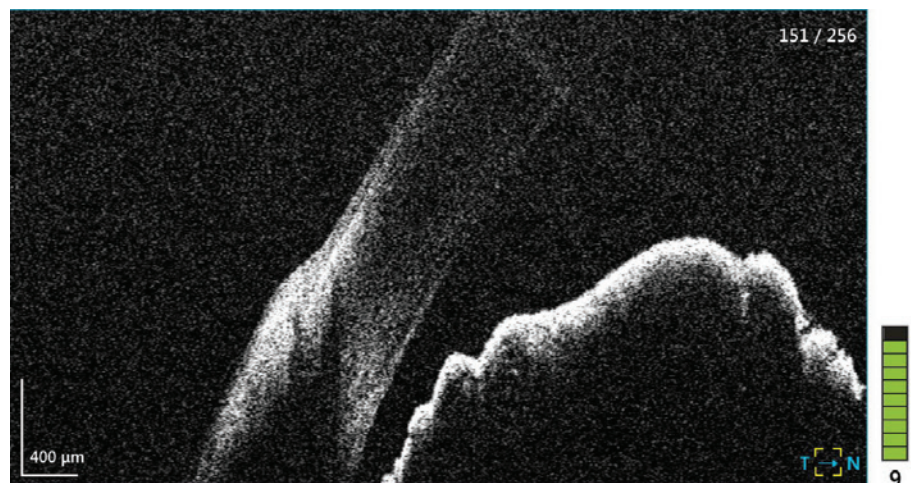
Tonometry techniques give a convenient screening result, but if the IOP is varying from moment to moment, with a low of 29 mmHg to a high over 30, it is often only the lower values that are recorded reliably with particular instruments, and thus the eye pressure is easily underestimated.

Placed in a clinical context, a screening, electronic eye pressure over approximately 20 mmHg should always be confirmed with Goldmann tonometry or equivalent non-digital applanation technique; however, all glaucoma suspects should have applanation tonometry performed. Whichever eye pressure technique is used, understanding the limitations

and benefits of that technique is important.

Similarly, if anterior eye slitlamp microscopy, Van Herrick examination of angles or an anterior OCT shows any unusual features or does not adequately explain the status of a patient's IOP, then gonioscopy should be performed. Any patients who have risk factors for glaucoma should have routine gonioscopy performed.

OCT assessment of the anterior angle should be a supplement rather than a replacement for gonioscopy. Additionally, gonioscopy allows a dynamic assessment of the anterior chamber angle. ▲



▲ Figure 3. 2-D anterior OCT illustrating plateau iris

# Therapeutic NEWS of note

## Associate Professor Mark Roth

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NEWENCO FAAO OAM

### Just a week of oral NSAIDs use linked to increased heart attack risk

Use of oral non-steroidal anti-inflammatory drugs (NSAIDs) for even one week is associated with increased risk for myocardial infarction, a study in *The BMJ* finds.

Researchers conducted a data meta-analysis drawn from Canadian and European data bases. A cohort of 446,763 individuals including 61,460 with acute myocardial infarction was acquired.

Compared with NSAIDs non-use, current use of each NSAID studied—including diclofenac, ibuprofen, naproxen, and celecoxib—was associated with increased myocardial infarction risk. Greater risk of myocardial infarction was documented for higher doses of NSAIDs. With use for longer than one month, risks did not appear to exceed those associated with shorter durations.

The authors concluded that all oral NSAIDs were found to be associated with an increased risk of acute myocardial infarction. Risk was greatest during the first month of NSAIDs use and with higher doses.

*BMJ* 2017; May. doi: 10.1136/bmj.j1909.

### OCT to monitor multiple sclerosis

A potential utility for OCT could be to help investigate the neuroprotective benefits of disease-modifying therapies in multiple sclerosis (MS).

There is increasing evidence suggesting that retinal changes and

in particular, neurodegeneration, mirror global central nervous system alterations in MS. Several studies have demonstrated that changes within the inner retina (primarily as a reflection of optic neuropathy) as assessed by OCT correlate with reduced quality of life, visual dysfunction and global disability in MS.

Longitudinal studies suggest that inner retinal thinning is an early phenomenon in MS and that retinal thinning may occur independently of previous symptomatic episodes of optic neuritis, significantly correlating with inflammatory disease.

Spectral-domain optical coherence tomography (SD-OCT) offers an inexpensive, rapid, non-invasive and reproducible way to attain high-resolution images of tissues such as the retina. The main advantage of SD-OCT over magnetic resonance imaging techniques in the assessment of neurodegeneration may be its ability to capture changes at the individual patient level.

*Curr Treat Options Neurol* 2017; 19: 4: 15.

### How does topiramate impair thinking?

A new study that associates the antiepileptic drugs topiramate and to a lesser extent, zonisamide with impaired cognition demonstrates the physiologic changes underlying patients' complaints that they 'can't think' when on the drugs.

Researchers conducted a retrospective analysis of cross-sectional data on 145 patients who were treated with topiramate (TPM), zonisamide (ZNS) and levetiracetam (LEV).

Patients were treated with LEV (median dose 2000 mg), ZNS (median dose 224 mg), or TPM (median dose 312.5 mg). In a presurgical evaluation, patients had functional magnetic resonance imaging while performing a verbal-fluency task. Other cognitive domains were tested separately.

TPM was associated with worse performance on verbal-fluency

task than ZNS and LEV. ZNS and TPM were associated with worse performance on digit span than LEV. On the verbal-fluency task, there was a decrease in activation in areas of the frontal and parietal lobe with ZNS and TPM; only TPM was associated with an impaired deactivation of the default mode network.

The researchers conclude that the study provides Class III evidence that in patients with focal epilepsy, TPM and ZNS, compared to LEV, lead to disruption of language and working memory networks.

*Neurology* 2017; Feb 17 (Epub ahead of print).

### Multifocal vs monofocal intraocular lenses post cataract surgery

Multifocal IOLs are effective at improving near vision relative to monofocal IOLs, but there is uncertainty about the size of the effect.

To assess the visual effects of multifocal IOLs in comparison with the current standard treatment of monofocal lens implantation, researchers searched nine electronic databases (CENTRAL, Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid Embase, the ISRCTN registry, ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform) for all randomised controlled trials comparing a multifocal IOL of any type with a monofocal IOL as control.

The study authors found 20 eligible trials that enrolled 2,230 people with data available on 2,061 people (3,194 eyes). Most of these trials compared multifocal with monofocal lenses; two trials compared multifocal lenses with monovision.

It was found that there was moderate-certainty evidence that the distance acuity achieved with multifocal lenses was not different from that achieved with monofocal lenses.



## Therapeutic NEWS of note

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However, people receiving multifocal lenses may achieve better near vision.

The authors concluded that improvement outweighs the adverse effects of multifocal IOLs, such as glare and haloes, and will vary between people. Motivation to achieve spectacle independence is likely to be the deciding factor.

*Cochrane Database of Systematic Reviews* 2016; Dec 12. doi:10.1002/14651858.CD003169.pub4.

### Phacoemulsification lowers IOP in patients with POAG

Phacoemulsification as a solo procedure lowers IOP in patients with primary open angle glaucoma (POAG), and reduces dependency on topical glaucoma medications. The effects appear to last at least 36 months with gradual loss of the initial effect noted after two years.

Investigators conducted a systematic review and meta-analysis to synthesise evidence quantifying the effect of phacoemulsification on IOP and the required number of topical glaucoma medications in patients with cataract and POAG.

The search strategy identified 1,613 records. Thirty-two studies (1,826 subjects) were included in quantitative synthesis. A 12 per cent, 14 per cent, 15 per cent and nine per cent reduction in IOP from baseline occurred six, 12, 24 and 36 months, respectively, after phacoemulsification. A mean reduction of 0.57, 0.47, 0.38 and 0.16 medications per patient of glaucoma medication occurred six, 12, 24 and 36 months, respectively, after phacoemulsification.

‘Certain populations appear to experience much greater reductions in IOP than others, and future work to identify these high-responding patients is needed,’ the researchers wrote.

*J Glaucoma* 2017; Mar 22 (Epub ahead of print).

### IOP in POAG patients highest in the morning

In a comparison of the diurnal IOP profiles of primary angle closure glaucoma (PACG) and POAG eyes, researchers found that IOP in primary glaucoma patients peaks in the morning and decreases over the course of the day in a non-clinical environment.

Fifty-three medically-treated eyes of 31 PACG and 22 POAG patients with no previous eye surgery were recruited. Diurnal IOP was measured five times per day at four-hourly intervals from 8:00 am to midnight for one week using rebound tonometry in a non-clinical environment. The diurnal IOP profiles were compared between PACG and POAG eyes.

The authors concluded that mean patient-measured IOP in the home environment was highest at 8:00 am, tended to drop over the course of a day, and was lowest by midnight in both PACG and POAG eyes in this study. The PACG eyes had lower diurnal IOP fluctuation than POAG eyes, and higher midnight IOP.

‘This study demonstrates the feasibility of diurnal IOP documentation by patients themselves using rebound tonometry in their ambient environments,’ the researchers wrote. ‘Such measurements may potentially be of clinical relevance in patient management.’

*PLoS One* 2017; 12: 3: e0173905.

### Complications more common for young adults with type 2 diabetes

According to research published in the *JAMA*, almost three quarters of teenagers and young adults with type 2 diabetes have a complication, compared with about one in three with type 1 diabetes.

In a prospective observational study at five US sites, researchers examined the prevalence of complications at least five years after diagnosis in 1,746 patients with type 1 diabetes and 272 with type 2 diabetes diagnosed before the age of 20 years.

Overall, 72 per cent of patients with type 2 diabetes, compared with 32 per cent of those with type 1 diabetes, had at least one diabetes-related

complication. After adjustment for other risk factors, patients with type 2 diabetes had significantly higher odds of diabetic kidney disease, retinopathy and peripheral neuropathy.

The researchers said that complications and comorbidities were frequent in both groups, although type 2 diabetes is particularly dangerous. They called for greater monitoring of young people with diabetes as well as careful surveillance for early signs of diabetic complications in order to initiate early interventions.

*JAMA* 2017; 317: 8: 825-835. doi:10.1001/jama.2017.0686.

### Modest links between systemic medication use, IOP in glaucoma

Use of systemic medications may modestly affect intraocular pressure (IOP), according to a post-hoc analysis of data from a large, multiethnic Asian cohort, *JAMA Ophthalmology* reports.

The post-hoc analysis was conducted of the Singapore Epidemiology of Eye Diseases study, a population-based study of 10,033 participants from three racial/ethnic groups (Chinese, Malays and Indians). Intraocular pressure was measured using Goldmann applanation tonometry.

Although systemic  $\beta$ -blocker use was associated with lower IOP and systemic angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statin and sulfonyleurea use was associated with higher IOP in this study, the associations were modest at best.

Only the associations with systemic hypoglycaemic agents were greater than 1 mmHg, a threshold that has translated to a 14 per cent greater risk of incident glaucoma across five years in other studies.

The study authors wrote: ‘At this point, the effect of systemic medication on IOP in eyes with glaucoma is not well elucidated but important. Our findings indicate that patients with glaucoma may potentially be at risk of higher or lower IOP, depending on medication class, and this would in turn affect management of IOP control.’

*JAMA Ophthalmol* 2017; 135: 3: 196-202. doi:10.1001/jamaophthalmol.2016.5318. ▲

## Clinical Quiz

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### Diagnosis

The patient was diagnosed with Salzmann's nodule, a degenerative condition of the cornea which appears as creamy white, opaque or semi-opaque, smooth, elevated lesion(s) on the surface of the cornea. Occasionally, they can appear with a yellow or blue tinge.

### Epidemiology

Salzmann's nodules are uncommon but the exact incidence is unknown. They are much more prevalent in women than in men.

### Aetiology

Salzmann's nodules are thought to be related to low-grade chronic inflammation; however, some cases appear to be idiopathic.

### Pathophysiology

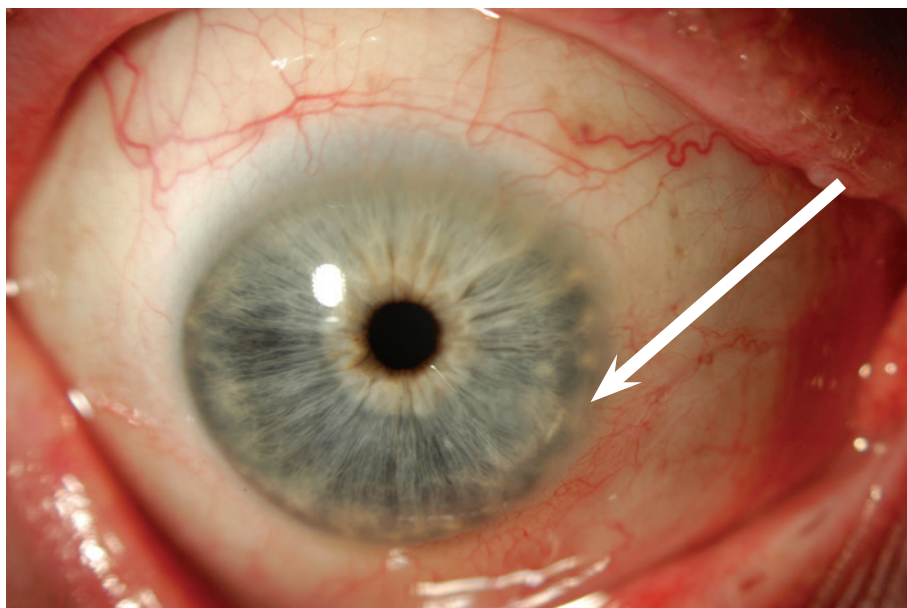
Nodules are typically composed of collagen plaques with hyaline between the epithelium and Bowman's layer.

### Risk factors

Salzmann's nodules are known to occur in patients with ocular surface inflammation secondary to meibomian gland dysfunction or dry eye disease, phlyctenular keratitis, vernal keratoconjunctivitis, trachoma, marginal keratitis, corneal trauma and long-term contact lens wear complications.

### Commonly associated conditions

Common coexistent conditions include the risk factors as described above in addition to epithelial basement



▲ Figure 2. Post phototherapeutic keratectomy. Image: Associate Professor Mark Roth

membrane dystrophy and cases that involve corneal surgery complications.

There may be a history of long-standing foreign-body sensation, pain, redness, tearing and photophobia, or minimal to no symptoms. If the nodules are near or on the visual axis, they may affect vision.

### Examination

Slitlamp examination shows single or multiple elevated yellow or blue/white corneal nodules. Typically, Salzmann's nodules are peripheral or mid-peripheral, but they may also be paracentral or central. There is no staining with vital dyes. A test to consider is corneal topography to evaluate for corneal astigmatism.

### Differential diagnosis

See risk factors (above). Also: corneal keloid and corneal amyloidosis.

### Treatment

If the condition is asymptomatic, no treatment is required other than to decrease risk factors for progression. However, if the condition is symptomatic, treatment may involve lubricants, gels, ointments, pulse-dose topical steroids or topical cyclosporin 0.05% drops.

If the patient is not responding to topical therapy, surgical removal of the nodule may be necessary; phototherapeutic keratectomy is the procedure of choice.

### General prevention

Treat underlying causes.

Maguire J, Murchison A, Jaeger E. Wills Eye Institute. 5-minute ophthalmology consult. 1st ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012. 626-627.

# Corneal foreign body removal

## Therapeutic treatment, management

### Elena-Marie Macris

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CORNEAL foreign body (FB) removal results in corneal nerve exposure, manifesting as pain and blepharospasm.<sup>1</sup> The remaining epithelial defect may also increase the risk of microbial keratitis.<sup>1</sup> Consequently, the literature focuses on managing corneal abrasions following FB removal; however, it has not arrived at a consensus. Management aims at reducing pain, accelerating epithelial healing and preventing infections. The choice depends on patient symptoms, FB material, factors affecting epithelial healing and size of the epithelial defect after removal. It is important to perform a dilated examination and Seidel test to investigate signs of a penetrating injury or intraocular FB.

### CASE REPORT

A 35-year-old male presented with an uncomfortable RE and no noticeable changes to his vision. Two days prior, he had felt something enter the eye while grinding metal. He had not been wearing protective eyewear. As the eye had been feeling uncomfortable, he had presented to the pharmacy that afternoon and been given saline. He had used saline as needed that day and the following day.

He presented to the optometrist two days after the injury because the discomfort had not resolved. He had no significant ocular history, unremarkable general health and was not taking medications.

### Clinical examination

BCVA OD 6/6 OS 6/6.  
Pupils PERRL, no RAPD.

### Slitlamp

- OD: Grade 2 diffuse bulbar conjunctival hyperaemia (CCLRU) with 0.5 x 0.5 mm metal FB at 10 o'clock 1.5 mm from the limbus surrounded by a rust ring, without corneal infiltrate. Sodium fluorescein (NaFl) staining showed a positively stained ring surrounding the FB. Lid eversion clear, Seidel test negative, AC quiet, lens clear.
- OS unremarkable

IOP 14 mmHg OU (iCare 12:15 pm).  
Fundus examination unremarkable.

### Diagnosis

Corneal metal foreign body.

### Management and review

1 drop oxybuprocaine 0.4% instilled  
OU to remove OD FB.

- Spud used for FB and Algerbrush for rust ring removal, NaFl post removal
- 1.5 x 2 mm epithelial defect extending to Bowman's layer
- Seidel test negative.

1 drop chloramphenicol 0.5% 4x/day  
RE only. Review in 24 hours expecting smaller epithelial defect and less discomfort.

On review, the patient was experiencing minimal discomfort. He used two drops 0.5% chloramphenicol before returning to the practice. OD Grade 1 bulbar hyperaemia (CCLRU). NaFl revealed diffuse SPK in region of epithelial defect but otherwise epithelium had healed.

The edges of healed defect site were irregular and slightly hazy. No infiltrate or rust ring and AC quiet. IOP 15 mmHg OU (iCare 12:30 pm). Patient was instructed to instill another two drops of 0.5% chloramphenicol that day only, and then cease. Additionally, the patient was advised to use Polyvisc

ointment once in the evening for one week. The patient was reminded to wear protective eyewear during hazardous industrial work and return to care if problems arose.

### Discussion

Ocular foreign bodies (FB) account for the most common occupational-related ocular injury.<sup>2</sup> In Australia, ocular FBs accounted for 63.5 per cent of 7,000 work-related eye injuries presenting to emergency,<sup>3</sup> predominantly affecting 20-40 year old males due to their work and hobbies.<sup>3,4</sup> On average, two days are missed from work, causing patient morbidity and socio-economic burden.<sup>4,5</sup> In Australia, eye injuries are estimated to cost \$155 million each year.<sup>3</sup>

Corneal FB removal results in corneal nerve exposure, manifesting as pain, tearing, photophobia and blepharospasm.<sup>1</sup> Other sequelae may include rust ring, traumatic uveitis, microbial keratitis, corneal scarring and recurrent corneal erosion.<sup>1,3,4,6</sup>

Corneal abrasions usually heal within 24-96 hours; however, this depends on their size, patient immune status and rust ring removal.<sup>1,5,6</sup> Incomplete rust removal can delay healing.<sup>6</sup> Treatment options are exhaustive and include lubricating eye-drops for comfort, prophylactic antibiotics, and topical non-steroidal anti-inflammatories (NSAIDs), oral analgesia or cycloplegia for pain management.<sup>7</sup>

### Role of antibiotics

Topical antibiotics are prescribed post-FB removal as prophylaxis against infection,<sup>1,2,4</sup> with 14-20 per cent of corneal FBs having positive bacterial culture.<sup>3,4,6</sup> The type of corneal FB can help guide management. In the presence of a heated metallic FB, lubricating eye-drops may be sufficient as heat sterilises the FB.<sup>8</sup> Similarly, glass and plastic are inert materials.<sup>8,9</sup> Small epithelial defects may not warrant antibiotics, as they will heal within hours.<sup>1,5,6</sup> Fingernail and decomposing matter corneal



## options and recommendations

FBs can introduce bacteria into the eye; therefore, antibiotics would be recommended.

Time of injury can affect prescribing methods. If occurring in the morning, the practitioner may choose not to prescribe antibiotics if the defect is small, and review at the end of the day, to see whether healing has occurred. In comparison, if the injury occurs in the evening, the ocular environment is soon to undergo a hypoxic state due to lid closure, increasing risk of infection; therefore, antibiotics could be prescribed.

Evidence recommends chloramphenicol for corneal FBs as it exhibits greater sensitivity over ciprofloxacin against isolated microorganisms, with 95 per cent and 90 per cent, respectively.<sup>4</sup> Chloramphenicol is a primarily bacteriostatic broad spectrum, affordable antibiotic which is widely available.<sup>9,10</sup> Chloramphenicol has staphylococcal cover, which has been identified as the most frequent isolated pathogen from corneal FBs.<sup>6</sup> However, chloramphenicol is resistant against *Pseudomonas* species and therefore, is not recommended as prophylaxis in contact lens wearers.<sup>8,10</sup> Antibiotics with pseudomonal cover such as tobramycin 0.3%, gentamicin 0.3%, ciprofloxacin 0.3% or ofloxacin 0.3% should be prescribed.<sup>1,9,12</sup>

Indications for antibiotic prescribing following corneal trauma include contact lens wear and vegetative matter, as they are associated with higher risk of secondary bacterial keratitis.<sup>12</sup> Others include immunocompromised patients, extension to the stroma and dry eye, due to reduced corneal healing.

At the Royal Victorian Eye and Ear Hospital, chloramphenicol is the most commonly prescribed antibiotic for corneal metal FBs.<sup>3</sup> Chloramphenicol use for corneal abrasions is a common practice in accident and emergency departments.<sup>6,11,13</sup> There is no consensus on dosage frequency with 2-5x/day suggested.<sup>6,10,13,15</sup> Given this patient was not a contact lens wearer, chloramphenicol 0.5% 4x/day was

appropriate to use. Chloramphenicol ointment could have been prescribed instead as it is preservative free and therefore, less likely to cause surface irritation but its increased viscosity would blur vision. As undertaken in this case, prophylactic antibiotic use can continue until the epithelium heals, to minimise risk of microbial keratitis.<sup>7</sup>

As patients can be non-compliant, an initial antibiotic, in-office, loading dose can be considered in addition to providing the patient with a prescription.

### OTHER MANAGEMENT OPTIONS

#### Topical NSAIDs

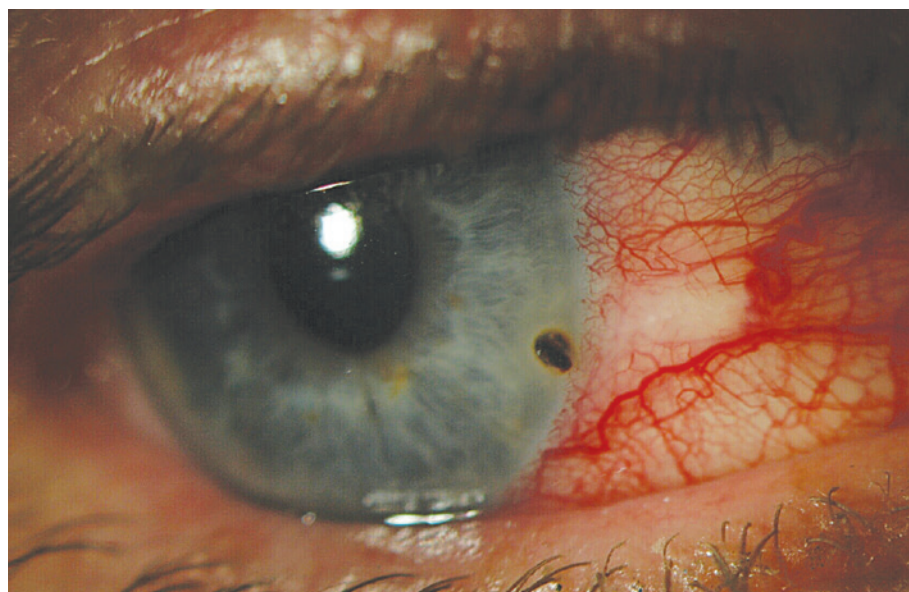
A meta analysis found that topical NSAIDs reduce pain at 24 hours; however, studies demonstrated variability with co-interventions and pain scales used.<sup>5</sup> Interventions included ketorolac 0.5% 4x/day, diclofenac 0.1% 4x/day and diclofenac six-hourly while awake for 24 hours, or until the defect closed.<sup>5</sup> Although co-interventions have a potential role, they confound results. Topical NSAIDs use may allow earlier return to work,

reducing socio-economic burden,<sup>11,14</sup> and enables less dependence on oral NSAIDs.<sup>16</sup> However, literature has not compared oral to ophthalmic NSAIDs.<sup>17</sup> Oral NSAIDs are more affordable than topical equivalents, but contraindications and precautions such as gastrointestinal ulcers must be considered.<sup>7,16,17</sup>

#### Oral analgesia

There is limited evidence surrounding the use of oral analgesics for corneal abrasions.<sup>1</sup> Corneal FBs have a good prognosis, therefore pain is often the primary concern due to nociceptor activation. Pain can be addressed with oral analgesia.<sup>1</sup> However, it is important to ask about concomitant medications due to drug-drug interactions, and comorbid conditions such as kidney and liver disease, which affect drug metabolism, prior to recommending oral analgesia. Analgesia was shown to be more effective with 400 mg ibuprofen (two tablets) with 56 per cent achieving 50 per cent pain relief, while reducing to 46 per cent for 500 mg paracetamol (two tablets).

**Continued page 24**



▲ Figure 1. Foreign body. Photo: Dr Henry Heron



# Corneal foreign body removal

From page 23

## Patching

Patching reduces mechanically-induced trauma from lid-cornea interactions;<sup>1</sup> however, a Cochrane review favoured no patching in the first 24 hours following corneal abrasion.<sup>18</sup> When considering pain, two studies favoured no patching, while none favoured patching.<sup>18</sup> There was no difference in the time to healing, and there were no complications.<sup>1</sup>

## Cycloplegia

Multiple studies have administered cycloplegia;<sup>15,16,19</sup> however, co-interventions confound results. Comparing homatropine 5% six-hourly to placebo, there was no difference in pain 24 hours following the abrasion.<sup>19</sup> Similarly, flurbiprofen 0.03% 4x/day for 48 hours, with or without a stat dose of homatropine 2%, had lower pain scores than the control group, or those given a stat dose of 2% homatropine.<sup>15</sup>

## Sequelae

Potential sequelae of corneal FBs include recurrent corneal erosion (RCE), rust rings and traumatic uveitis. A retrospective chart review of RCE identified 45 per cent as having a history of trauma.<sup>20</sup> Lacrilube ointment was prescribed for one week, to reduce the risk of a future RCE. However, literature suggests that epithelial-stromal adhesion can take at least six weeks to heal<sup>21</sup> and therefore, longer treatment duration would be suggested. Nightly Lacrilube for two months has been investigated for preventing RCE following fingernail-induced corneal abrasion.<sup>22</sup> Those patients prescribed Lacrilube had a higher prevalence of symptoms suggestive of RCE.<sup>22</sup> Although this suggests ointment is not beneficial, outcomes were based on symptoms not signs, and included only fingernail injuries.<sup>22</sup> A Cochrane review acknowledges that further research is required for prophylactic regimens following traumatic corneal abrasion.<sup>23</sup>

Rust rings form within three to four hours of the foreign body; however,

removal is easier 24-48 hours later.<sup>24</sup> The burr is superior to manual removal of a rust ring and therefore, as inadequate removal can delay visual outcomes, a burr should be used, as performed in this case.<sup>3</sup>

Traumatic uveitis accounts for approximately 12 per cent of uveitis presentations, and the most common treatment modality is local steroids;<sup>25</sup> however, treatment may not be required as immune response reduces as healing occurs. Therefore, signs and symptoms should guide management.

## Other considerations

Protective eyewear is important to discuss with patients presenting with ocular injuries, as 90 per cent can be prevented with adequate protection.<sup>3</sup> It is important to be specific with recommendations because 45 per cent of corneal metallic FB injuries occurred while wearing eye protection.<sup>3</sup>

## Prognosis

Corneal abrasions heal within 24-96 hours, depending on their size and patient immune status.<sup>1,11,5</sup> Given there is a risk of microbial keratitis while a breach in the corneal barrier exists, it is feasible to review a patient daily until the epithelium is healed. The other option is to inform the patient to return to care if symptoms worsen as in most cases, abrasions resolve. If symptoms are worsening, considerations include retained FB material and penetrating injury. ▲

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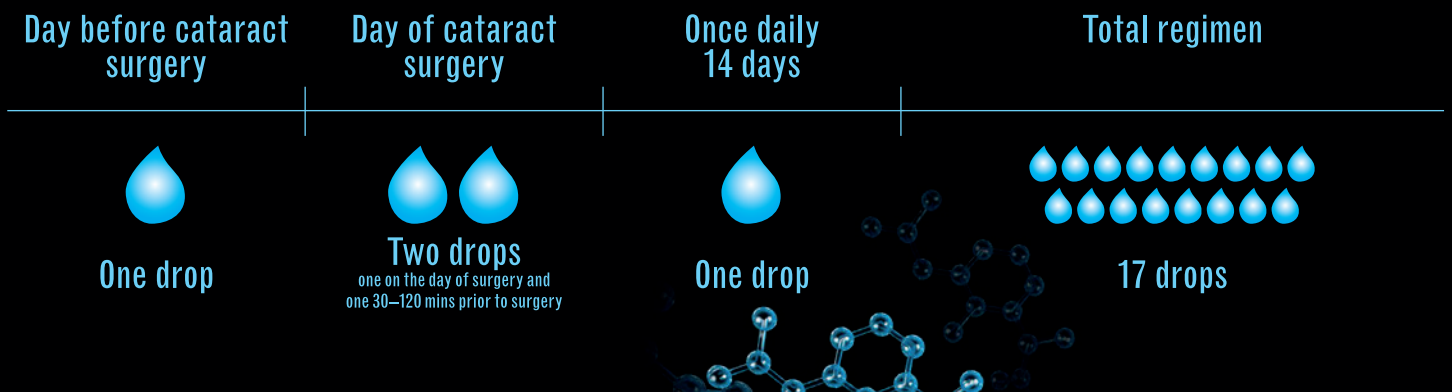
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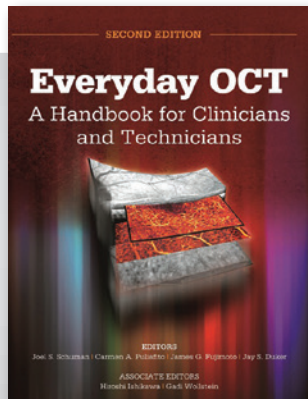
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NSAID: non-steroidal anti-inflammatory drug.

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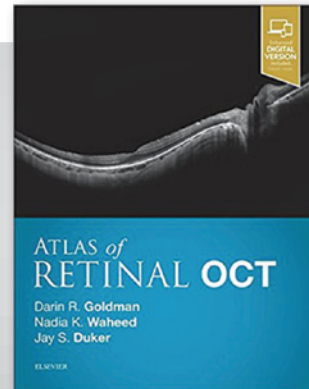


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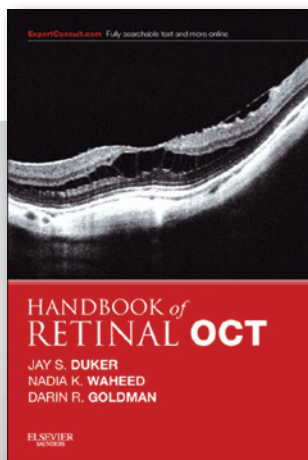
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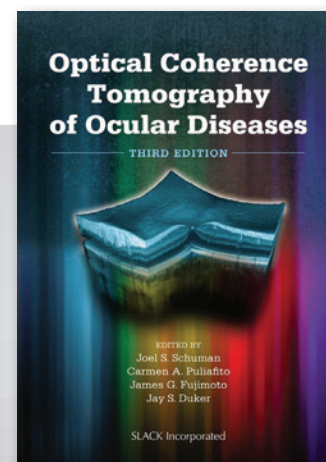
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