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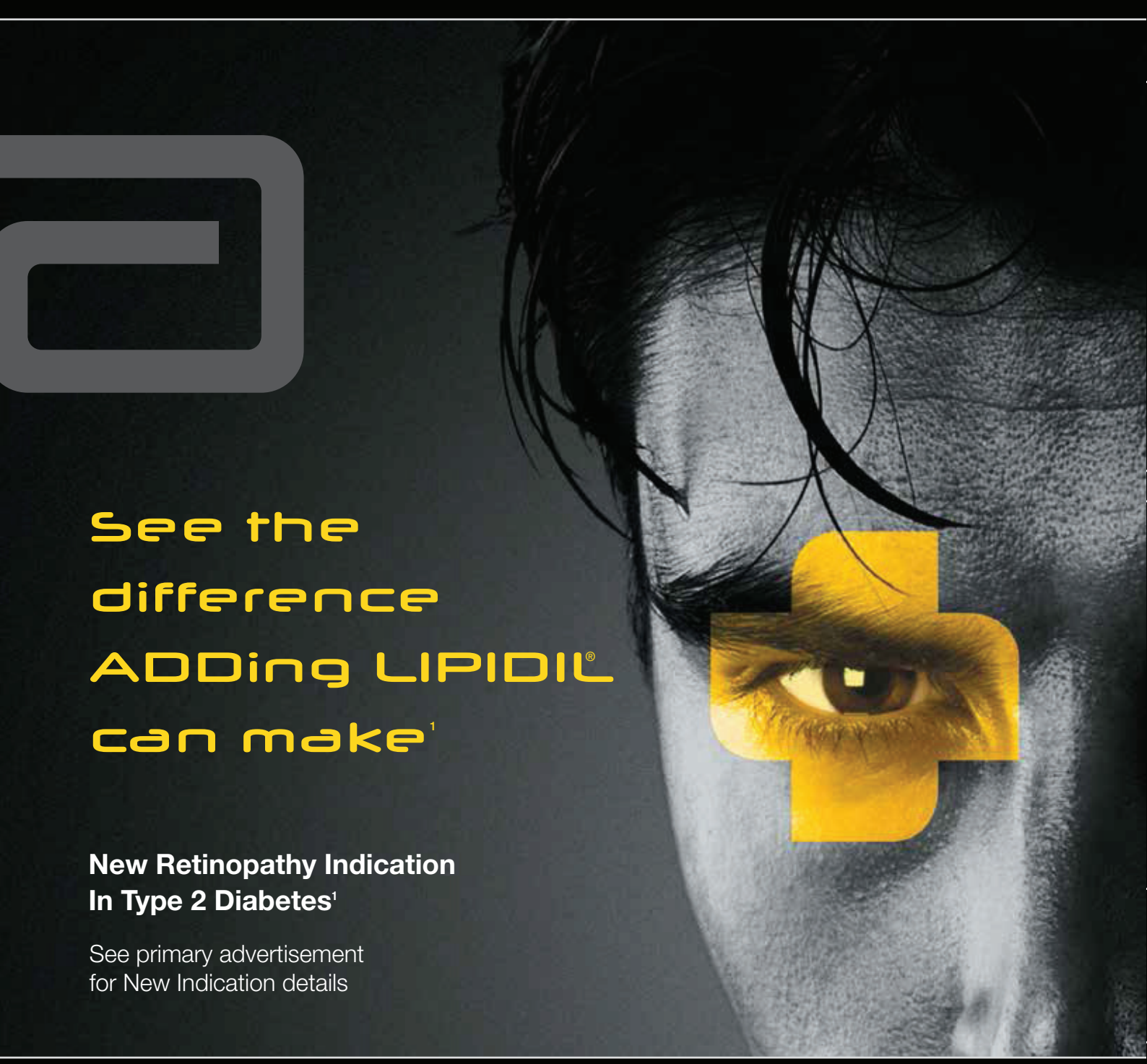
Setting our sights on the looming crisis

Optic nerve head drusen
Detection and controversial treatment options

CXL for keratoconus
Clinical results and complications

Alzheimer's disease
Towards a non-invasive analysis of ocular biomarkers



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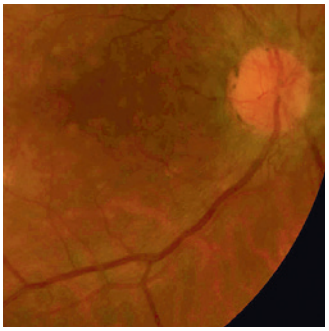

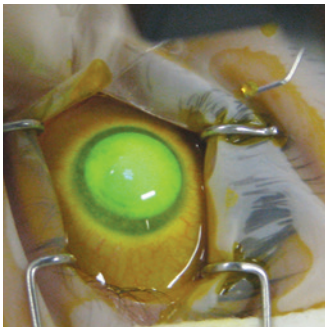

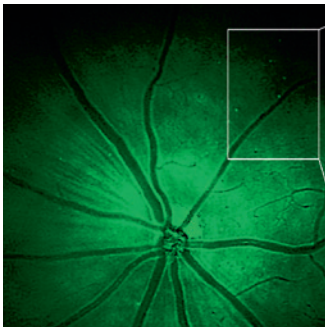

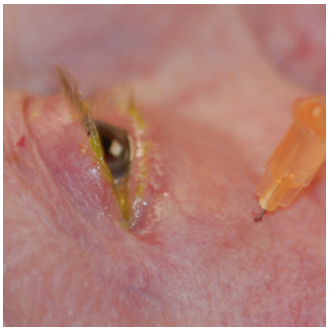

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New guidelines for diabetic

Optometry's vital

Jeff Megahan

HEALTH CARE organisations in Australia are increasingly advocating a multidisciplinary approach to diabetes, in which optometrists are expected to play a key role in early diagnosis, monitoring and patient awareness.

In April 2014, the Royal Australian College of General Practitioners updated its General Practice Management of Type 2 Diabetes Guidelines. Optometry Australia's revised diabetes guidelines were released in June 2014.

Optometry Australia had established its own working group* to review its diabetic retinopathy clinical guidelines and the 12-month review process concluded in May 2014.

The National Health & Medical Research Council (NHMRC) last revised its Clinical Practice Guidelines for the Management of Diabetic Retinopathy in 2008. Developed by the Australian Diabetes Society's expert panel and citing literature only up to 2006, the NHMRC guidelines were soon outdated.

While drawing heavily on the NHMRC's guidelines, Optometry Australia's guidelines for the Examination and Management of Patients with Diabetes recognise technologies such as digital retinal imaging and OCTs, as well as the new treatment modalities for diabetic macular oedema, particularly anti-VEGF therapy.

Tacitly acknowledging the changing role optometry plays in the diagnosis and monitoring of mild to moderate non-proliferative diabetic retinopathy,

Retinopathy stage	Findings on ophthalmoscopy	Management and review/referral timeframe[42]
No apparent retinopathy	No abnormalities	In line with AOA , AAO and JDC, OAA recommends annual review
Minimal NPDR	Microaneurysms (MA) only	Review 6-12 months taking into consideration proximity of MA to fovea
Mild to moderate NPDR	More than just MA but less than severe NPDR This may include: • Dot haemorrhages • Blot haemorrhages • Cotton wool spots • Intraretinal microvascular anomalies (e.g. venous beading)	Refer (see footnote)[43] or closely monitor Depending on level of DR present, 3-6 monthly or annually.
Severe NPDR	Any of the following: • More than 20 intraretinal haemorrhages in each of 4 quadrants • Definite venous beading in 2+ quadrants • Prominent IRMA in 1+ quadrant AND no signs of proliferative retinopathy	Ophthalmology referral – see footnote[41]
PDR	One of the following (or unexplained fall in visual acuity): • Neovascularisation • Vitreous/pre-retinal haemorrhage	Urgent ophthalmology Referral (days–weeks)*
Macula oedema		
Absent	No retinal thickening or hard exudates (HEx) in posterior pole	Follow-up or need to refer should be based on the level of NPDR or DR
Present	MILD – some retinal thickening or HEx in posterior pole but distant from the macula MODERATE – retinal thickening or HEx approaching the centre of the macula but not involving the centre SEVERE – retinal thickening or HEx involving the fovea	Ophthalmology referral and management (within 4 weeks for HEx within 1DD of fovea)*

* Optometry Australia recommends that optometrists communicate with ophthalmologists to determine their preferred referral timelines to prevent vision loss

▲ Table 1. International Clinical Diabetic Retinopathy and Diabetic Macular Oedema Disease Severity Scale and recommended referral patterns

retinopathy

role in shared care of patients

the revised guidelines advocate the use of the International Clinical Diabetic Retinopathy and Diabetic Macular Oedema Disease Severity scale (Table 1). The scale simplifies classification of diabetic retinopathy and is seen as a more clinically useful measure than the Wisconsin scale it replaces.

Multidisciplinary approach

Optometry Australia's new guidelines offer optometrists a concise resource to facilitate consultations and to encourage optimum health outcomes for the 1.6 million Australians diagnosed with diabetes mellitus.

The principal optometrist at the Centre for Eye Health, Paula Katalinic, was a member of the working group that contributed to the revised guidelines. Ms Katalinic, who completed a three-year tenure at the renowned Joslin Diabetes Center in Boston, says that one of the main points the working group wanted to stress was the important role of optometry in a multidisciplinary diabetes team.

'Whether or not a person with diabetes has signs of diabetic retinopathy may influence the clinical decision-making of GPs and endocrinologists in terms of the optimal level of glycaemic control for that particular patient, and treatment of other risk factors for diabetic retinopathy such as blood pressure and cholesterol,' Ms Katalinic said. 'It's important that the results of the eye exam be communicated to the patient's GP or endocrinologist following every visit.

'Understanding that the level of diabetic retinopathy is predictive of the rate of progression to vision-threatening disease is important. It will minimise unnecessary referrals to ophthalmologists for those who could be safely monitored by optometrists, and allow more appropriately-timed referrals,' Ms

Continued page 4

Procedure	Comments
Visual acuity (with correction)	Distance and Near, monocularly, including pinhole acuity if indicated
Pupil reactions	Direct/Consensual and Near pupillary responses
Ocular motility	Extent, fluency and symmetry of ocular movements in all directions of gaze, ruling out eye movement anomalies. Relevant history taking regarding the onset and direction of double vision is necessary. If diplopia is manifest, cover test and prism neutralization is also indicated.
Visual field screening	• Confrontation • Note: visual field screening and baseline testing in the absence of actual or suspected pathology of the visual pathways or brain will not attract a Medicare rebate for item 10940 or 10941.
Refraction	• On indication • Where patient reports a change in vision or visual function (e.g. increased glare sensitivity) or where a change in habitual visual acuity is measured.
Slit lamp biomicroscopy	• Recommended at every visit • Examination for iris neovascularisation (NV), diabetic cataract, corneal integrity
Tonometry	As indicated, recommended pre- and post- pupil dilation
Stereoscopic fundus examination with pupil dilation	• NHMRC guidelines describe pupil dilation using 0.5 to 1.0% tropicamide as safe (noting dilated ocular fundus examination increases the sensitivity of DR screening) and so consider it mandatory in performing ophthalmoscopy or slit lamp biomicroscopy* unless contraindicated by the presence of potentially occludable anterior chamber angles • 2.5% phenylephrine hydrochloride, unless contraindicated, may help achieve maximum pupillary dilation in patients with DM, particularly those of Aboriginal and Torres Strait Islander descent and patients with heavy iris pigmentation • OAA pupil dilation guidelines can be viewed here • Symptoms of VA reduction or distortion of vision or a significant change of DM control should always prompt dilated pupil examination

Diabetic macular oedema is important to detect, as it is the most frequent cause of visual loss from retinopathy. DMO is best assessed using fundoscopy with slitlamp biomicroscopy (with pupil dilation), grading stereoscopic macular photographs or OCT.

* Guidelines for the Management of Diabetic Retinopathy NHMRC 2008 http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/di15.pdf accessed May 2013

▲ Table 2. Recommended examination procedures for examining patients with diabetes

New guidelines

From page 3

Katalinic said. 'For instance, a person with mild non-proliferative diabetic retinopathy has only a minimal risk of progressing to significant levels of retinopathy in 12 months and can be safely monitored by the optometrist if the optometrist feels they have the clinical skills and knowledge to do so.'

Table 2 (Page 3) lists recommended examination procedures for examining patients with diabetes.

Beyond the vitally important functions of diagnosis, monitoring and referral, optometrists can play a key role in educating diabetic patients and encouraging adherence to a diabetes care plan by turning the discussions about their OCT scans and retinal images into opportunities to educate. For patients with diabetes, seeing the early visible clinical manifestations of diabetic retinopathy reinforces the importance of blood glucose control and regular eye examinations.

Paula Katalinic suggests saving a few de-identified images of late-stage diabetic retinopathy to show to patients so they can understand that the better care they take of themselves, the lower their risk of vision loss due to diabetes will be. 'It really is true that a picture is worth a thousand words when it comes to the education of a person with diabetes,' she said.

'It's important for optometrists to build a professional relationship with their local ophthalmologist and GP,' Ms Katalinic said. 'It is worth letting them know that you want to work with them to best manage the patient's visual needs. This, in turn, will lead to future referrals of other patients.

'Practising to the standard of care, dilating all patients with diabetes, accurately grading the level of diabetic retinopathy and macular oedema, and referring in a timely manner will build respect and are likely to enhance the relationship with your fellow health-care providers,' she said.

Following the TGA's approval of fenofibrate as an indication to slow the progression of existing diabetic retinopathy in people with type 2 diabetes, timely referral to GPs has become critical. As the new guidelines explicitly spell out, everyone with diabetes is at risk of developing diabetic retinopathy, and thorough eye examinations are important for early diagnosis and treatment to prevent vision loss. As never before, optometrists are ideally placed to detect previously undiagnosed cases of diabetic retinopathy.

By familiarising yourself with the risk factors for developing diabetic retinopathy, the severity scales and recommended referral patterns, you can actively participate in the kind of multidisciplinary diabetes team that is necessary to ensure optimal patient care.

Download the full Clinical guidelines for examining and managing patients with diabetes from the Optometry Australia website > For Optometrists > Guidelines. ▲

* The working group participants were: Giuliana Baggoley (convener until December 2013); Simon Hanna, Optometry Australia clinical policy adviser (convener from February 2014); Graham Fist, optometrist; Eve Hsing, optometrist; Paula Katalinic, Principal Optometrist, Centre for Eye Health and professional services manager, Optometry NSW/ACT; Josephine Li, optometrist, Australian College of Optometry; Lisa Penrose, optometrist and observer to the board of Optometry Queensland & Northern Territory; Roman Serebrianik, Lead Optometrist Primary Care, Australian College of Optometry.

REFERRAL PADS

With this issue of *Pharma* is a complimentary pad of 50 diabetes report forms for members of Optometry Australia. The forms are a quick and easy way to share the results of your examinations with other members of the diabetes management team, and build your reputation as a good communicator.

DrivetimeRadio CD

This issue of *Pharma* also includes an audio CD with two 10-minute segments on diabetic retinopathy and a case study.

Multidisciplinary approach to diabetic retinopathy

Mike Jackson

BOptom (UNSW)
GOVOceania.com

Dr Michael Chilov

MB BS FRANZCO
Retina Associates

CASE REPORT 1

Optometrist

THE STORY of this patient was first reported in November of 2013 in *Australian Optometry*. A 50-year-old male presented for a check-up at our Sydney optometric practice only because he had to complete a form for the Roads and Traffic Authority (RTA) of NSW. Because of his unstable diabetes, he had been required by the RTA to have his health assessed regularly to keep his licence. He had not had an eye examination for some time and was using ready-made spectacles that he had purchased from a petrol station.

Visual acuity was 6/12 in each eye and refraction did not help. His previous history included laser treatment and Avastin injections. He said he had not visited his ophthalmologist for two years because he could not afford the cost. It was my impression that he had not thought about his eyes since his previous consultation.

A fundus examination revealed that the patient had a long history of diabetic retinopathy. (Figures 1 and 2) There were scars from previous laser treatment, some lipid deposits and a haze around the discs, which were probably from new vessels. The left eye was marked by a large pre-retinal haemorrhage reaching down and around the macula.

Given the magnitude of the situation, the patient and I had a long conversation about his situation and the severity of his condition. During our discussion, he told me he had been seeing an ophthalmologist but stopped going when he could no longer afford to continue the visits. Rather than asking the ophthalmologist what he could do, he simply gave up and stopped attending.

The changes in his retina were affecting his vision but he managed until he met me. When I explained how urgently he needed to see an ophthalmologist, he said he would sell everything he owned so that he could afford to pay for specialist care.

At this point I contacted Dr Michael Chilov, a retina sub-specialist at the Retina Associates ophthalmic centre in Sydney to explain the situation. Dr Chilov asked me to send the patient to the centre the same day.

Ophthalmologist

The patient seen by Mr Jackson was examined by me on the same day. He had high-risk proliferative diabetic retinopathy with a left vitreous/preretinal haemorrhage. He had a 20-year history of diabetes with suboptimal glycaemic control and he had not seen an ophthalmologist for almost two years.

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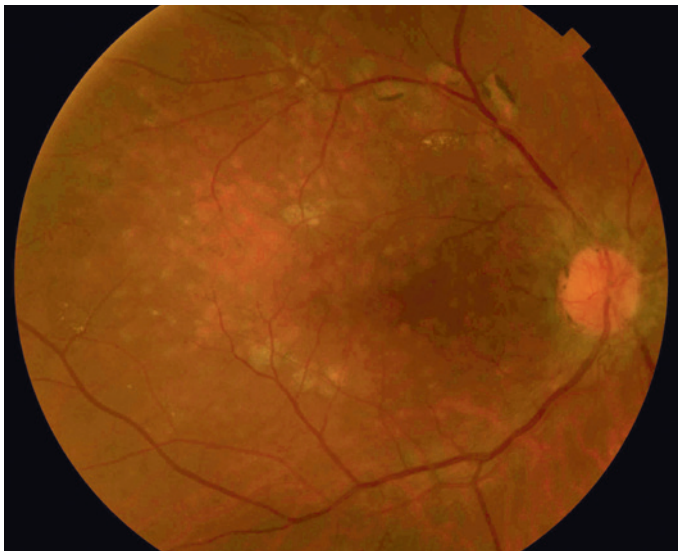
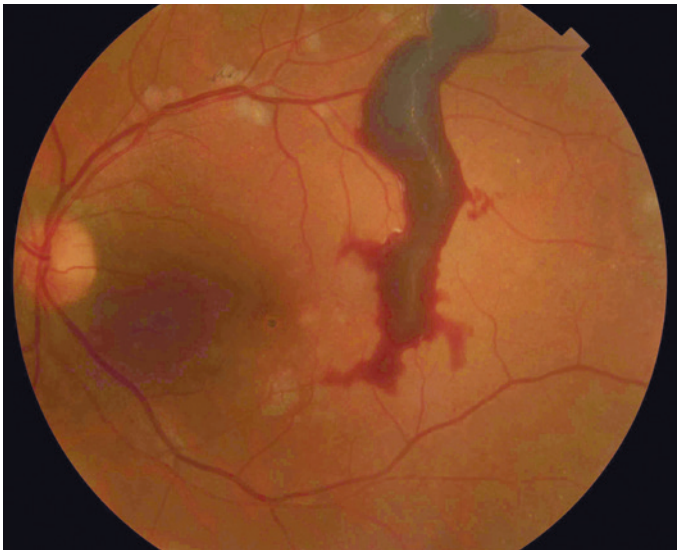
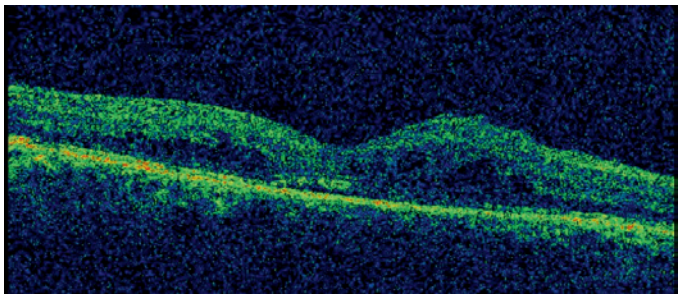


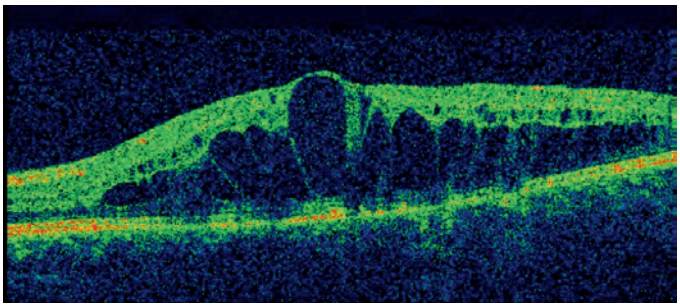
▲ Figure 1. Case 1. Fundus of right eye reveals laser treatment scars, lipid deposits and a haze around the discs



▲ Figure 2. Case 1. Fundus of left eye shows enormous pre-retinal haemorrhage



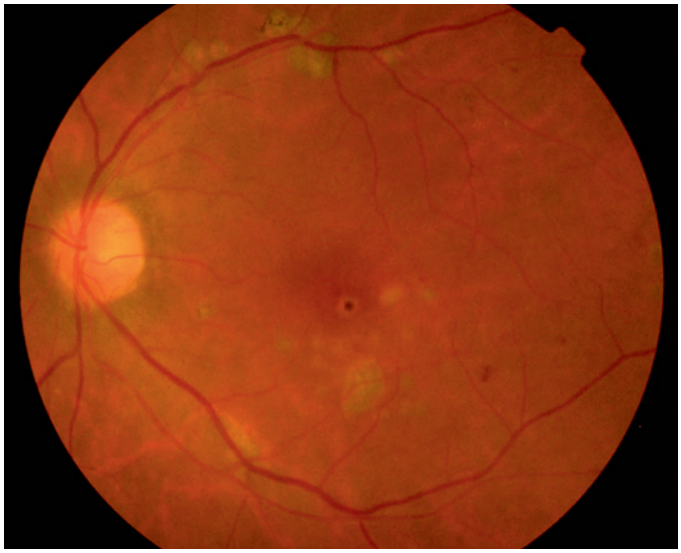
▲ Figure 3. Case 1. Extensive neovacularisation at the right disc (bilateral proliferative diabetic retinopathy)



▲ Figure 4. Case 1. Preretinal haemorrhage in the left eye

Multidisciplinary approach

From page 5



▲ Figure 5. Case 1. Left eye post-treatment

When I examined him, there was bilateral proliferative diabetic retinopathy, with a preretinal haemorrhage in the left eye and extensive neovascularisation at the right disc. The macula OCT also demonstrated macular oedema (Figure 3, right eye and Figure 4, left eye).

Prompt treatment was required in the left eye to prevent further bleeding. In patients with both proliferative retinopathy and macula oedema, Avastin (bevacizumab) is often used in the first instance. While panretinal photocoagulation remains the mainstay of proliferative diabetic retinopathy, it does take longer to have an effect on neovascularisation and can worsen diabetic macular oedema. Avastin has the ability to rapidly induce new vessel regression, prevent further bleeding and treat the coexisting macular oedema, and is followed by PRP laser surgery when the macular oedema is improved.

The other aspect to this patient's treatment was his diabetic control. His glycated haemoglobin (HbA1C) was 12.3 per cent (the general target is less than seven per cent) suggesting poor glycaemic control. In an effort to address this, I arranged a referral via his GP to an endocrinologist.

Once the diabetic macular oedema had come under control, I commenced PRP. Unfortunately, he has more recently developed macular oedema and is requiring ongoing Avastin injections to manage this. His visual acuity is Right 6/7.5 and Left 6/7.5+ (Figure 5, left eye post-treatment).

Ultimately, the patient satisfactorily completed his RTA health assessment and was able to maintain his drivers licence and return to his hobby of four-wheel driving.

Importance of timely examinations

This case amply demonstrates a number of the challenges in managing patients with diabetic retinopathy. All optometric practices will have diabetic patients and will be able to relate this case to patients they may have.

It is important that optometrists are active in the management of their diabetic patients—ensuring regular examination, developing a long-term relationship with the patients, attending to their vision and refractive needs, educating them, reinforcing need for regular screening to prevent vision loss and organising appropriate and timely referral when required.

The screening for diabetic retinopathy as part of a comprehensive eye examination is a critical part of diabetic management. This assessment should be by way of a dilated fundus examination.

Unfortunately, the circumstances surrounding the presentation in this case report are not uncommon in my

practice. Whether it is the patient who wakes with acute vision loss from a vitreous haemorrhage as a result of proliferative diabetic retinopathy, or the patient who fails their vision test for their drivers licence from diabetic macular oedema, the goal of these examinations is to detect early signs of retinopathy to allow early intervention and prevent this from occurring.

Many cases of sight-threatening retinopathy are not in patients in whom the signs were missed, but rather patients who have slipped through the gaps. Many patients with potentially sight-threatening retinopathy will often be relatively asymptomatic and not understand the need for regular assessment—or simply just forget.

It is important to educate patients about the need for ongoing annual reviews, even if they appear asymptomatic. Optometric practices should have reminder systems in place to ensure their patients return for regular review as per the screening guidelines.

Importance of timely referrals

Optometrists should aim to report their findings to the patient's GP and an endocrinologist (if involved). If managing a patient in conjunction with an ophthalmologist, the ophthalmologist should receive a diabetes report form with a summary of findings or concerns the optometrist may have.

Referral to an ophthalmologist depends on retinopathy grade and presence of diabetic macular oedema. All patients with sight threatening retinopathy—diabetic macular oedema or proliferative retinopathy, as in this patient—should be promptly referred to an ophthalmologist. Additionally, any patient complaining of reduced vision or unexplained reduced acuity should be referred to an ophthalmologist for further assessment.

Optometry Australia's newly revised clinical guidelines for the examination and management of patients with diabetic retinopathy provide some guidance in this regard. The guidelines recommend the need for follow-up, referral and appropriate management according to retinopathy grade based on recognised disease severity scales. (See Page 2)

The optometrist's role extends beyond assessment to diagnose retinopathy. Optometrists must be key players and active participants within a multidisciplinary diabetes health-care team. Patients who are receiving active treatment for diabetic retinopathy with an ophthalmologist should continue to see their optometrist. Their optometrist can attend to the patient's ongoing refractive needs, monitoring for treatment side-effects, such as raised intraocular pressure and cataract, and provide a valuable educational and support role for these patients.

CASE REPORT 2

Optometrist

THIS PATIENT'S visit with me was also prompted by the need to complete a form for the RTA of NSW. These required assessments commonly reveal serious pathologies in patients who otherwise would remain untreated.

On examination, we found his vision to be RE 6/12 and LE 6/15. This was due to his background retinopathy and probably some amblyopia. His retina showed signs of drusen and some dot, blot and flame haemorrhages.

Continued page 8

Dr ANITA SHARMA
General practitioner

MBBS FRACGP

Dr Anita Sharma has 24 years of experience as a general practitioner, with special training in treating diabetes and chronic diseases. She says that optometrists are ideally placed to advocate for optimal diabetes and health management, provided they work as part of a team.

'OPTOMETRISTS who familiarise themselves with the different classifications for diabetic retinopathy and the evidence-based review and referral schedules have a huge impact on the quality of patient care,' she said.

Dr Sharma was keen to point out that even if the patient is being referred on to an ophthalmologist, it is essential to keep the GP informed, as a professional courtesy, for legal purposes and to achieve the best health outcomes for the patient. 'The GP is generally the most frequently-visited health-care professional, even by the most non-compliant patient, so collaboration and communication of this information with the GP is vital,' she said.

'Optometrists are really well-placed to proactively identify diabetic retinopathy and refer these patients to GPs for consideration of fenofibrate and offer tactful reminders about better glycaemic control as part of "whole patient care".'

Patients generally turn to the GP for most advice on whether to commence a therapy so optometrists should leverage off of that,' she said.

Dr Sharma says that the level of glycaemic control, which is crucial for prevention of worsening diabetic retinopathy, is an important piece of information that is too often omitted in the correspondence between diabetes team members.

'All members of the multi-disciplinary team should be aware of the patient's level of glycaemic control and reiterate this point in their correspondence,' she said. 'This will go a long way in ensuring that action will replace clinical inertia.'

Multidisciplinary approach

From page 7

The patient, who was 67 years old, was being treated for diabetes, hypertension and cholesterol. His vessels showed crossing changes, consistent with hypertension.

He just narrowly passed the RTA standard but we referred him to Dr Michael Chilov at Retina Associates for a thorough review of his retinopathy.

Dr Chilov wrote back, outlining how he had found the patient's blood pressure and sugar level were too high and how he encouraged him to work with his GP for better control to avoid future blindness. Dr Chilov told the patient that he wanted to see him again in one year and to attend a review at our optometric practice in six months.

Ophthalmologist

This patient illustrates many of the points raised in the first case. When I first saw him, he had mild to moderate non-proliferative diabetic retinopathy and no macular oedema. I was happy to review him in 12 months but wanted him to see optometrist Mike Jackson to monitor his progress six months following his initial consultation with me.

I have found that it can often be helpful to alternate reviews with the patient's optometrist and my scheduled reviews. This allows the patient to maintain a relationship with their optometrist, attend to any new refractive needs, provide a further opportunity to educate the patient about diabetic retinopathy and detect any unexpected changes. Unfortunately, this patient did not follow my recommendations and did not attend follow-up despite reminders.

Optometrist

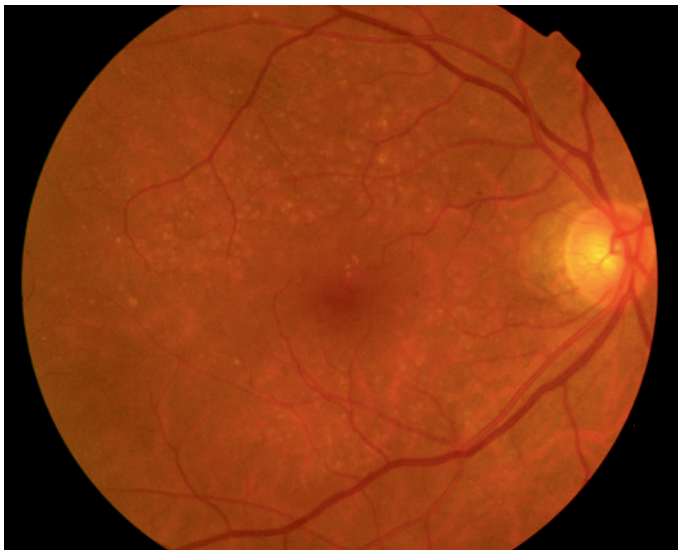
About two years later, the patient returned to our practice with another RTA form. His vision had slipped a little to RE 6/12 LE 6/18. He reported that his blood pressure was better but his limited English made me unsure. I was unable to determine how his blood sugar levels had been, but I clearly established that he had not been back to Dr Chilov.

His fundus still showed roughly the same level of retinopathy as his previous consultation, except for a tiny diamond-like embolus in the right eye, just over the macula, a Hollenhorst plaque. The presence of a Hollenhorst plaque is significant to the patient's health and the standard practice is to have a carotid Doppler test performed to check for blockage in the internal carotids.

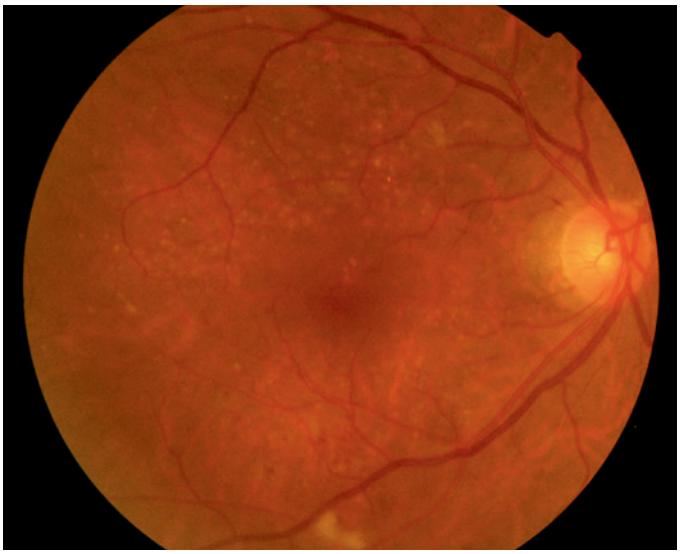
Ophthalmologist

During the two-year interval between examinations, the patient had developed the cholesterol embolus and his retinopathy had progressed to the severe non-proliferative stage. (Figures 6 and 7)

When I reviewed him, I arranged for a carotid Doppler study to exclude a carotid source for the embolus. Because I was also concerned about the worsening of his diabetic retinopathy, I arranged for him to see his GP for review of his glycaemic and cardiovascular risk factor control. No active ophthalmic intervention was required as there was no diabetic macular oedema and no proliferative retinopathy. ▲



▲ Figure 6. Case 2. Right fundus photograph at initial presentation demonstrating microaneurysms, grade one hypertensive retinopathy (AV nipping, copper wire reflex changes) and multiple hard drusen (intermediate and large)



▲ Figure 7. Case 2. Right fundus image two years later demonstrates a cholesterol emolus lodged at a vessel bifurcation superior to the macula. There is progression of the retinopathy with cotton wool spots, retinal haemorrhages and early venous beading.

Improve patient adherence

Eye-drop dispensers assist delivery of IOP medication

Helen Carter

GLAUCOMA EYE-DROP regimens have long been a significant problem for some patients but there is a growing number of strategies and devices available to help improve their adherence to ocular hypertensive therapy.

Among the most common reasons that patients give for their poor use of prescribed IOP drops are difficulties instilling eye-drops, inability to master a technique, physical barriers and medication side-effects.

Recent studies corroborate these patient comments, showing that many glaucoma patients are not administering their drops correctly and suggesting that education about instillation techniques can improve a patient's ability to instil drops correctly.[1]

Some studies suggest that optometrists should routinely show patients how to instil drops, watch them as they do it and then assess the patient's ability to instil drops at each follow-up consultation.

If patients are asked to demonstrate the technique, an opportunity for teaching may present itself if the patient is having difficulty. Demonstrating and teaching proper drop instillation to glaucoma patients using artificial tears can be done by an optometrist or another member of the practice staff who usually trains patients in contact lens insertion and removal.

Findings

A study published in the J*ournal of Glaucoma* in March 2012 found that nine out of 10 glaucoma patients were not administering their drops correctly.[2] Only six of 70 patients tested 'were able to correctly instil the eye-drop', that is, squeeze out one drop and instil it into the conjunctival sac without bottle tip contact.

The study, entitled 'Evaluating eye drop instillation technique in patients', focused on the often overlooked cause of adherence problems—the unintentional, improper dosing and instillation of glaucoma medication. The researchers observed 70 primary open-angle and primary angle-closure glaucoma patients, aged from 35 to 70 years, who had been self-administering glaucoma medications for at least six months. Those with arthritis, tremors and other impairments that might interfere with their ability to correctly instil drops were excluded.

Patients were asked to instil one drop from a bottle of artificial tears into one eye using the same technique that they use for glaucoma drops. The number of drops they squeezed out ranged from one to eight.

It is of concern that 31 per cent dropped the eye-drops on their eyelids or cheeks, and 75 per cent touched the tip of the bottle to their eye or periocular tissue, while only 28 per cent correctly closed their eyes after instilling drops. Just five per cent occluded their puncta.

In another inquiry into adherence strategies,[3] entitled the 'Eye drop instillation technique in patients with glaucoma' study, researchers found that there was a significant association between education relating to eye-drop instillation technique and the patient's ability to instil drops correctly.

Continued page 10

▲ Owen Mumford Autosqueeze Eye Drop Dispenser and Owen Mumford Autodrop Eye Drop Dispenser. Reusable, lightweight plastic devices that assist with the application of eye-drops. They are available from Diabetes and Medical Supplies.

▲ Pfizer's Xal-Ease plastic eye-drop dispenser and cap opener suitable for use with Xalatan and Xalacom eye-drops. The dispenser is available from Ophthalmologist FOC and can be ordered in by the patient's chosen pharmacist from Pfizer. It is complimentary for Xalatan/Xalacom patients.

Adherence strategies

From page 9

In the study, participants used self-administered topical medication for glaucoma or ocular hypertension and were asked to demonstrate how they usually instil eye-drops using a 5 ml bottle of sterile artificial tear solution.

More than half—54.1 per cent or 46 of 85 patients—had a poor drop technique, 11.8 per cent missed the eye, 15.3 per cent touched the tip of the bottle to the bulbar conjunctiva or cornea, and 27.1 per cent touched the eyelid or lashes with the bottle tip. Most—81.2 per cent—could not recall being shown how to instil eye-drops but previous instruction regarding drop instillation technique was significantly associated with good technique and increasing age was associated with poor technique.

The study authors recommended that the assessment of a patient's ability to instil eye-drops correctly should be a routine part of a glaucoma examination.

Strategies

Therapeutically-endorsed Gippsland optometrist Ken Thomas believes the biggest adherence issue is getting elderly, immobile patients to maintain regular contact with either an optometrist or an ophthalmologist.

'I am concerned that a number of patients, especially in rural areas, simply rely on their GP repeating the glaucoma script, and do not receive appropriate monitoring of intra-ocular pressures, fields and optic nerve head appearance,' he said. 'The challenge for our profession is to try and stop these people "falling through the cracks".'

Working in a rural area, he often has patients alternate visits between him and their ophthalmologist, or primarily see him and have infrequent trips to their ophthalmologist.

'This is primarily to minimise their travel. Glaucoma patients generally are in the older age group, they often don't drive and often have co-morbidities that contribute to mobility issues,' he said. 'This can make it difficult to get to their specialist. They are often dependent on family or friends to take time off work to transport them to Melbourne and they don't like to impose on them.

'Many patients appreciate the fact that field testing and OCT scans have lower cost when performed in an optometric setting compared to an ophthalmological clinic, and we are happy to provide copies of these reports for our patients to present to their glaucoma specialist.'

Thomas says the high use of prostaglandins (nearly 50 per cent of PBS glaucoma prescriptions) and increasing uptake of combination agents (29 per cent of PBS glaucoma scripts) means most patients are on monotherapy and require only one drop per day.

'This is a huge advantage in ensuring adherence to the treatment regimen. Ensuring that the drop is always taken at the same time of day is important for compliance, more than for IOP control,' he said. He suggests to patients that it might help if they stick a permanent note near their toothbrush, to remind them to have their eye-drops.

'If patients report difficulty with their drops, I usually instruct them to lie back, close their eyes and apply the drop to the inner canthal region,' Thomas said. 'Then the eyes are opened and this achieves adequate delivery of the medication. Most patients are surprised to hear that the eye retains only one-fifth to one-tenth of an eye-drop.'

Thomas doesn't usually recommend eye-dropper aids but says they work well for some patients.

Side-effects can be another reason for poor adherence.

'Alpha agonists have a high rate of allergic reaction, with up to 25 per cent of patients developing a problem. Median time for these follicular or dermatological reactions is 12 months so often the optometrist will be the first person to notice this change,' he said. 'Other reactions other than redness are not commonly encountered. It is vital for the optometrist to communicate with the initiating ophthalmologist before changing any medications.'

Head of the Sydney Eye Hospital Glaucoma Unit, Glaucoma Australia president and Clinical Associate Professor of Ophthalmology, University of Sydney, Professor Ivan Goldberg said that probably about two-thirds of glaucoma patients were non-compliant but suggested the term 'non-adherence' be used.

'It's a very complicated area of study with wide variations in the reasons different patients don't adhere,' he said. 'Some are personal reasons including disease "philosophy", understanding and education, while for others there are socio-economic reasons. Some have side-effect induced reasons and others have physical barriers to self-administration—"discompliance"—such as tremor, arthritis, muscle weakness and poor hand-eye co-ordination.

'Some reasons are disease-related and while glaucoma is relatively asymptomatic, chronic and incurable, progress is often slow so there is no immediate "price" paid by the patient that they notice for omitted medications.

'This truly needs to be individualised if solutions are to be found to help each patient, as each is unique and what motivates and influences long-term adherence and persistence varies enormously and might well change for an individual over time,' Goldberg said.

Professor Goldberg suggested various aids be mentioned so patients can consider them when necessary. 'Pfizer did some work with its Xalatan-bottle device and found it was a significant aid for 50 per cent of patients,' he said. 'Alcon also did work with its Travatan Dosing Aid (TDA) and found a similar figure. One of the challenges is that the various bottles are so different. What would work for a bottle of Xalatan won't work for Cosopt.

The national executive officer of Glaucoma Australia, Geoff Pollard, said the organisation supplied a limited number of free aids depending on the eye-drop manufacturers supplying them to the foundation. ▲

▲ The Opticare eye-drop dispenser fits securely around the eye, prevents touch contamination and ensures that drops go into the eyes and not down the cheek. The UK-designed product is sold in Australia by the Melbourne-based distributor Intelligent Health Systems.

▲ Autodrop Eyedrop Dispenser. A plastic dispenser, shaped and contoured to fit over a bottle of eye-drops, and around the eye socket to assist with easy, accurate dispensing of drops. Available in Australia from Diabetes and Medical Supplies.

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Dr Laura Downie

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ABSTRACTS

Association between reproductive factors and AMD in post-menopausal women

A population-based, cross-sectional study conducted in Korea has described an association between female reproductive factors and the development of late-stage AMD in post-menopausal women.

A nationally-representative dataset that included reproductive and ocular health information for 4,377 post-menopausal women (aged ≥ 50 years) was analysed from the 2010-2012 Korea National Health and Nutrition Examination survey.

Prevalence rates of early and late AMD were 11.2 per cent (95% confidence interval [CI], 10.1-12.5) and 0.8 per cent (95% CI, 0.5-1.2), respectively. Multivariate logistic regression analyses revealed that age (OR, 1.12 per one year), duration of lactation (OR, 0.91 per six months), and duration of use of oral contraceptive pills (OCP) (OR, 1.10 per six months) were associated factors for late-stage AMD.

The authors concluded that after controlling for confounders, a longer duration of lactation appeared to protect against the development of late AMD. A longer duration of OCP use was associated with a higher risk of late-stage AMD.

PLoS One 2014; 9: 7: e.102816.

Preventing pseudophakic cystoid macular oedema following cataract surgery

A review has found weak evidence for the use of topical non-steroidal anti-inflammatory drug (NSAIDs) therapy in controlling post-operative inflammation after cataract surgery.

The systematic review has compared the efficacy of topical corticosteroid treatment with topical non-steroidal anti-inflammatory drugs therapy, following uncomplicated cataract surgery. The main outcome measure was defined as post-operative inflammation and pseudophakic cystoid macular oedema (PCME), in patients undergoing phacoemulsification with posterior chamber intraocular lens implantation for age-related cataract.

A total of 15 randomised clinical trials were identified from the systematic literature search. Post-operative inflammation was reported to be less in patients randomised to NSAIDs. The prevalence of PCME was significantly higher in the corticosteroid group than in the NSAID group (3.8 per cent vs 25.3 per cent; risk ratio: 5.35, 95% CI, 2.95-9.76). There was no significant difference in the number of adverse events between the two treatment groups.

It was concluded that there was low to moderate quality of evidence that topical NSAIDs are more effective in controlling post-operative inflammation after cataract surgery. High-quality evidence was found to support the premise that topical NSAIDs are more effective than topical corticosteroids in preventing PCME.

The authors recommended the use of topical NSAIDs to prevent inflammation and PCME after routine cataract surgery.

Ophthalmology 2014; June 13. Epub ahead of print.

Smoking deception and AMD

Smoking deception rates for patients with AMD were found to be higher than generally reported in the US population.

Smoking has been consistently identified as the most important modifiable risk factor for age-related macular degeneration (AMD). Smoking deception, or failing to self-report as a smoker, is a concern in studies of smoking-related disease.

Data from the 2005 to 2008 National Health and Nutrition Examination Survey were used to produce estimates of smoking deception among three ethnic groups within the United States population. Comparisons of self-reported rates of cigarette use, any nicotine product use, and serum cotinine levels were used to produce estimates of potential smoking deception among adults older than 40 years with any-level of AMD and those at risk of late-stage disease.

Any-level AMD was evident in 6.7 per cent (95% CI, 5.6-7.8 per cent) of this cohort. Excluding those with late-stage AMD, 9.7 per cent (95% CI, 8.3-11.0 per cent) were at risk of developing late-stage disease. Among individuals with any level of AMD, 5.4 per cent (95% CI = 2.1-8.6 per cent) were potential smoking deceivers. A similar rate was seen among those at risk of late-stage disease at 5.0 per cent (95% CI = 2.3 per cent to 7.6 per cent).

The findings suggest that as many as 450,000 adults in the USA who are at risk of late-stage AMD misclassify their smoking status.

Optom Vis Sci 2014. June 26. Epub ahead of print.

How do Müller cells work?

A paper in the prestigious journal *Nature Communications* has described the wavelength-dependent wave guiding properties of retinal Müller cells.

Retinal Müller cells separate between wavelengths to improve day vision with minimal effect on night vision.

Using computational modelling and experimental imaging methods, the authors found that Müller cells, which are the major type of glial cells in the retina, concentrate the green-red part of the visible spectrum onto cone photoreceptors, thereby allowing the blue-purple part to leak onto nearby rods.

Light propagation by Müller cells through the retina was reported to be an integral part of the first step in the visual process, increasing photon absorption by cones while minimally affecting rod-mediated vision.

Nat Commun 2014; 5: 4319.

A novel ciprofloxacin-releasing silicone hydrogel contact lens

A novel silicone hydrogel contact lens designed for the extended release of ciprofloxacin may be beneficial to supplement or augment future

treatments for microbial keratitis.

Model silicone hydrogel contact lens materials were synthesised using a molecular imprinting technique to augment ciprofloxacin-release kinetics. Various contact lens properties, including light transmission and surface wettability were determined, and the *in vitro* ciprofloxacin-release kinetics elucidated using fluorescence spectrophotometry. The synthesised materials were then evaluated for their ability to inhibit *Pseudomonas aeruginosa* growth, both *in vitro* and in a rabbit model of microbial keratitis.

The synthesised contact lenses were described to have material properties similar to those of commercial lens materials and released ciprofloxacin for more than eight hours. It was reported that *in vivo*, there was no statistically significant difference between the number of colony forming units (CFU) recovered from corneas treated with ciprofloxacin eye drops (0 CFU/cornea) and those treated with one of two modified contact lenses (mean: 4.3x10^3 CFU/cornea and 2.1x10^3 CFU/cornea).

Invest Ophthalmol Vis Sci 2014; Jul 15. Epub ahead of print.

Contact lens-assisted collagen cross-linking

A report in the *Journal of Refractive Surgery* describes a novel method of contact lens-assisted corneal collagen cross-linking (CXL) in eyes with corneal thicknesses that would typically preclude standard CXL.

Findings from 14 eyes with progressive keratoectasia and corneal thicknesses between 350-400 microns, following epithelial debridement, were included in the case series. After epithelial abrasion, iso-osmolar riboflavin 0.1 per cent in dextran was applied every three minutes for 30 minutes. An ultraviolet (UV) barrier-free soft contact lens soaked in iso-osmolar riboflavin 0.1 per cent for 30 minutes was placed on the cornea.

Once the minimum corneal thickness value was confirmed to be greater than 400 microns with the contact lens in situ, UVA irradiance was commenced; iso-osmolar 0.1 per cent riboflavin was also instilled in the pre-corneal and pre-contact lens region during the procedure. The mean depth of CXL stromal demarcation was 252.9 ± 40.8 µm (range: 208 to 360 µm), with no significant effect on endothelial cell count ($p = 0.06$).

The authors concluded that based on the corneal stromal demarcation line depth and the absence of adverse corneal outcomes, this technique appeared to be safe and effective in performing CXL in relatively thin corneas.

J Refract Surg 2014; 6: 366-372.

Girls benefit from cheese

A prospective study conducted in Australian adolescents has found that the consumption of dairy products, in particular cheese may have a beneficial effect on blood pressure (BP), particularly among girls.

The study aimed to prospectively assess whether dairy food consumption (milk, cheese, yoghurt) was associated with BP and retinal microvascular signs among adolescents. A total of 2353 12-year-olds and 1216 17-year-olds were examined; longitudinal analyses involved 888 subjects with complete baseline and follow-up data.

After multivariable adjustment, in girls each serve/day increase in total dairy intake was concurrently associated with 1.04 ($p = 0.03$) and 1.10 mmHg ($p = 0.02$) decreases in mean diastolic and arterial BP respectively; each serve/day increase in cheese intake over five years was concurrently related to 7.18 ($p = 0.001$), 5.28 ($p = 0.002$) and 5.79 mm Hg ($p = 0.001$) decrease in mean systolic, diastolic and arterial BP, respectively.

Nutr Metab Cardiovasc Dis 2014. June 14. Epub ahead of print.

Cataract surgery improves sleep for patients with IOLs

It has been found that a patient's overall sleep quality and sleep latency is improved after cataract removal, irrespective of the type intraocular lens (IOL) that is implanted.

This study investigated the level of sleep disturbance in patients both before and after cataract surgery, and compared the effect of the implantation of UV-blocking or blue-filtering IOLs. Quality of sleep was quantified in 961 patients undergoing cataract surgery using a validated questionnaire.

Prior to cataract surgery, approximately half of patients reported poor sleep. Cataract removal was found to significantly improve overall sleep quality and sleep latency at one month post-operatively; this effect was sustained at 12 months.

It was concluded that these data demonstrate that implantation of blue-filtering IOLs do not have a negative impact upon the sleep-wake cycle, compared with UV-blocking IOLs.

Invest Ophthalmol Vis Sci 2014. June 26. Epub ahead of print.

Corneal sensitivity and tear function in neurodegenerative disease

Neurodegenerative diseases may be associated with reduced corneal sensitivity and abnormal tear function.

In this study, corneal sensitivity and tear function were measured in patients with different forms of neurodegenerative disease and findings were compared with age- and sex-matched controls.

Patients with Alzheimer's disease ($n = 20$), multiple sclerosis ($n = 20$), Parkinson's disease ($n = 30$), Friedreich's ataxia ($n = 10$) and epilepsy ($n = 21$) were recruited from a tertiary neurology department. Corneal sensitivity was measured using the Cochet-Bonnet aesthesiometer. Tear function tests included tear-break-up-time (TBUT) and Schirmer test without anaesthesia.

Compared with control subjects, mean corneal sensitivity was significantly reduced in all of the pre-defined patient groups with neurodegenerative disease ($p < 0.05$), except for patients with Friedreich's ataxia ($p > 0.05$). Mean TBUT was also significantly shorter in patients with Alzheimer's disease and multiple sclerosis than controls ($p < 0.05$). Mean Schirmer test was relatively lower only in epilepsy patients ($p < 0.05$).

These findings suggest the presence of varying degrees of abnormality in corneal sensitivity and tear function in different forms of systemic neurodegenerative disease.

Curr Eye Res 2014; Jun 23:1-6. ▲

Optic nerve head drusen

OCT analysis and controversial treatment options

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OPTIC nerve head drusen (ONHD) is not an uncommon finding with a reported prevalence of between 0.4 and 3.7 per cent of the population.[1] Its inheritance is considered autosomal dominant linked with small ONH and a small optic foramen, and the drusen bodies are calcified acellular deposits. They range in size from five to 1,000 microns and are located in the prelaminar portion of the optic nerve head.

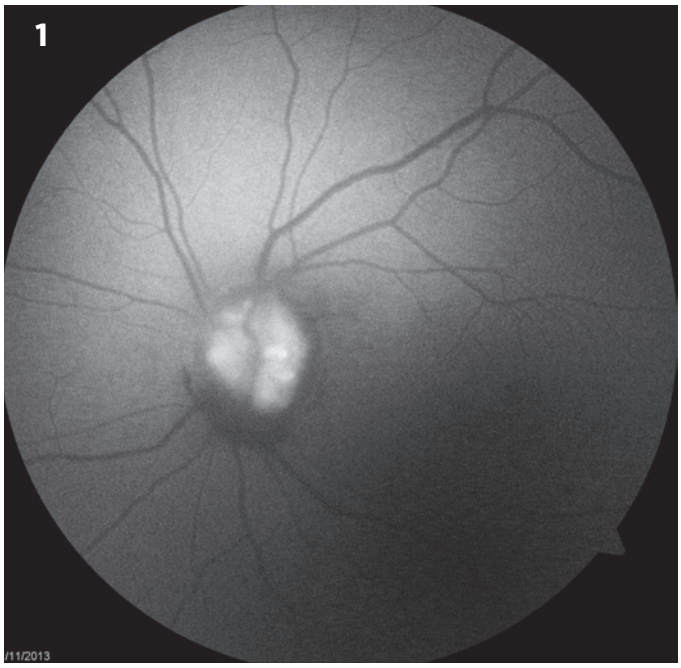
ONHD is often buried when young and as the glial tissue overlying the retina thins, the drusen become more obvious and fluoresce (Figures 1 and 2). Fundus autofluoresence highlight the drusen due to the refractile nature of the calcium; however, the definitive test is B scan ultrasonography. Differential diagnosis from true papilloedema is essential as the latter signifies raised intracranial pressure that can be life threatening

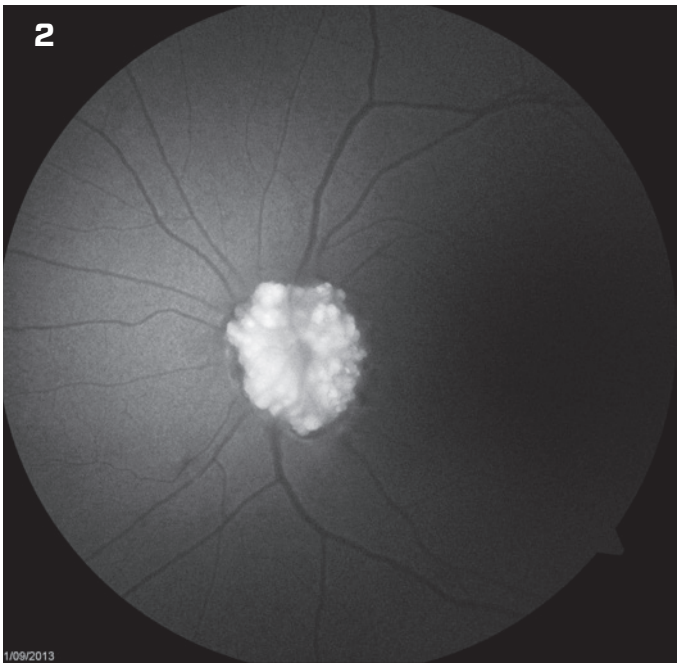
As the drusen become more visible, visual field defects emerge due to direct pressure on the axons as well as ischaemia as a result of the compromise to the vascular supply. Literature reports the incidence of visual field defects varying from 24 up to 87 per cent,[1] typically arcuate and not dissimilar to primary glaucoma.

OCT analysis details a thinning of the retinal nerve fibre layer in accordance with the loss (Figure 3, and normative data details, Figure 4), and the loss can be devastating. All eye-care practitioners should be aware of the greater risk of ischaemic optic neuropathy with ONHD and caution patients on sudden unilateral loss of either field or vision.

Treatment options

Treatment for visual field loss with ONHD is controversial. Modalities range from no treatment through to medical therapy and on to surgical options such as ONH decompression and radial optic neurotomy. Success





▲ Figures 1 and 2. Fundus autofluoresence highlights the drusen due to the refractile nature of the calcium, but the definitive test is B scan ultrasonography.

of the modalities seems to be based on anecdotal evidence as in general, the number of cases is small and the changes are slow and occur over a long period.

Grippo and colleagues (2008)[2] studied 103 eyes with ONHD and found that in the group of 22 who had coincidental ocular hypertension, 90.9 per cent had visual field loss compared with 66.7 per cent who were normotensive.

It is unclear whether ONHD masks glaucoma or whether ONHD is a risk factor for glaucoma. Certainly, the use of glaucoma medications seems a logical step given this association, and it is intuitive to try to reduce the intraocular pressure and also improve the vascular perfusion of the optic nerve.

Change appears to be the catalyst to begin treatment. Baseline visual fields and OCT is essential, along with careful monitoring of the patient. Loss is generally slow; however, if there are signs of progression then therapy should be considered. Brimonidine has shown neuroprotective characteristics in the rat model[3] but it has a greater incidence of allergy. Current theory suggests hypotension should be avoided to preserve vascular perfusion relegating beta blockers to second-tier treatment. Prostaglandins may therefore be first-line course of action.

Prescribing of glaucoma agents for ONHD is considered an 'off label' process, so the cost to the patient is not subsidised by the government. This is an important consideration, given that the use of glaucoma medication is speculative in ONHD and the cost may be prohibitive for some. Careful counselling should be undertaken and patients given informed choices—even though no good scientific studies support the benefit, the rationale is solid and if there is a chance of preserving vision and field with a safe and proven medication, then it should be considered. ▲

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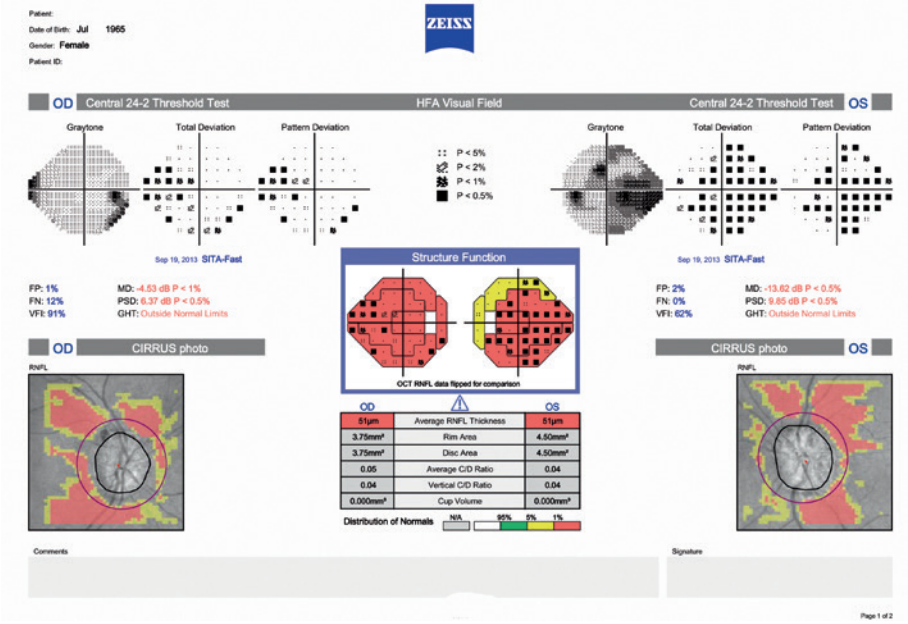
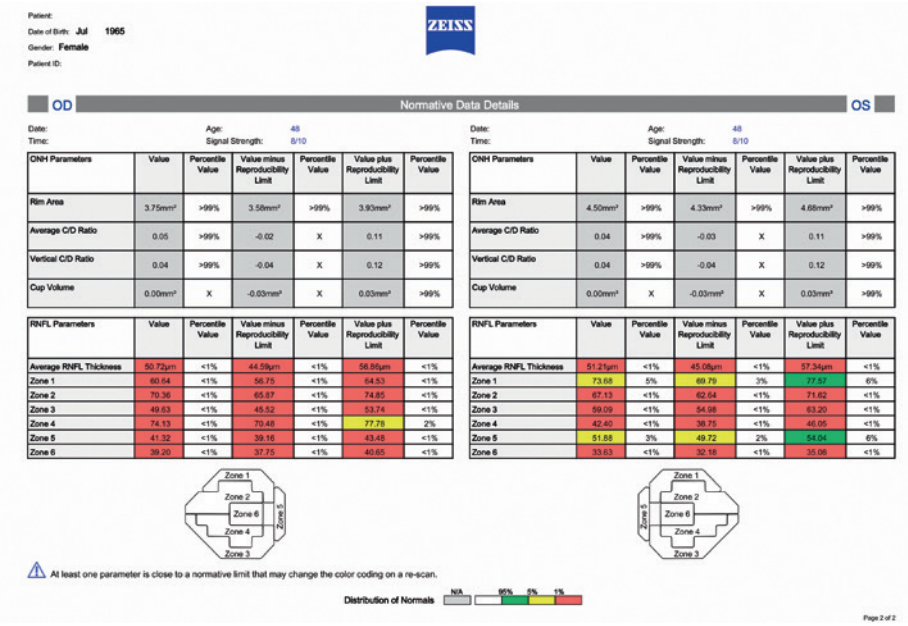


▲ Figure 3. OCT analysis shows a thinning of the retinal nerve fibre layer



▲ Figure 4. Normative date details

Corneal collagen cross-linking for keratoconus

Dr Elsie Chan

FRANZCO

CORNEAL collagen cross-linking (CXL) was introduced in 1998 as a treatment that could potentially halt the progression of keratoconus.[1] Since the first clinical study of CXL was published in 2003,[2] CXL has been rapidly incorporated into clinical practice. A growing number of modifications to the treatment protocol are now being explored in an effort to increase the efficacy and safety of the treatment.

Background

CXL is based on the theory that the decreased biomechanical strength in keratoconus is related to a reduction in cross-links within collagen fibres.[3] The treatment utilises a photosensitiser, riboflavin (vitamin B2) which is exposed to ultraviolet A (UVA) irradiation to produce an oxygen-dependent chemical reaction, leading to cross-linking. Riboflavin also absorbs UVA to limit the depth of its effect.

The procedure is performed under topical anaesthesia, followed by a nine-millimetre epithelial debridement. This is necessary as riboflavin does not penetrate through an intact epithelial layer. Riboflavin drops are then instilled for 30 minutes followed by UVA irradiation (3mW/cm^2) for a further 30 minutes, during which the riboflavin drops are continued.[4]

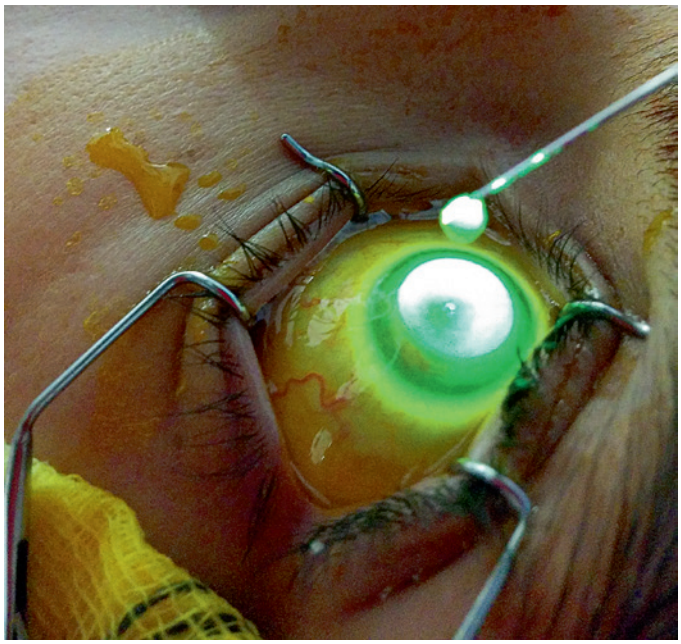
Pre-clinical studies have shown that CXL increases the corneal collagen diameter by 12.5 per cent, increases its stiffness by over 300 per cent and increases its stability to enzymatic digestion.[5-7] The treatment depth has also been demonstrated to be limited to the anterior 300-350 µm, with endothelial cell damage occurring when the corneal thickness falls below 400 µm.[4,8] (Figure 1)

Clinical results

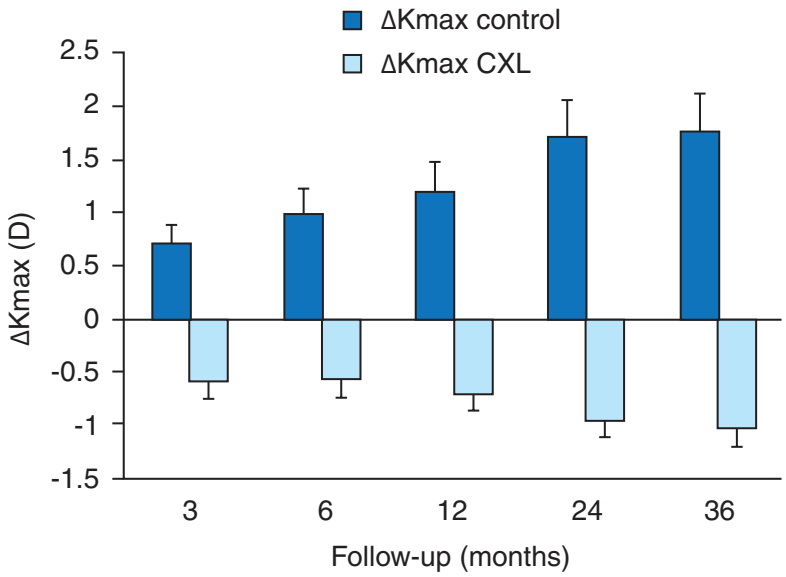
In 2003, Wollensak and colleagues published the first clinical results of CXL for progressive keratoconus.[2] They reported that progression stopped in all treated eyes with a mean improvement of -2.01 D in the maximum keratometry value (Kmax) on corneal topography after an average follow-up period of 23 months. Since then, numerous case series have been published supporting these results, with reported improvements in Kmax ranging from -0.49 D to -2.66 D.[9,10] Changes in uncorrected visual acuity (UCVA) and best spectacle-corrected visual acuity (BSCVA) have been more variable, with several studies reporting a modest or no change in UCVA,[11] whereas Caporossi and colleagues reported an improvement in UCVA by 2.85 Snellen lines and BSCVA by 2.03 lines.[12]

One of the only randomised, controlled trials comparing eyes treated with CXL and control eyes has been conducted in Melbourne at the Centre for Eye Research Australia and the Royal Victorian Eye and Ear Hospital. In this trial, we found that Kmax flattened by a mean of -1.03 D after three years in treated eyes, whereas eyes in the control group steepened by +1.75 D. A similar trend was seen in UCVA.[13] (Figure 2)

Studies focusing on the paediatric population have reported more variable results compared to the adult age group, with changes in Kmax ranging from an improvement of -1.27 D after two years[14] to 55 per cent of eyes progressing by three years.[15] There may be a less sustained effect due to a more rapidly progressing disease in this younger age group.



▲ Figure 1. Intra-operative photograph demonstrating the ultraviolet light source irradiating the cornea, which has been soaked with riboflavin



▲ Figure 2. Bar graph showing the mean change in maximum simulated keratometry value (Kmax) between baseline and 3, 6, 12, 24 and 36 months after treatment for the control and treatment groups. In the control group, there was a significant increase in Kmax compared with continued flattening observed in the treatment group. The columns represent the mean change in Kmax from baseline (ΔKmax) in dioptres (D) and the error bars represent the standard error. CXL = corneal collagen cross-linking.[13]

Overall, most studies report stabilisation in Kmax in over 80 per cent of treated eyes. Longer term studies suggest stability of the treatment until at least four to six years.[16]

Complications

Complications following CXL have been reported. While a temporary stromal haze is seen in almost 90 per cent of treated eyes (Figure 3), up to 8.6 per cent of cases have been reported to permanently affect visual acuity.[17] Other complications include treatment failure, sterile infiltrates (up to 7.6 per cent of eyes), scarring,[18] infectious keratitis[19] and irreversible corneal oedema.[20] Rare complications include corneal melting and perforation.[21]

Variations in CXL treatment protocol

• Trans-epithelial treatment

There has been much interest in the establishment of a technique to enable CXL to be performed without epithelial debridement. Trans-epithelial or 'epithelium-on' CXL has the advantage of minimising post-operative pain and reducing the risk of infectious keratitis. It may also be useful in the treatment of thin corneae and the paediatric age group. One of the more popular means to enhance penetration of riboflavin across the epithelium has been to use additional agents such as EDTA and benzalkonium chloride in combination with riboflavin. Despite the popularity of trans-epithelial CXL, clinical results have been variable, ranging from flattening of Kmax by -2.97 D[22] to progression by +0.48 D,[23] suggesting that this technique may be less effective than conventional treatment.

• Accelerated CXL

Treatment protocols using decreased irradiation times are gaining popularity. While the conventional protocol achieves a total UVA exposure of 5.4J/cm^2 with 30 minutes of UVA at 3mW/cm^2, a similar exposure is possible by increasing the irradiance and decreasing the treatment time according to the Bunson-Roscoe law of reciprocity. While devices offering UVA at higher irradiances are commercially available and being used widely, there remains limited evidence for accelerated CXL in the peer-reviewed literature. There may also be a limit to the minimum treatment time, as oxygen depletion may occur with higher oxygen usage rates at high irradiances. Hammer and colleagues demonstrated that the *in vitro* stiffening effect of CXL using UVA at 18mW/cm^2 for five minutes was unchanged compared to control eyes.[24] A clinical study comparing accelerated (30mW/cm^2 for three minutes) and conventional CXL found an improvement in Kmax in the conventional group and Kmean (mean keratometry value) in both groups compared to baseline after 12 months.[25]

• Treatment of thin corneae

Treatment of corneae less than 400 µm has been shown to lead to endothelial cell damage.[26] Modifications in the treatment protocol are therefore necessary before treatment can be considered these eyes. One option is the use of hypotonic riboflavin to swell the cornea, although there are limited published results using this technique. Two studies suggest stabilisation of keratoconus 12 months following treatment without any damage to the endothelial cells.[27,28] Our own unpublished data also support the safety and efficacy of using hypotonic riboflavin.

• CXL with refractive surgery

As CXL gives only modest improvements in visual acuity, there has been much interest in combining CXL with refractive procedures such as intra-corneal ring segments, PRK and phakic intraocular lenses. Results suggest that refractive procedures combined with CXL can lead to significant improvements in visual acuity for at least 12 months.[29-31] Some authors also advocate using CXL to stabilise the cornea during refractive procedures for patients at risk of developing ectasia,[32] although there remains a lack of clinical data to support the efficacy of CXL for this indication.

Other indications

The efficacy of CXL for keratoconus has led to its use in other corneal ectasias including post-LASIK ectasia and pellucid marginal degeneration.

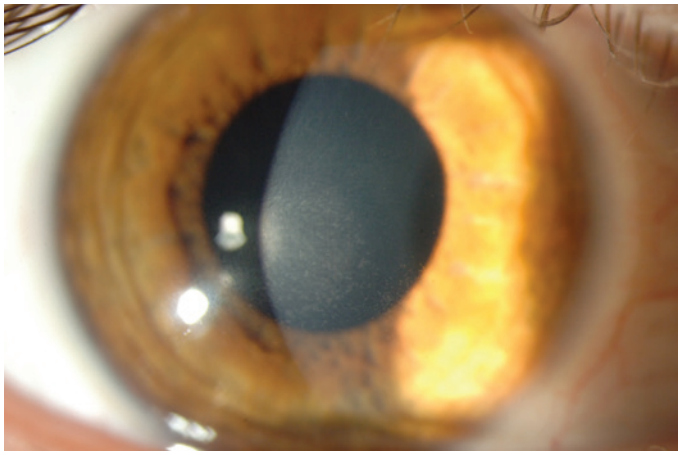
Continued page 18

CXL for keratoconus

From page 17

Conclusion

The current recommendations for CXL are in eyes with documented progression of keratoconus where the corneal thickness is above 400 µm at the time of treatment. While results show a modest improvement in corneal topography and visual acuity measurements, stability can be achieved in over 80 per cent of treated eyes with only a small risk of treatment-related complications. Further clinical studies with extended follow-up are needed to establish the safety and efficacy of alternative treatment protocols. ▲



▲ Figure 3. Slitlamp photograph of post-operative haze one month following treatment

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Alzheimer's disease and the eye

Group investigates retinal Aß plaques

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THE ABILITY to non-invasively visualise neurons and blood vessels is an attribute unique to the eye. This window provides an unparalleled view into general health, as many cardiovascular and brain disorders can have manifestations in the eye.[1,2,3] These attributes render the eye and in particular, the neuro-vascular retina an ideal surrogate or 'biomarker' for systemic and neural disease.

Optometrists know that using the eye as an indicator of systemic disease is not novel. In current optometric care, assessing the eye for signs of diabetic change is standard practice and can offer perspective of the detection and the progression of the diabetes, as well as the effectiveness of ongoing treatment.

More recently, changes in retinal vessel diameter have been shown to be early predictors of stroke[4] and studies are ongoing to make this assessment commonplace among ocular health professionals.

In addition to vascular disease, the eye can also give insight into brain disorders. The eye is an out-pouching of the brain and if parallel changes occur in both of these organs, then the retina may provide a unique way to assess cortical disease.

Retinal imaging may provide a simple and inexpensive alternative to cortical imaging, which is limited by the skull. This barrier prevents simple optical imaging of the brain and necessitates the use of expensive and complex cortical imaging techniques such as PET and MRI.

Need for a biomarker

Alzheimer's disease is a brain disorder that is in desperate need of a viable biomarker. Alzheimer's is characterised by a progressive decline in memory and executive functions, and its hallmark is the deposition of cerebral beta-amyloid (Aß) deposits. There remains no effective long-lasting treatment for Alzheimer's and its annual economic cost globally has been estimated at US$600 billion.[5]

Australia's baby-boomer bulge means that in the coming decade, a dramatic shift in the demand for health care will manifest itself—from cardiovascular disease and cancer to neurodegenerative conditions.[6]

At present, the only definitive diagnosis for Alzheimer's disease is post-mortem confirmation of plaques in the brain.[1] Recent clinical findings suggest that successful treatment needs to start in the prodromal stages of the disease, thus making it imperative to have an early biomarker.

The inability to make definitive early diagnosis and monitor disease progression frustrates the development of a cure for Alzheimer's disease. Less than one in 10 drugs progresses to market,[7] in part due to the lack of effective biomarkers.[7] Recent advances in PET imaging show promise in defining biomarkers for Alzheimer's disease;[8,9,10] however, the technology is expensive and its use in everyday practice is limited. An inexpensive,

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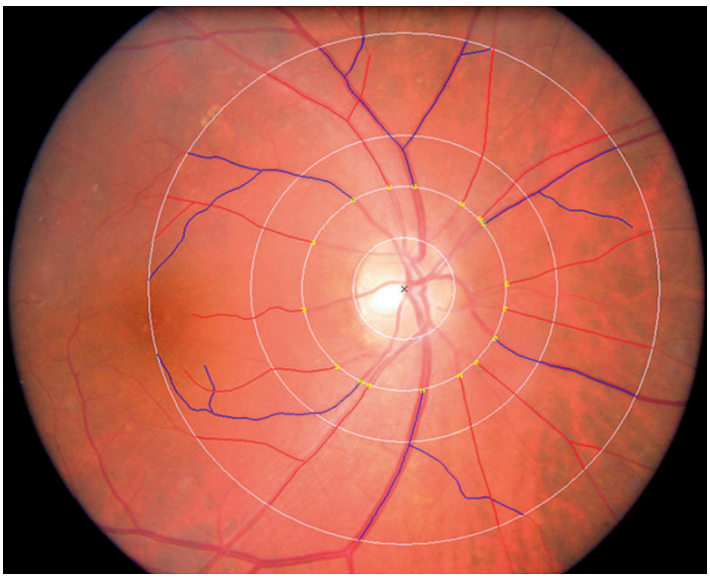


▲ Figure 1. Retinal vessel analysis when used in conjunction with fundus photography provides further insight into cardiovascular[4] and brain health[15]

Alzheimer's disease

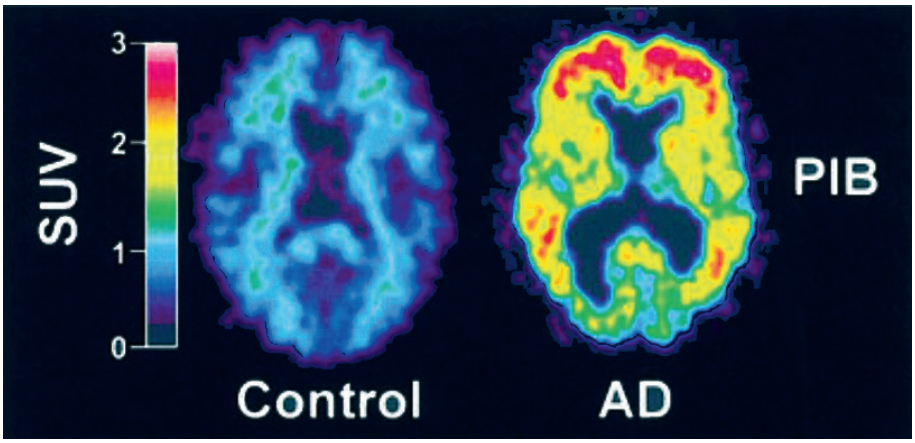
From page 19

specific and quantitative ocular biomarker of Alzheimer's disease would improve the likelihood of finding a cure.

Eye as a biomarker for Alzheimer's

While changes in the brain are well recognised in Alzheimer's disease, growing evidence shows that the disease also affects the eye.[1] Visual symptoms are frequent early complaints in patients with Alzheimer's disease, including deficiencies in colour vision, contrast sensitivity and motion perception.[11,12] Although the origin of some of these symptoms may occur at the visual cortex, other studies have shown that changes do occur in the retina.

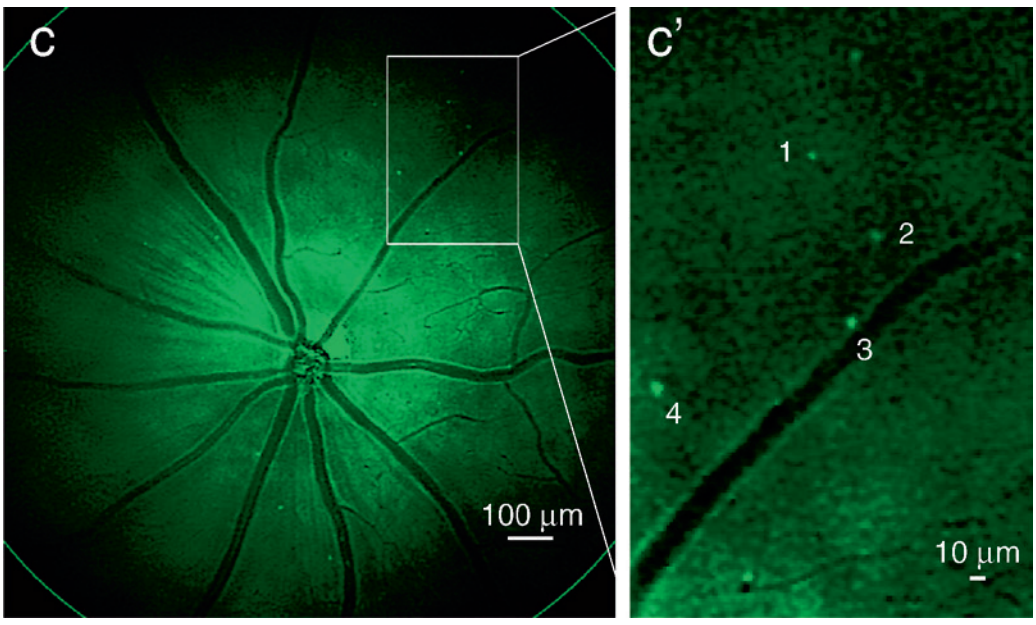
Multiple studies have indicated that Alzheimer's patients exhibit thinning of retinal nerve fibre layer and an associated reduction in the electroretinogram.[1,13] Alzheimer's disease patients exhibit cerebral blood flow reduction[14] and recent studies indicate that retinal vascular changes can also be seen in Alzheimer's disease.[11,15] The hallmark Aß plaque deposits that occur in the brains of Alzheimer's patients have also been shown to occur in their retinas. Retinal Aß plaques have been identified in tissue from both human Alzheimer's patients[10,16] and rodent Alzheimer's models.[17] A recent study has imaged retinal Aß plaques *in vivo* in a rodent model (Figure 1) following injection of a contrast agent, curcumin.[10]



▲ Figure 2. PET imaging using Pittsburgh Compound-B6 is a specific biomarker of Alzheimer's disease but is expensive as an everyday screening tool

At the University of Melbourne, our group is investigating vascular, neural and structural developments as ocular signs of Alzheimer's disease and developing non-invasive techniques to analyse them. It is hoped that these studies will translate to a clinical tool that can identify the presence of Alzheimer's disease and monitor its progression.

This work is supported by the Melbourne Neuroscience Institute through an MNI fellowship to Dr Christine Nguyen and a Strategic Australian Postgraduate Award (STRAPA) doctoral award to Jeremiah Lim. If successful, future optometrists may be able to screen their patients for Alzheimer's disease, thus playing a key role in early detection of this devastating illness. ▲



▲ Figure 3. Plaques (numbered 1 to 4) in Alzheimer's disease can be viewed *in vivo* in the retina with (green) curcumin staining in rodent eyes[10]

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Breakthrough could end eye injections

RESEARCHERS at the University College London have demonstrated that it is possible to create formulations of tiny nanoparticles loaded with the AMD drug Avastin and deliver significant concentrations to the back of the eye.

In an article published in the nanotechnology journal *Small* entitled 'Topical delivery of Avastin to the posterior segment of the eye *in vivo* using annexin A5-associated liposomes', the authors explain that they overcame the bypass barriers within the eye by loading tiny nanoparticles with the drug Avastin and then suspended those nanoparticles in liquid and used that liquid in the form of eye-drops to treat the eyes of rats and rabbits.

The results showed that the medication had been as effective as it has already been shown to be via injection. The researchers suggested that, in theory, other drugs such as Lucentis could effectively be delivered by this method.

'The development of eye-drops that can be safely and effectively used in patients would be a magic bullet—a huge breakthrough in the treatment of AMD and other debilitating eye disorders,' lead author Professor Francesca Cordeiro said.

Small 2014; 10: 8. doi: 10.1002/smll.201303433

Coffee reduces risk of type 2 diabetes

INCREASING coffee consumption by on average one and half cups per day over a four-year period reduces the risk of type 2 diabetes by 11 per cent.

Study authors used observational data from three large, prospective, US-based studies in their analysis. Information on diet, lifestyle, medical conditions and other chronic diseases was collected every two to four years for more than 20 years.

The authors found that participants who increased their coffee consumption by more than one cup/day over a four-year period had an 11 per cent lower risk of type 2 diabetes in the subsequent four years compared to those who made no changes in consumption. Participants who decreased their coffee intake by one cup a day or more had a 17 per cent higher risk for type 2 diabetes. Changes in tea consumption were not associated with type 2 diabetes risk.

The authors concluded that those with highest coffee consumption and who maintained that consumption had the lowest risk of type 2 diabetes, 37 per cent lower than those who consumed one cup or less per day.

Diabetologia 2014; March 21. Epub ahead of print.Small 2014; 10: 8. doi: 10.1002/smll.201303433

Two players behind diabetic retinopathy

CHEMICALLY reactive molecules must come from both the bone marrow as well as the retinal cells themselves to cause the events that destroy healthy blood vessels and form leaky new ones and ultimately, ruin vision.

According to the study published in the online publication *PLOS ONE*, it is a cascade that requires these two players to signal the next event that causes the damage.

Excessive glucose in the blood prompts excessive production of reactive oxygen species (ROS), and the light-sensitive retina is particularly vulnerable. The research team had previously documented that ROS from white blood cells produced by the bone marrow as well as from retinal cells were the major instigators in diabetic retinopathy, but they were not sure which mattered most.

They looked at different scenarios, including mice lacking the ability to produce ROS by either the retinal or white blood cells, and found that if either was lacking, future damage was essentially eliminated. Essentially, one alone cannot do it.

PLOS One 2013; December 17. doi: 10.1371/journal.pone.0084357

Strategies for severe chronic

Benefits and potential

Lucas Genereux BS

Dr Leonid Skorin Jr

OD DO MS FAAO FAOCO

CHRONIC ocular pain can arise as a result of a variety of aetiologies. Pathology such as neovascular glaucoma, end stage glaucoma, intraocular tumour, corneal ulcer and trauma are all possible causes of chronic ocular pain. To alleviate the patient's pain, one must first determine its cause. The patient's description of the discomfort can help determine the cause or causes.

Patients who describe their pain as superficial are typically suffering from pathology of the cornea or conjunctiva.[1] Superficial pain is often described as sharp or shooting. Those who describe their pain as deeper in nature are often suffering from pain that may also originate from the cornea, but more likely stems from pathology of deeper structures such as the sclera, iris, ciliary body, orbital muscles or the sinuses.[1] Deeper pain is usually described by the patient with adjectives like 'dull',' constant' and 'aching'.

If after a thorough ophthalmic examination—including intraocular pressure assessment, and anterior and posterior segment evaluation—the cause of ocular pain is not clear, imaging may be required to elucidate the cause.

OCT scans of the orbit may be used to investigate possible orbital wall fracture or foreign body. Magnetic resonance imaging may be used to look for soft tissue causes such as retrobulbar swelling or orbital tumour.

Anatomy

The sensation of pain from the orbit is carried through branches of the trigeminal nerve, specifically those of the ophthalmic division. With the trigeminal nerve's broad coverage throughout the facial region, it is possible that pain experienced in the orbit is of a referred origin. The ophthalmic division of the trigeminal nerve contains three of its own major branches: the frontal, lacrimal and nasociliary.

These branches decussate posterior to the extraocular muscle cone and anterior to the trigeminal ganglion. The frontal branch provides innervation to the upper eyelids, superior orbital rim and scalp areas. The lacrimal branch provides innervation to the lacrimal gland, as well as to the conjunctiva and the lateral aspect of the upper eyelid. The nasociliary nerve innervates the cornea, the lower eyelids and portions of the skin of the nose.[2] The latter distribution is the anatomy behind Hutchinson's sign in herpes zoster ophthalmicus.

CASE REPORT

A 94-year-old female presented to our clinic complaining of extreme ocular pain in her right eye that had awoken her two nights prior to her visit. She had been self-medicating with ice packs and extra strength acetaminophen, but said that these were no longer effective.

Her ocular history was positive for wet age-related macular degeneration in her right eye including a prominent disciform scar resulting in severe vision loss. She was pseudophakic in both eyes, and had been followed as a glaucoma suspect. Her medical history was unremarkable aside from an allergy to sulfa medications.

Her entering visual acuities were finger counting at three meters in her right eye and 6/6 in her left eye. Initial intraocular pressure in her right eye was 60 mmHg as measured with Goldmann applanation tonometry. Slitlamp examination of the right eye revealed normal lids and lashes, diffuse injection of the bulbar conjunctiva, diffuse corneal oedema, deep and quiet anterior chamber, a stable posterior intraocular lens, neovascularisation of the iris and ectropion uveae. Examination of the left eye yielded normal findings of all structures. Gonioscopy could not be performed at this time as the corneal oedema would not allow for visualisation of the angle structures.

Dilated fundus examination revealed evidence of widespread blot haemorrhages in all quadrants of the right eye. Detailed examination was difficult due to corneal oedema, and as such, no information of the optic nerve health could be attained at this time.

It was suspected that our patient had recently suffered an ischaemic central retinal vein occlusion in the right eye, which the patient had not noticed due to her previously noted profound acuity reduction in this eye. The ischaemic central retinal vein occlusion then resulted in neovascular glaucoma with significantly increased intraocular pressure.

Treatment

Pharmacologic attempts to reduce pressure using brimonidine 0.1% were unsuccessful. Due to the patient's sulfa allergy, oral acetazolamide tablets could not be administered. The patient was referred to the emergency room to receive an intravenous mannitol solution at a dose of one gram per kilogram of body weight, given over the course of 45 minutes. Mannitol and topical pharmacologic attempts to lower the patient's intraocular pressure were unable to yield safe and comfortable pressure levels.

ocular pain

side-effects of retrobulbar injections

Panretinal photocoagulation laser therapy was performed, but extensive haemorrhaging blocked much of the retinal tissue, limiting the effectiveness of the procedure. After multiple return visits, the patient's ocular pain had not subsided and her intraocular pressure continued to be in the 50 mmHg range. At this point cryotherapy, enucleation, and retrobulbar alcohol injection were presented as further treatment options. Our patient decided to undergo retrobulbar alcohol injection.

Retrobulbar alcohol injection

A retrobulbar needle was used to administer a 1% lidocaine solution with 1:100,000 epinephrine into the muscle cone. The injection was done into the lateral third of the lower lid just superior to the inferior orbital rim. To ensure correct application, the needle was directed as close to the back of the globe as possible. A total of 2 ml of the anaesthetic was initially injected into the retrobulbar space. Anaesthetic is injected first to prevent the severe burning sensation that a patient would otherwise experience from the injection of absolute alcohol.

After the anaesthetic injection, a pause of five minutes was observed to allow full anaesthetic effect. During this time, the syringe containing the anaesthetic was detached, but the needle position was not altered (Figure 1). After the five minute period, a separate syringe containing 2 ml of absolute alcohol was attached to the previously placed needle, and the alcohol was injected (Figure 2). Gentle pressure was then applied over the globe for two minutes, to help distribute the medication.

On the day of this procedure the patient had reported that her pain level was 'nine out of 10'. The following day, the patient noted that her pain level was 'five out of 10'. Two days after the injection the pain had subsided to a reported 'two out of 10'. At a follow-up appointment nine weeks after the injection, the patient reported that she was happy with the results of the retrobulbar injection She reported that about once every week she would have a flare-up of ocular pain and would need a dose of acetaminophen, but that on a day-to-day basis she had been almost pain free, with a reported pain level of one out of 10.

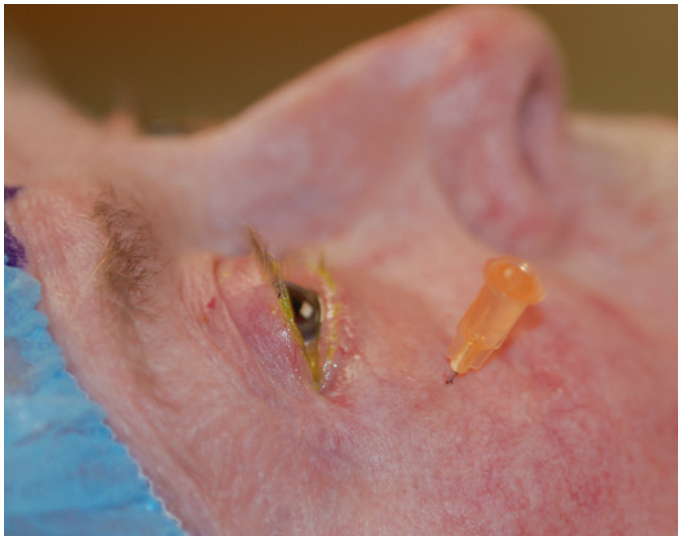
Discussion

A variety of treatment approaches for chronic severe ocular pain secondary to elevated intraocular pressure exist (Table 1). The most drastic of these treatment approaches is enucleation, which is reserved as a final measure; however, even this does not ensure resolution because pain persists in as many as seven per cent of patients after enucleation.[3]

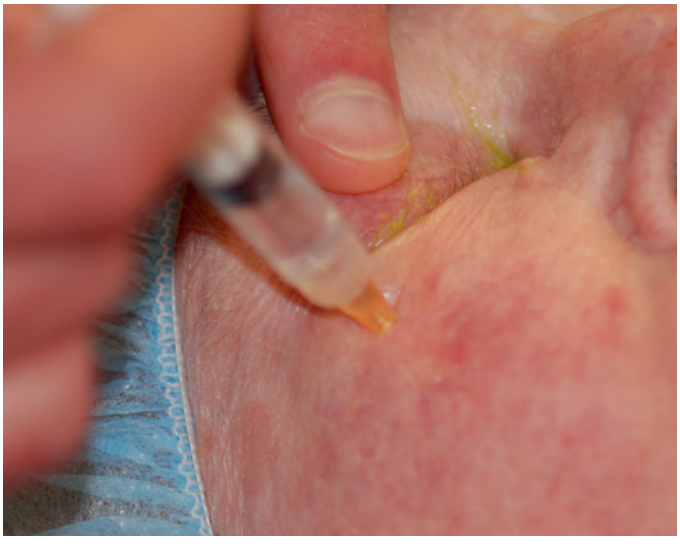
Less invasive techniques come by way of retrobulbar injections. The main pharmacologic agents used in these situations are absolute alcohol 97% and chlorpromazine at a dose of 25 mg/mL.[4,5]

Oral pain medications are often not effective. Even when they are effective, these medications often lose their efficacy as the chronicity of the condition drags on.

Continued page 24



▲ Figure 1. Retrobulbar needle in place after anaesthetic injection, prior to absolute alcohol administration



▲ Figure 2. Delivery of absolute alcohol to the retrobulbar space

Severe ocular pain

From page 23

Topical and oral glaucoma medications
Oral pain medications
Panretinal photocoagulation laser
Cyclocryotherapy
Retrobulbar absolute alcohol injection
Retrobulbar chlorpromazine injection
Enucleation of the eye

▲ Table 1. Treatment options for severe chronic ocular pain secondary to neovascular glaucoma

Panretinal photocoagulation is a first line therapy for neovascular glaucoma. The process works by destroying retinal tissue with argon or diode laser. Destruction of tissue decreases the oxygen requirement of the retina, thereby decreasing the release of vascular endothelial growth factor, which decreases the amount of neovascularisation in the anterior chamber angle. Cyclocryotherapy is effective at decreasing ocular pressure by destroying the ciliary processes, which are responsible for aqueous humour production.

Retrobulbar alcohol injections have been used in the management of pain in blind eyes since the early 1900s.[4,5] Alcohol achieves analgesia, through nerve cell destruction via phospholipid and cholesterol extraction as well as precipitation of mucoprotein and lipoprotein.[1]

Alcohol does not work by diffusion, which can both help and hinder the outcome. This helps the outcome in that it reduces unwanted destruction of neighbouring structures. The lack of diffusion creates a challenge in that it requires the injection to be given in close proximity to the targeted nerves for full destruction.[1] If the nerves are not sufficiently destroyed, they will regenerate earlier and bring back the symptoms of pain.[3-5] Successful injections have been shown to provide pain relief for up to two years, with 20-87 per cent lasting for at least three months.[3-5]

Retrobulbar injection of chlorpromazine

Another medication that can be administered via retrobulbar injection is the phenothiazine anti-psychotic mediation chlorpromazine. Chlorpromazine is thought to cause anaesthesia by cell lysis and/or membrane stabilisation.[1,4,5] Chlorpromazine injection has been proposed to have a efficacy of 80 per cent to 90 per cent and to possess a longer duration of relief than alcohol injection.[6] The most notable advantage of chlorpromazine over other treatment methods is in the treatment of seeing eyes. Chlorpromazine has become the treatment of choice for treating pain in eyes that have useful vision. One study showed that 50 per cent of patients with seeing eyes that underwent chlorpromazine injection retained vision after injection.[6]

Alcohol and chlorpromazine injections have similar potential side-effects. Both medications carry the risk of eyelid oedema, conjunctival chemosis, external ophthalmoplegia, cellulitis and blepharoptosis.[1,4,5] Retrobulbar alcohol injections also carry the risk of neurotrophic keratopathy. Chlorpromazine injections carry additional risk of nausea, vomiting, brief loss of consciousness and fat necrosis.[1] It is also possible for patients receiving chlorpromazine injection to experience transient loss of vision due to membrane stabilising effects on the optic nerve.[1,4,5]

Conclusion

Retrobulbar injections have made the management of both seeing and non-seeing painful eyes less devastating. When a patient presents with this magnitude of misfortune, the idea of having an eye removed may be perceived as not a treatment, but as more misfortune. By having these retrobulbar injection options available for patients, we can set their minds at ease, and improve their quality of life. ▲

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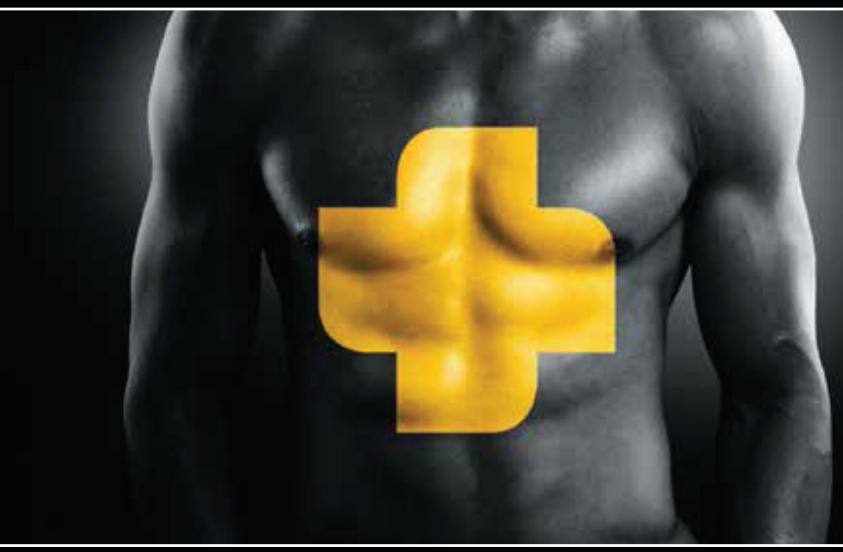
New Eye Indication*[1]

*LIPIDIL is indicated for the reduction in the progression of diabetic retinopathy in patients with Type 2 diabetes and existing diabetic retinopathy.

LIPIDIL does not replace appropriate control of blood pressure, blood glucose and blood lipids in reducing the progression of diabetic retinopathy.



In addition

LIPIDIL is indicated as an adjunct to diet in the treatment of:[1]

- Dyslipidaemia associated with Type 2 diabetes
- Types II, III, IV and V dyslipidaemia
- Hypercholesterolaemia

LIPIDIL® 145mg
fenofibrate

PBS Information: Restricted Benefit. For use in patients that meet the criteria set out in the General Statement for Lipid-Lowering Drugs. Not listed for the treatment of diabetic retinopathy.

Please review the full Product Information (PI) before prescribing. Full PI available on request from Abbott Australasia by calling 1800 225 311 or at: www.medicines.org.au/files/abplipid.pdf

Lipidil® (fenofibrate): 145 mg tablets, 30's; 48 mg tablets, 60's. **Indications:** Adjunct to diet in the treatment of hypercholesterolaemia, types II, III, IV and V dyslipidaemia, dyslipidaemia associated with Type 2 diabetes. Reduction in the progression of diabetic retinopathy in patients with Type 2 diabetes.* Does not replace appropriate control of blood pressure, blood glucose and blood lipids. **Dosage:** Dyslipidaemia and Diabetic Retinopathy: 145 mg tablet to be taken with or without food. Consider dose of 48 mg in patients with renal impairment (CrCl<60ml/min). **Contraindications:** Children; liver dysfunction; severe renal dysfunction; existing gallbladder disease; coadministration with another fibrate; hypersensitivity to fibrates or ketoprofen; chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridaemia. **Precautions:** Attempt diet and lifestyle modifications before initiating therapy for dyslipidaemia; effect on CHD mortality/morbidity not established*; renal impairment; may increase LFT; hepatic impairment, cholelithiasis; pregnancy and lactation; drugs exacerbating hypertriglyceridaemia (oestrogen, b-blocker, thiazides); fructose and/or galactose intolerance (including, Lapp lactase deficiency or galactose malabsorption); lecithin or related product allergy. **Interactions:** Oral anti-coagulants; HMG-CoA reductase inhibitors (risk of muscle toxicity is increased if used concurrently); other fibrates; cyclosporine (monitor renal function); phenylbutazone; drugs metabolized by cytochrome P450 isoenzymes CYP2C19, CYP2A6, and CYP2C9. **Adverse Effects:** GI disorders; skin reactions (including rash and photosensitivity); raised LFT; increase in serum creatinine; pancreatitis; gallstones; thromboembolism; muscle toxicity and rarely rhabdomyolysis.

*Please note changes in Product Information.

References: 1. Lipidil Approved Product Information. Lipidil® is a registered trademark of Abbott Australasia, 32–34 Lord St, Botany NSW 2019. Free call: 1800 225 311. Date prepared: November 2013. AU-LIP-2013-91c

Abbott
A Promise for Life

FOR wAMD†

20/200

20/100

20/70

20/50

20/40

20/30

20/25

20/20

ONE INJECTION EVERY TWO MONTHS*

***EYLEA® wAMD† TREATMENT IS INITIATED WITH ONE INJECTION PER MONTH FOR THREE CONSECUTIVE MONTHS, FOLLOWED BY ONE INJECTION EVERY TWO MONTHS[1]**

PBS Information: Authority Required. Refer to PBS Schedule for full Authority Required information for wet AMD. EYLEA is not PBS listed for CRVO.

BEFORE PRESCRIBING, PLEASE REVIEW FULL PRODUCT INFORMATION AVAILABLE ON REQUEST FROM BAYER AUSTRALIA LTD, ABN 22 000 138 714, 875 PACIFIC HIGHWAY, PYMBLE, NSW 2073 or go to www.ebs.tga.gov.au

MINIMUM PRODUCT INFORMATION EYLEA® [aflibercept (rch)] INDICATIONS: EYLEA (aflibercept) is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (wet AMD); visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)*. **DOSAGE AND ADMINISTRATION:** Injection volume of 50µL EYLEA (equivalent to 2mg aflibercept). For wet AMD: Treatment is initiated with one intravitreal injection per month for three consecutive months, followed by one injection every two months. For CRVO*: Treatment is initiated with one intravitreal injection per month. After the first three monthly injections, the treatment interval may be extended based on visual and anatomic outcomes. The treatment between doses should not be shorter than one month. Monitoring should be done at the injection visits. During treatment interval extension, the monitoring should be determined by the treating physician based on the individual patient's response. **CONTRAINDICATIONS:** Known hypersensitivity to aflibercept or excipients; ocular or periocular infection; active severe intraocular inflammation. **PRECAUTIONS:** Endophthalmitis, increase in intraocular pressure; arterial thromboembolic events*; see full PI for effects on fertility, pregnancy, lactation, effects on ability to drive or use machines. **ADVERSE EFFECTS:** Very common: conjunctival haemorrhage, eye pain. Common: retinal pigment epithelium tear, detachment of retinal pigment epithelium, cataract, cataract nuclear, cataract subcapsular, corneal erosion, corneal abrasion, intraocular pressure increased, vision blurred, vitreous floaters, corneal oedema, vitreous detachment, injection site pain, foreign body sensation in eyes, lacrimation increased, eyelid oedema, injection site haemorrhage, conjunctival hyperaemia, ocular hyperaemia. Others: see full Product Information. Date of most recent amendment: November 2013

*Please note changes in Product Information.

Reference: 1. EYLEA Product Information. †wAMD = Wet age-related macular degeneration

EYLEA®
aflibercept (rch)
solution for intravitreal injection