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Optometry AUSTRALIA | Pharma

September 2015

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Cover design
False-colour SEM of retina featuring central fovea. Professor P Motta, Department of Anatomy, University La Sapienza, Rome.
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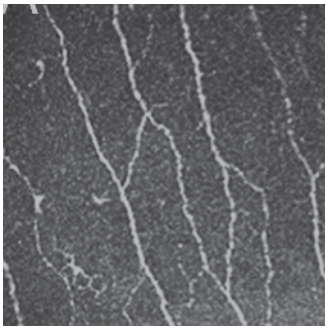

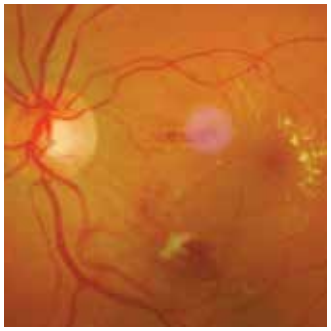

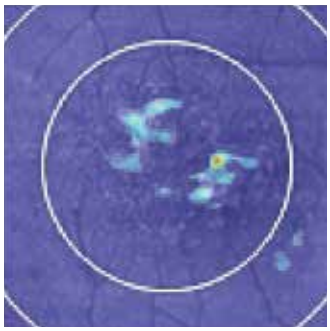

Intravitreal injections for diabetic macular oedema

Dr Devinder Chauhan

MBBS FRCOphth MD FRANZCO

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DIABETIC macular oedema (DME) is the main cause of vision loss in diabetes, affecting 27 per cent of type 1 diabetic patients within nine years of onset[1] and up to 28 per cent of type 2 diabetic patients within 20 years of diagnosis.[2] As the development of DME is insidious, many patients are asymptomatic until it involves the fovea; earlier detection is possible only through routine diabetic retinopathy screening and monitoring, ideally in a primary care setting.

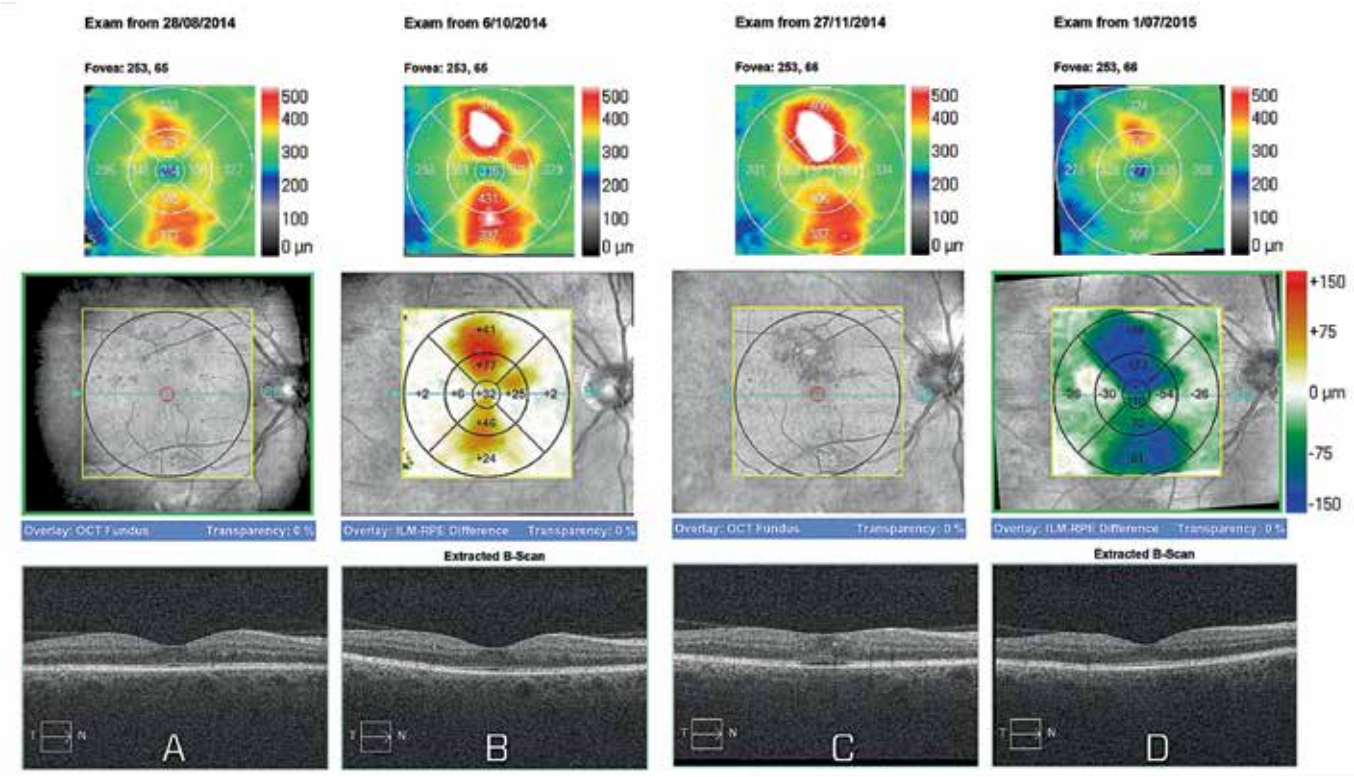
Laser treatment for DME was first established as beneficial in 1981 and has remained the gold standard[3] until recently. The primary goal of treatment of DME has historically been prevention of further vision loss. While the use of intravitreal agents is increasing, particularly with the recent PBS approval of ranibizumab for DME, focal laser treatment retains an important role, particularly in the treatment of DME, that may fit the definition of clinically significant macular oedema (CSME) but does not involve the foveal centre.

The Diabetic Retinopathy Clinical Research (DRCR) Network studies[4,5,6] compared the use of intravitreal ranibizumab, an anti-VEGF autoantibody fragment used extensively to treat neovascular age-related macular degeneration (nvAMD), with both focal laser photocoagulation and intravitreal triamcinolone (corticosteroid).

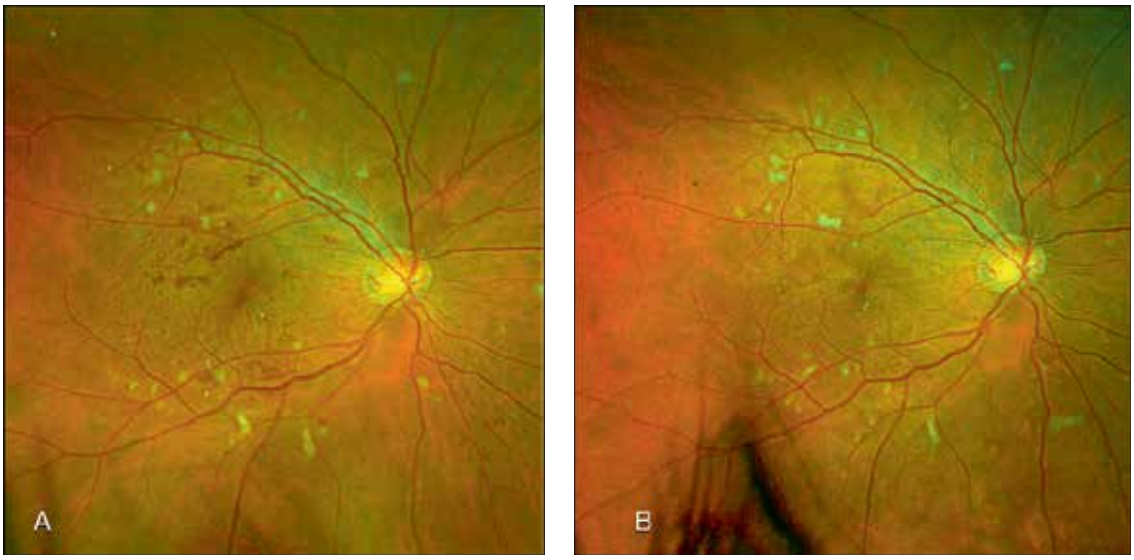
The subjects in these studies had centre-involving DME with a foveal thickness of 250 microns or more and visual acuity of 6/9 or worse.

The studies also looked at the role of focal laser combined with intravitreal ranibizumab, either at the onset of treatment or as a 'rescue' therapy after six months of intravitreal injections if the DME was persistent. The ranibizumab was injected monthly and the steroids every three months for the first six months of the trial. The need for subsequent injections was determined using a combination of optical coherence tomography (OCT) and visual acuity criteria.

The most significant findings of these studies relate to the visual acuity outcomes over the first two years in particular. It was shown that ranibizumab alone, with 'rescue' laser after six months had a better visual



▲ Figure 1. The OCT images with macular thickness maps and change analysis maps demonstrate the progression of diabetic macular oedema (DME) from August 2014 (A) to October 2014 (B). The vision at this stage was not affected but dropped to 6/12 in November 2014 (C), when monthly intravitreal anti-VEGF (initially a single bevacizumab and subsequently ranibizumab) were started. Image D demonstrates significant reduction in DME with a return visual acuity of 6/6.



▲ Figure 2. Colour images of the same eye as in Figure 1 from in August 2014 (A) and July 2015 (B) demonstrate a significant reduction in intraretinal haemorrhages and an improvement in venous irregularity. There was an improvement in grading of the diabetic retinopathy from severe non-proliferative to moderate non-proliferative.

acuity outcome at two years than ranibizumab with laser at the onset, which, in turn, had a better outcome than triamcinolone alone. Nearly twice as many eyes had an improvement in vision of greater than 15 letters with ranibizumab than with laser.

The other findings of interest were that the visual acuity benefit of triamcinolone was equivalent to ranibizumab in eyes that were pseudophakic at the start of the trial and that the visual acuity benefit of laser alone increased by three years and was almost as good as in the ranibizumab arms of the study.

Finally, the most surprising finding of all was that there was reversal of retinopathy grade in many patients. That is, some patients had a reduction in grade of retinopathy, such as from severe non-proliferative retinopathy to mild-moderate non-proliferative. This was seen in about one quarter of all patients on ranibizumab and some patients with triamcinolone and laser; it was statistically significant only for ranibizumab in patients with severe non-proliferative retinopathy or worse.

Unlike the lifelong need for ongoing intravitreal injections in nvAMD, the regimen of intravitreal ranibizumab injections consisted essentially of monthly injections for the first six months, with an average number of injections in the second six months between two and three. Subsequently, two to three injections were required in the second year and fewer in the third year of the extension study.

Many have adopted the DRCR protocol in the management of DME, but using pragmatic variants, often based on a 'treat and extend' regimen. As a result, many retinal specialists and their patients are seeing the benefits demonstrated in the DRCR studies. While the treatment burden of increasing numbers of patients treated is significant, this is only for a limited number of injections for most. The use of intravitreal triamcinolone in pseudophakic eyes certainly reduces the treatment burden to the patient, doctor and society. With lower doses, such as 2 mg, rather than the standard 4 mg, similar results can be achieved with lower intraocular pressure raising complications.

Most Australian retinal specialists have used bevacizumab until relatively recently and would use aflibercept if it gains PBS approval. Both of these are also anti-VEGF agents and have been shown to be of little difference compared with ranibizumab in eyes with better visual acuity. However, in eyes with worse vision (~6/15 or worse) aflibercept is better than ranibizumab, which is better than bevacizumab.[7]

Critics of the high uptake of intravitreal therapy have mostly been concerned about the abandonment of laser in cases that are suitable; the cost to society of repeated injections in many patients where a similar visual result can be achieved with one or two laser treatments may be too high.

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Systemic complications of diabetes

Incidence, sub-types and pathogenesis

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DIABETES is a common metabolic condition affecting millions world-wide—7.4 per cent of Australians have diabetes; 16.3 per cent of the Australian population has pre-diabetes with a predicted lifetime diabetes risk of greater than 50 per cent.[1]

Diabetes is classified as type 1, type 2 or gestational.[2] Type 1 diabetes arises from immune-mediated destruction of pancreatic islets resulting in diminished insulin, and glucagon production. Individuals suffer severe hypoglycaemia and hyperglycaemia.

Type 2 diabetes is characterised by insulin resistance and beta cell dysfunction. It is associated with obesity, physical inactivity, diets high in saturated fats, genes, medical illness and drugs, such as corticosteroids. Type 2 diabetes, hypertension, deranged lipids and obesity are collectively known as the Metabolic Syndrome.

Gestational diabetes is considered a pre-type 2 diabetic condition. Affected women are overweight and have a lifetime risk of type 2 diabetes.

Acute symptoms and complications

Uncontrolled hyperglycaemia is associated with metabolic acidosis and electrolyte disturbances. Diabetic ketoacidosis (DKA) ensues if untreated and results in multi-organ failure and coma. In milder situations, patients experience increased thirst, urination, unexplained weight loss, severe fatigue and blurred vision. They can develop infections of skin, urine and chest. Management is by increasing fluid intake orally or intravenously, replacing electrolytes, taking extra doses of oral anti-diabetic medications or insulin, and antibiotics for infection.[3]

Chronic complications

Chronic complications arise from years of poor glycaemic control.[4] They are categorised into macrovascular, microvascular and neuropathic.

Macrovascular complications include diseases of the cardiovascular, cerebrovascular, peripheral vascular systems and limb amputations. Microvascular complications include retinopathy, nephropathy and cognitive impairment.

Dilated eye examinations can detect early diabetic retinopathy and are regarded as an integral part of optometry. People with diabetes are encouraged to have a dilated retina eye examination annually, but many diabetes sufferers do not attend regular eye check-ups. It is important to remember that the best way for a diabetic patient to prevent unnecessary vision loss is through annual retina eye examinations.

As the readers of *Pharma* are familiar with diabetic ocular complications, this aspect will not be discussed in this article. Neuropathic complications are categorised into peripheral or autonomic.

Cardiovascular

Diabetic individuals suffering heart attacks often describe non-specific symptoms such as fatigue or shortness of breath. They are investigated with electrocardiogram, exercise stress test or coronary angiogram.[5] They are started on anti-platelet and lipid lowering agents, and encouraged to stop smoking. They may be suitable for percutaneous coronary intervention (PCI) such as balloon angioplasty with stenting or coronary artery bypass grafting (CABG). Patients who survive heart attacks develop chronic heart failure, reduced exercise tolerance and greatly diminished quality of life.

Cerebrovascular

An early warning of stroke is a transient ischaemic attack (TIA). Typical symptoms are tingling of an extremity, face or body, incoherent speech or acute confusion. Symptoms may last for up to 24 hours but persistence indicates a stroke in progress. Immediate assessment with brain CT or MRI, carotid duplex ultrasound and blood work is recommended. Anti-platelet and lipid lowering agents are commenced. Glycaemic, blood pressure and anti-smoking strategies must be instituted. Carotid endarterectomy may be proposed. This involves removing atheromatous plaques adherent to carotid endothelium. Individuals with recurrent strokes develop vascular dementia.[6] However, diabetes is also a risk factor for Alzheimer's disease.[7]

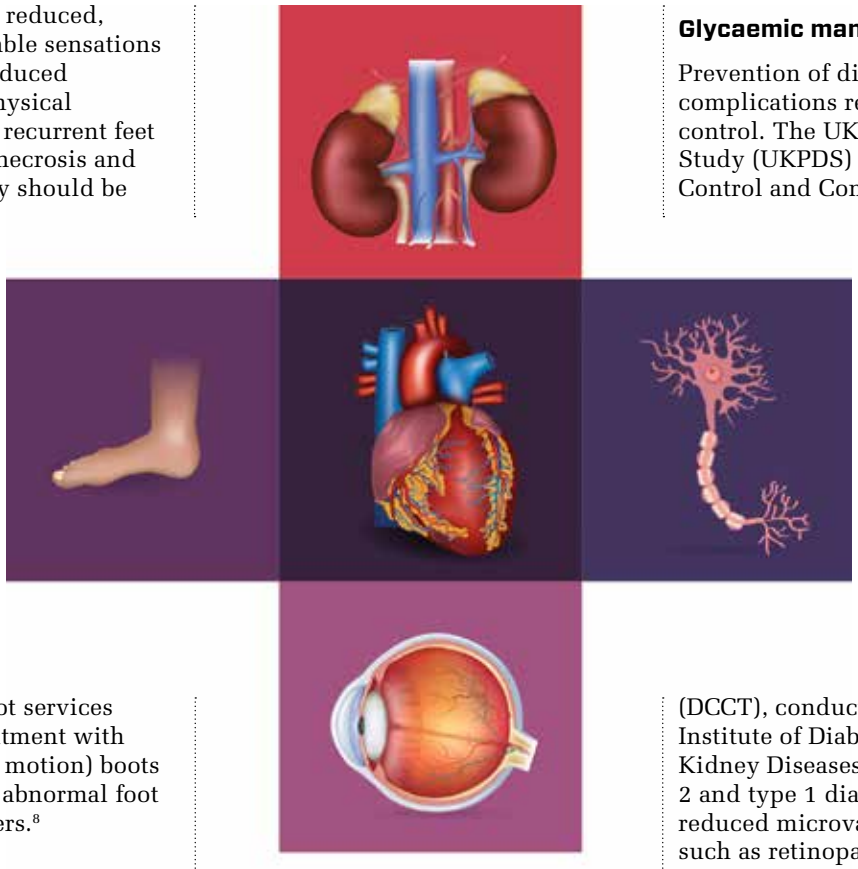
Peripheral vascular

Atheromatous accumulation leads to occlusion of peripheral limb arteries. Patients experience intermittent claudication pains exacerbated by walking. Collateral vessel formation can form natural bypasses and creates a stable situation for years. However, acute thrombus occlusion results in severe rest pain and threatens the limb. Patients may present with dusky, pulseless foot. They should be investigated with arterial leg Doppler ultrasound and referred for percutaneous endoluminal angioplasty or femoropopliteal bypass surgery.

Peripheral neuropathy

Individuals affected by peripheral

neuropathy experience reduced, altered and uncomfortable sensations of extremities. Their reduced ability to sense their physical environment results in recurrent feet ulcerations, infection, necrosis and limb amputations. They should be referred to high-risk foot services at major hospitals for fitment with CAM (controlled ankle motion) boots which can redistribute abnormal foot pressures and heal ulcers.[8]



Autonomic neuropathy

The autonomic nervous system controls heart rate, blood pressure, sweating, gastro-oesophageal and bowel functions, and penile erection. Affected individuals describe symptoms that include postural hypotension, bradycardia, dry skin, nausea, gastro-oesophageal reflux, chronic diarrhoea or constipation and erectile dysfunction.

Nephropathy

The kidney has millions of nephrons comprising glomerular capillaries, and nephron tubules. Chronically elevated blood glucose damages the glomerulus, resulting in protein leakage into urine, which can lead to the nephrotic syndrome characterised by fluid retention, and pulmonary oedema. When sufficient nephron units fail, renal failure ensues and dialysis treatment is eventually needed.

Glycaemic management

Prevention of diabetes-related complications requires good glycaemic control. The UK Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT), conducted by the US National Institute of Diabetes and Digestive and Kidney Diseases, showed that type 2 and type 1 diabetic patients have reduced microvascular complications such as retinopathy, and nephropathy if they can achieve HbA1c less than seven per cent.[9]

Ten years on, these individuals were protected from subsequent heart attacks, strokes and death;[10,11] however, individuals who are aggressively managed report weight gain and frequent hypoglycaemia.

The ACCORD study in 2008 showed that rapidly achieving tight glycaemic control is associated with increased mortality in older diabetic patients with pre-existing cardiovascular complications.[12] Therefore, glycaemic management must be individualised.[13]

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Australia's first optometric clinical

How do you know if your clinical management can be improved and how should you go about it?

Helen Carter

FEW OPTOMETRISTS undertake clinical audits, mainly due to a lack of tools and exposure, and practitioners are not routinely trained in the process.

Australia's first clinical audit tool for optometrists has been developed in Melbourne and is freely available to help practitioners audit the care provided to their diabetic patients.

Keying patient information into spreadsheets enables optometrists to assess their practice's management of diabetic patients and identifies areas for improvement, enabling practitioners to improve their care and patient outcomes.

University of Melbourne optometrists Dr Laura Downie and Associate Professor Peter Keller, who developed the tool after receiving a Victorian Optometrists Training and Education (VOTE) grant, said that while clinical audit was routinely adopted in many areas of health care, there was a need to improve uptake of this important process within the optometry profession.

'Clinical audit seeks to improve the quality and outcome of patient care through structured review and involves clinicians examining their practices against agreed explicit standards and where indicated, modifying practices to improve patient care,' Downie said.

'It involves finding out whether current care practices are appropriate and identifying any potential shortfalls in patient care. It allows clinicians to assess whether they are adopting best practices, as informed by high-quality clinical research. The ultimate aim is to improve provision of patient care.'

The idea to develop the optometric clinical care audit tool (CCAT) was inspired by comment received from attendees of the VOTE-funded evidence-based-practice workshop series that Downie and Keller delivered to Victorian optometrists in 2014.

'When we surveyed 80 attendees about their auditing practices, less than five per cent had undertaken any form of audit. A major barrier was lack of available tools,' Downie said.

'We were inspired to develop a tool for management of patients with diabetes, as diabetic retinopathy is a major public health issue and there are well-established NHMRC Guidelines (for the Management of Diabetic Retinopathy 2008) to use as a basis for auditing clinical practices.'

The tool audits diagnostic accuracy, appropriateness of therapy, rate/timeliness of referrals, referral accuracy and quality of record-keeping.

Details of up to 100 patients, in this case with diabetes, are entered into an Excel spreadsheet. If more than 100 are included in a retrospective audit, a second spreadsheet is used.

The authors suggest practitioners consider a three-, six- or 12-month audit. Longer duration enables information to be captured about longer-term patient behaviour including whether patients are attending for biennial reviews.

A summary statistics worksheet automatically populates key information comparing the practitioner's current practices with NHMRC guidelines for managing patients with diabetes. This allows easy implementation of the analysis component by the practitioner without having to invest significant time to analyse patient data.

	A
1	**AUDIT PERIOD:**
2	
3	**AUDIT PARTICULARS:**
4	Number of patients:
5	Number of comprehensive visits:
6	Average number of comprehensive visits/patient over audit period:
7	
8	**General Patient Information**
9	% patients whose DOB was noted
10	% patients whose gender was noted
11	% patients whose ethnicity was noted
12	% patients whose GP details were noted
13	
14	**DR Risk Factors**
15	% patients whose type of diabetes was noted
16	% patients whose duration of diabetes was noted
17	% patients whose HbA1c was noted
18	% patients whose blood pressure status was noted
19	% patients whose systemic lipid status was noted
20	% patients where FH of diabetes (+/-) was noted
21	
22	**Essential exam procedures for DR assessment**
23	% of visits where monocular VA was noted
24	% of visits were slit lamp findings were noted
25	% of visits where any form of posterior eye exam was performed
26	% of visits where a DFE was performed
27	% of visits where indirect ophthalmoscopy was performed
28	
29	**Other recommended exam procedures**
30	% of visits where a retinal fundus photo was taken
31	% of visits where a macular OCT was performed
32	
33	**Diagnosis (Dx) of DR**
34	% of (eye) visits where severity of DR was noted on record card
35	% of (eye) visits where severity of DR grading is considered accurate
36	% of (eye) visits where DME considered to be accurately identified
37	% of (eye) visits where CSME considered to be accurately identified
38	
39	**Management (Mx) of DR**
40	% of patient visits where a letter was written to the GP
41	% of patient visits where Mx was consistent with NHMRC guideline
42	% of patient visits where patients followed management advice

audit tool for diabetes

As data are added, the page highlights areas of relative strengths and potential areas of under-performance in clinical practice. The practitioner can then identify reasons and develop strategies for improving care.

For example, if only a few patients were returning for review within the practitioner's recommended period, the optometrist may consider implementing a new patient recall system to assist with improving patient review.

To assess the effectiveness of this strategy, the practitioner would audit their practices again after a period of time to see if there had been improvement in this area.

'Practice support staff may be able to assist with audit by identifying relevant patient records but we consider it is essential for the practitioner to directly input data into the tool,' Dr Downie said.

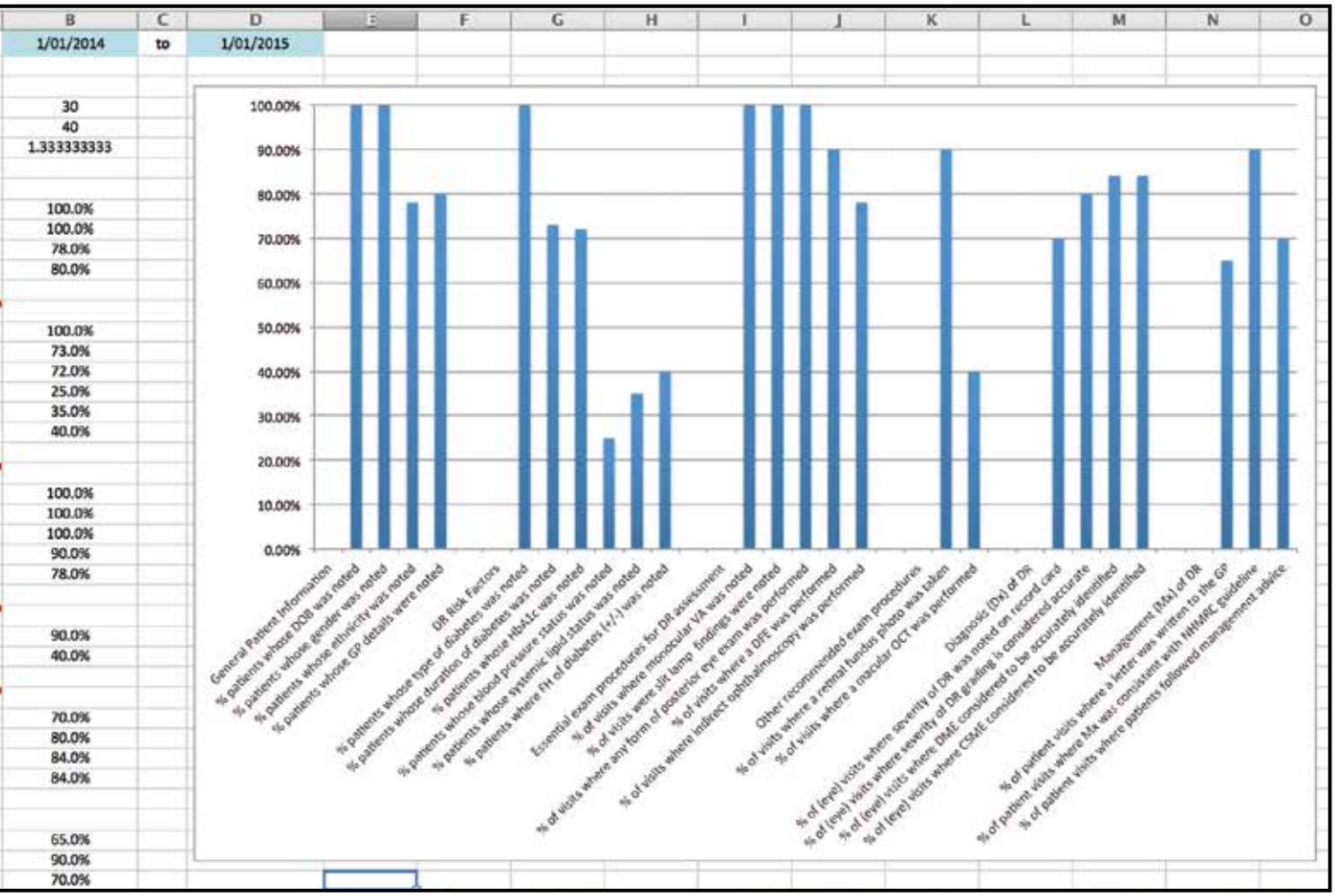
'We have constructed the CCAT to have drop-down menus and self-populating fields. Diagnosis and management worksheets should be used in association with the NHMRC Guidelines as they may require clinical interpretation of relevant retinal findings.'

More than 100 optometrists and students attended its launch and an educational seminar on its use. A pilot study of independent practitioners is evaluating its usefulness.

Other practitioners from Victoria and interstate who are interested in becoming involved with the project can contact Dr Downie at ldownie@unimelb.edu.au.

'We foresee an opportunity for further development to directly interface with existing optometric practice management software systems,' she said.

* The CCAT uses a Microsoft Excel template. There are Mac and PC versions and a document with step-by-step instructions freely available for download on the Department of Optometry and Vision Sciences University of Melbourne website, www.optometry.unimelb.edu.au/community/ccat.php ▲



▲ The optometric clinical care audit tool (CCAT) enables practitioners to improve their care and patient outcomes

Diabetic retinopathy

Collaborative care of patients relies on strong professional relationships

Mike Jackson

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CASE REPORT

THE ROLE of the optometrist in diagnosis, monitoring and referral of patients with diabetes is vitally important. As this case study shows, it is equally vital to build a frank, professional relationship with your local GP and ophthalmologist.

Initial presentation

In 2008, a 45-year-old type 1 diabetic patient with hypertension presented to my practice. She was in her mid-40s and came from a lower socio-economic background. It was difficult to communicate with her; her ability to follow instructions was poor and she seemed to lack motivation to look after herself.

She reported good blood pressure and sugar control. Her spot checks were 6-8 mmol/L, which seemed pretty good. As Figure 1 (RE) and Figure 2 (LE) show, the fundus appeared relatively good, with no bleeding or signs of retinopathy. Visual acuity was still 6/6 in each eye.

2011

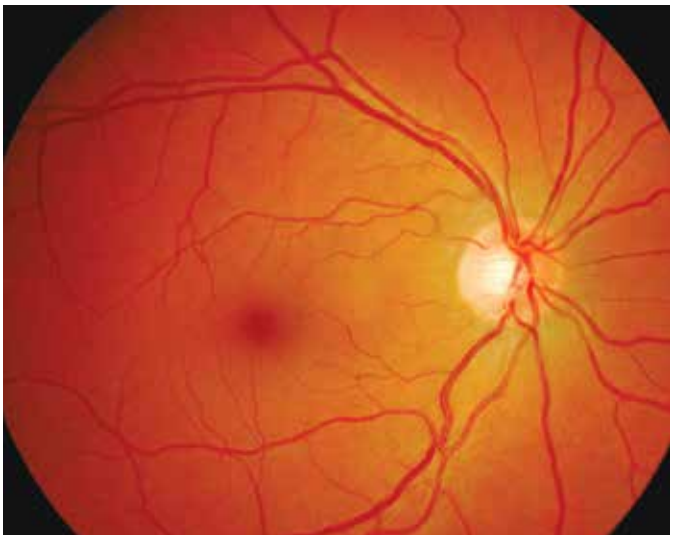
The patient returned for a routine check-up but now spot checks were sometimes up to 11 mmol/L. Her fundus had begun to show minor changes. We referred her back to her GP with a report asking the GP to review her sugar levels and advising of the damage we were seeing (image not sent with report).

Six months later, the patient returned. We learned that her GP had been so worried about her condition that he had sent her to a dietician to help her with her diet and lifestyle, which were exacerbating her condition. As the GP explained, sometimes there is no point in increasing the medication if the patient has not altered their lifestyle. At this visit, we noticed that her retinopathy was slightly worse.

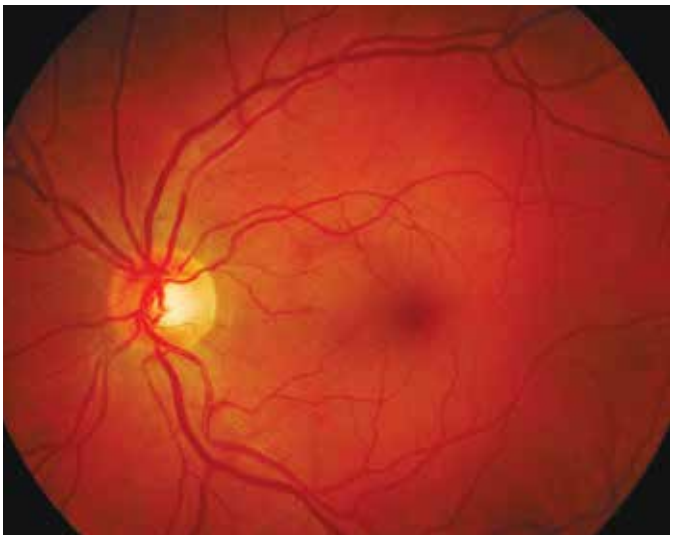
2012

By the next visit, things were much worse. Her A1C* test was now eight per cent, which meant her risk of blindness had doubled. As well, her blood pressure reading was 160/100. The combination of high blood pressure and high sugar levels can result in a synergy causing more damage than just the sum of both.

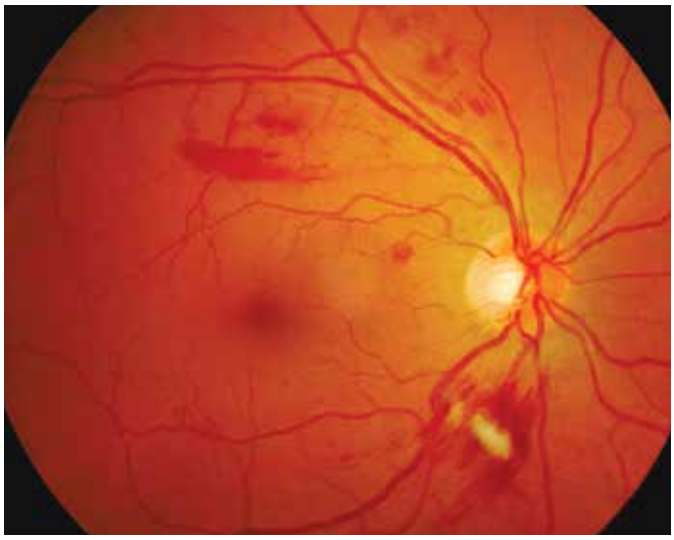
As Figure 3 (RE) and Figure 4 (LE) show, there were scattered haemorrhages around the fundus, which had not been present before.



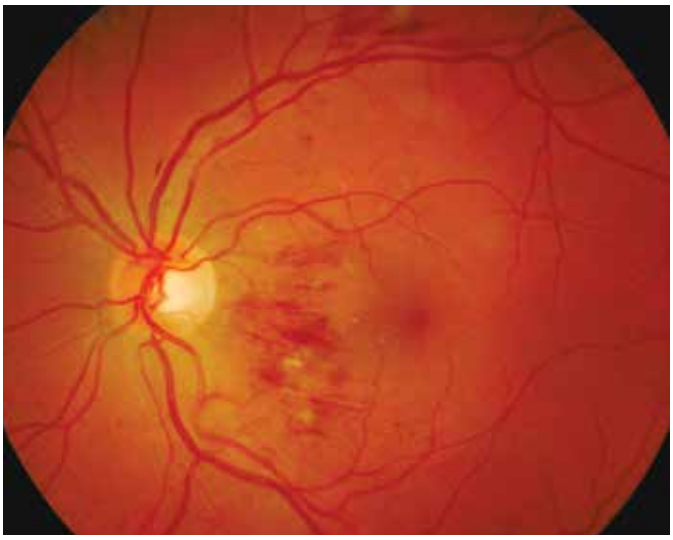
▲ Figure 1. Initial presentation RE



▲ Figure 2. Initial presentation LE



▲ Figure 3. 2012 presentation RE



▲ Figure 4. 2012 presentation LE

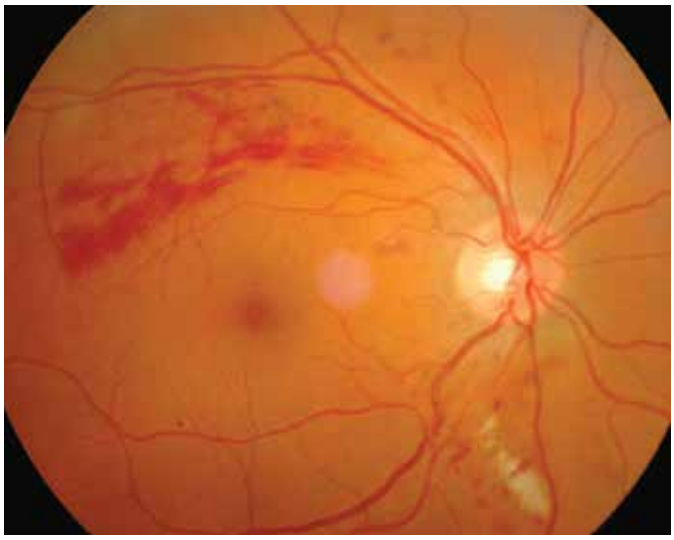
The white area over the haemorrhage on the right eye is a cotton wool patch (CWP) where the 'sick' nerve fibres have lost their natural clarity and become cloudy. It was determined that the patient's condition was progressing and becoming a concern, so we referred her to Dr Michael Chilov, a retina subspecialist at the Retina Associates ophthalmic centre in Sydney.

Due to the patient's financial hardship, at our request Dr Chilov bulk-billed the consultations.

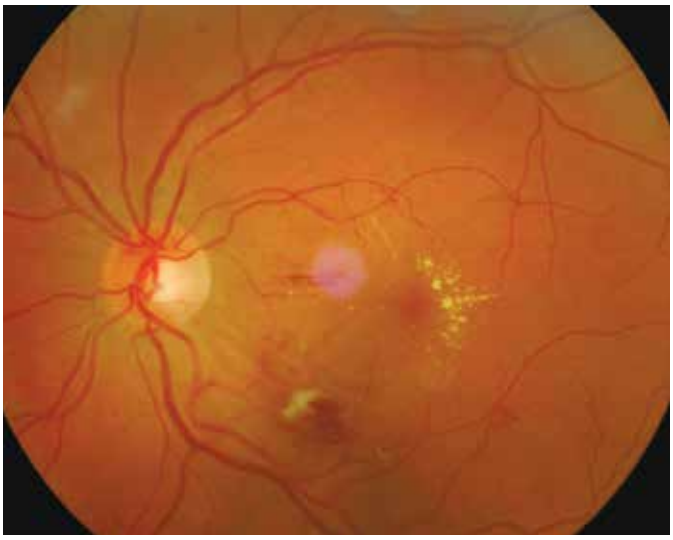
In his report, Dr Chilov found that the patient's retinopathy, while concerning, was probably resolving itself. The patient had reported an improvement in her sugar levels before seeing him. Dr Chilov noted the presence of some hard exudate, which often begins to form after the fluid reabsorbs as the retinopathy eases. The patient's A1C score had dropped to 7.5 per cent and blood pressure was 130/76.

The patient's condition was reviewed later in 2012; the bleeding was spreading but not progressing, as shown in Figure 5 (RE) and Figure 6 (LE). The patient continued to see Dr Chilov, who had performed OCT scans to check for retinal oedema. He has not yet needed to perform laser treatment, although the patient has not attended my practice for further visits and may have been lost to follow-up.

* The A1C test is a blood test that provides information about a person's average levels of blood glucose, also called blood sugar, over the past three months. The A1C test is sometimes called the haemoglobin A1c, HbA1c, or glycohaemoglobin test. The A1C test is the primary test used for diabetes management and diabetes research. ▲



▲ Figure 5. Late 2012 presentation RE



▲ Figure 6. Late 2013 presentation LE

IMP: DEL A&A from Rx ... !?

Jeff Megahan

IT'S LONG BEEN a comedic trope that medical prescriptions are illegible and confusing and that poor handwriting is an attribute of every health-care provider, including optometry therapeutic prescribers. Abbreviations and dose expressions on prescriptions are also a major cause of medical errors and are potentially dangerous.[1]

In the wider medical community, errors related to illegible prescriptions have been a subject of concern for many years. A 2005 study to identify the impact of prescribing errors in a large US urban teaching hospital found that 29 per cent of prescriptions contained a dangerous abbreviation.[2]

In 2007, one of the first studies to specifically quantify the harmful effect of abbreviations on prescriptions was undertaken by the University of Michigan in the USA. Researchers analysed 643,151 medication errors in records submitted to the US Pharmacopeia MEDMARX program from 682 facilities in 2004–2006. They found that 29,974 errors (4.7 per cent) were attributable to abbreviation use.

These findings lent support to the established 'Do Not Use Abbreviation List' (Table 1), and led the authors to conclude: 'A simple risk-versus-benefit analysis of abbreviation use versus prohibition will reveal that whereas using abbreviations may save minutes, prohibiting abbreviations may save lives.'[3]

In 2008, the Australian Commission on Safety and Quality in Healthcare published its 'Recommendations for Terminology, Abbreviation and Symbols used in the Prescribing and Administration of Medicine'[5] (updated 2011).

Do not use	Potential problem	Use instead
U (unit)	Mistaken for '0' (zero), the numeral '4' (four) or 'cc'	Write 'unit'
IU (International Unit)	Mistaken for 'IV' (intravenous) or the numeral '10' (ten)	Write 'International Unit'
Q.D., QD, q.d., qd (daily) Q.O.D., QOD, q.o.d., qod (every other day)	Mistaken for each other; period after the 'Q' mistaken for 'I' and the 'O' mistaken for the 'I'	Write 'daily' Write 'every other day'
Trailing zero (X.0 mg)* Lack of leading zero (.X mg)	Decimal point is missed	Write 'X mg' Write '0.X mg'
MS	Can mean morphine sulfate or magnesium sulfate; confused for one another	Write 'morphine sulfate' Write 'magnesium sulfate'

* Exception: a 'trailing zero' may be used only where required to demonstrate the level of precision of the value being reported, such as for laboratory results, imaging studies that report sizes of lesions, or catheter/tube sizes. It may not be used in medication orders or other medication-related documentation.

▲ Table 1. The Joint Commission's 'Do Not Use' Abbreviation List. Applies to all orders and all medication-related documentation that is hand-written (including free-text computer entry) or preprinted forms.[4]

The ACSQH argues convincingly that a rethinking of the language used to communicate medication prescribing and administration is necessary. 'Patients and carers have a right to understand what is being prescribed to them and the use of abbreviations is a critical patient safety issue,' they write.

'Prescriptions should not contain ANY abbreviations other than those that are in universal and common use, such as the term "prn" meaning "when required". All drug names, protocols and procedures should be in English and written in full.'[5]

Dr Isabelle Jalbert, who teaches ocular therapeutics at the University of New South Wales, uses the ACSQH document from the outset of her courses. 'It's one of the required readings,' she said. 'I tell my students that their scripts have to be legible and clear and not confusing. It's common sense. If you write out your prescription, make it as clear as possible.'

Anthony Tassone, Victorian president of the Pharmacy Guild of Australia, agrees. 'It comes back to this: we can't be careful enough when we are prescribing, dispensing or talking to patents about medicines,' he said.

Tassone, a practising pharmacist, says that there has been genuine improvement in prescription legibility. 'From my experience and the experiences of my colleagues, I can say it is improving with optometrists prescribing. There has been quite a lot of care taken by prescribing optometrists,' he said. 'Of course there is always the opportunity for further improvement, but I think we are on the right path.'

Tassone attributes at least some of the progress to the gradual adoption of electronic prescriptions, particularly among optometrists, but he also explains that legible, clear prescriptions are all part of co-operating with the pharmacist.

For the prescriber, the choice is to either adopt these suggestions of accepted terminology when writing

Principles for consistency

1. **Use plain English**, avoid jargon.
2. **Write in full**, avoid using abbreviations wherever possible, including Latin abbreviations.
3. **Print all text**, especially drug names.
4. **Use generic drug names**.

   Exceptions may be made for combination products, but only if the trade name adequately identifies the medication being prescribed. For example, if trade names are used, combination products containing a penicillin (for example: Augmentin, Timentin) may not be identified as penicillins.

   Exceptions may also be made where significant bioavailability issues exist, for example, cyclosporin, amphotericin.
5. **Write drug names in full**.

   Never abbreviate any drug name. Some examples of unacceptable drug name abbreviations are: G-CSF (use filgrastim or lenograstim or pegfilgrastim), AZT (use zidovudine), 5-FU (use fluorouracil), DTIC (use dacarbazine), EPO (use epoetin), TAC (use triamcinolone).

   Exceptions may be made for modified release products. For slow release, controlled release, continuous release or other modified release products, the description used in the trade name to denote the release characteristics should be included with the generic drug name, for example, tramadol SR, carbamazepine CR.

   For multi-drug protocols, prescribe each drug in full and do not use acronyms, for example, do not prescribe chemotherapy as 'CHOP'. Prescribe each drug separately.
6. **Do not use chemical names/symbols**, for example, HCl (hydrochloric acid or hydrochloride) may be mistaken for KCl (potassium chloride).

   Do not include the salt of the chemical unless it is clinically significant, for example, mycophenolate mofetil or mycophenolate sodium. Where a salt is part of the name, it should follow the drug name and not precede it.
7. **Dose**
   - **Use words or Hindu-Arabic numbers**, in other words: 1, 2, 3 and so on.

     Do not use Roman numerals, in other words: do not use 'ii' for 'two', 'iii' for 'three', 'v' for 'five' and so on.
   - **Use metric units**, such as gram or mL.

     Do not use apothecary units, such as 'minims' or 'drams'.
   - **Use a leading zero in front of a decimal point for a dose less than 1**, for example, use '0.5' not '.5'.
   - **Do not use trailing zeros**, for example use '5' not '5.0'.
   - **For oral liquid preparations**, express dose in weight as well as volume, for example, in the case of morphine oral solution (5 mg/mL) prescribe the dose in mg and confirm the volume in brackets, for example, 10 mg (2 mL).
   - **Express dosage frequency unambiguously**, for example use 'three times a week' not 'three times weekly' as the latter could be confused as 'every three weeks'.
8. **Avoid fractions**, for example:
   - 1/7 could be interpreted as 'for one day', 'once daily', 'for one week' or 'once weekly'.
   - 1/2 could be interpreted as 'half' or as 'one to two'.
9. **Do not use symbols**
10. **Avoid acronyms or abbreviations for medical terms and procedure names on orders or prescriptions**, for example, avoid EBM meaning 'expressed breast milk'.

▲ Table 2. Principles for consistent prescribing terminology[5]

prescriptions or modify their electronic prescription software, which is easier and eliminates bad handwriting as well.

'When someone is having an eye procedure or is undergoing a treatment, it can be quite overwhelming,' Tassone said. 'Writing clear prescriptions means that you value the contribution that your community pharmacists can offer in making sure that patients can get their medicine and understand how to take it properly.'

Dr Jalbert has been teaching this to her students for years. 'We have a duty of care to write a clear and legible script for the pharmacist. It's safer and there's less chance that the patient will be put at risk,' she said. 'That's reason enough for me.'

Dr Jalbert says that even in busy practices, time has to be made to ensure the prescriptions are written clearly and legibly. 'Given how infrequently the practising optometrist actually writes out a prescription compared to, say, a general practitioner, it's not an onerous task to take the time and do it the right way.'

Continued page 12

1. JCAHO. Sentinel Event Alert—Medication errors related to potentially dangerous abbreviations: Joint Commission on Accreditation of Healthcare Organisations, 2001.
2. Garbutt J, Milligan P, McNaughton C, Waterman B, Clairborne Dunagan W, Fraser V. A practical approach to measure the quality of handwritten medication orders. *J Patient Saf* 2005; 1: 195-200.
3. Brunetti L, Santell JP, Hicks RW. The impact of abbreviations on patient safety. *Jt Comm J Qual Patient Saf* 2007; 33: 576-583.
4. The Joint Commission: National Patient Safety Goal on abbreviations clarified, implementation revised. *Jt Comm Perspect* 2003; 23: 14–15.
5. Australian Commission on Safety and Quality in Healthcare, (2011). Recommendations for terminology, abbreviations and symbols used in the prescribing and administering of medicines. [online] Available at: http://www.safetyandquality.gov.au/wp-content/uploads/2012/01/32060v2.pdf [Accessed 23 July 2015]. ▲

IMP: DEL A&A from Rx ... !?

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This table lists the terms and abbreviations that are commonly used and understood and therefore considered acceptable for use. Where there is more than one acceptable term, the preferred term is shown first in the right hand column.

Intended meaning	Acceptable terms or abbreviations
Dose frequency or timing	
(in the) morning	morning, mane
(at) midday	midday
(at) night	night, nocte
twice a day	**twice a day**
three times a day	**three times a day**
four times a day	**four times a day**
every 4 hours	**every 4 hrs, 4 hourly, 4 hrly**
every 6 hours	every 6 hrs, 6 hourly, 6 hrly
every 8 hours	every 8 hrs, 8 hourly, 8 hrly
once a week	once a week *and* specify the day in full, for example, 'once a week, on Tuesdays'
three times a week	three times a week **and** specify the exact days in full, for example, 'three times a week on Mondays, Wednesdays and Saturdays'
when required	**prn**
immediately	stat
before food	before food
after food	after food
with food	with food
Route of administration	
intravenous	IV
left eye	**left eye**
oral	PO
right eye	**right eye**
topical	topical
Units of measure and concentration	
gram(s)	g
International unit(s)	International unit(s)
unit(s)	unit(s)
litre(s)	L
milligram(s)	mg
millilitre(s)	mL
microgram(s)	microgram, microg
percentage	%
millimole	mmol
Dose forms	
cream	cream
eye-drops	**eye-drops**
eye ointment	**eye ointment**
injection	injection
metered dose inhaler	metered dose inhaler, inhaler, MDI
mixture	mixture
ointment	ointment, oint
powder	powder
tablet	tablet, tab
patient controlled analgesia	PCA

▲ Table 3. Acceptable terms and abbreviations[5] with common eye terms highlighted

Diabetes duration link to retinopathy

DIABETES DURATION is linked to the risk of microvascular complications in smaller blood vessels such as those in the eyes, a large Australian-led study has found. For each five-year increase in duration of type 2 diabetes, the multiple adjusted risk of microvascular events such as new or worsening retinopathy was increased by 28 per cent.

Researchers said this meant that younger people with diabetes were more at risk of microvascular complications as they were more likely to have diabetes for longer over their lifetime than those diagnosed at an older age.

'A refocus towards intensive management of hyperglycaemia at diagnosis, particularly in younger people, may be warranted if the long-term risk of microvascular complications is to be minimised,' researchers wrote in *Diabetologia*.

'With the increasing number of non-pharmacological and pharmacological approaches to improve glycaemic control, this objective should be achievable.'

Researchers investigated associations between age, age at diagnosis of diabetes, diabetes duration and vascular complications in a study of a large and diverse population of 11,140 people with type 2 diabetes. Diabetes duration was independently associated with the risk of microvascular complications, and the effects of diabetes duration were greatest at younger rather than older ages.

'Intensive glycaemic control of young people diagnosed with type 2 diabetes is warranted early to minimise the risk of microvascular complications,' they said.

'Our data further suggest that both intensity of hyperglycaemia and a more susceptible microvasculature may explain the greater risk of microvascular complications in younger people than older people with type 2 diabetes.'

They said people who develop type 2 diabetes at a younger age may have a different phenotype from those who develop it later, so that worse glycaemic control and greater microvascular damage is experienced.

The research, led by Associate Professor Sophia Zoungas from The George Institute for Global Health, University of Sydney, also involved Victorian colleagues from the University of Melbourne, Monash University and Baker IDI Heart and Diabetes Institute and researchers from overseas.

Zoungas S et al. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. *Diabetologia* 2014; 57: 12: 2465-2474. doi: 10.1007/s00125-014-3369-7. ▲

Therapeutic NEWS of note

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Ocular surface disease in patients using antiglaucoma eye-drops

According to a study published in *Optometry and Vision Science*, patients using topical antiglaucoma eye-drops have a significantly higher occurrence of ocular surface disease than those who are not on any medications.

Ramli and colleagues conducted a cross-sectional, case-comparison study to assess the prevalence of ocular surface disease (OSD) in relation to various medications.

The researchers compared OSD presence among 105 glaucomatous participants using topical antiglaucoma medications and 102 control participants not using topical medications. OSD presence was evaluated using Ocular Surface Disease Index (OSDI) questionnaire grading, corneal staining, Schirmer's test and the tear film break-up time (TBUT) test.

It was found that more glaucoma participants had corneal staining, moderate OSDI symptoms and abnormal Schirmer's tests than control participants. An association was found between abnormal TBUT and higher numbers of topical medications and eye-drops that contained benzalkonium chloride (BAK).

Significantly, participants using an eye-drop with BAK were three times more likely to show abnormal OSDI. The authors suggested that the number of ocular surface disease cases may increase with the growing number of eye-drops that contain the preservative BAK.

Ramli N et al. *Optom Vis Sci* 2015; doi: 10.1097/OPX.0000000000000542.

Sleep quality in patients linked to glaucomatous structural damage

The authors of a cross-sectional study have found that decreased function of intrinsically photosensitive retinal ganglion cells (ipRGC) affects pupillary response and sleep quality.

Both eyes were tested on the patients in the study (45 participants – 32 with glaucoma and 13 healthy subjects). Pupillary light reflex and polysomnography were used to evaluate the function of ipRGCs and correlate it with structural damage in glaucoma.

For pupillary light reflex, glaucoma patients had significantly lower peak responses to the 250 cd/m^2 blue flash and the average rapid eye movement latency and lower sustained responses to the 250 cd/m^2 blue flash and arousal parameters, both associated with a thinner mean RNFL.

For the polysomnography, a thinner mean RNFL thickness was associated with a poorer oxygen desaturation index in glaucoma patients.

Patients with glaucoma had significantly lower average total sleep time, sleep efficiency and minimum oxyhaemoglobin saturation compared with the healthy subjects. Patients with glaucoma had significantly higher arousal durations after falling asleep and more periodic limb movements.

The authors suggested that concerns about sleep disturbances in patients with glaucoma should be incorporated into clinical evaluations.

Gracitelli C et al. *Ophthalmology* 2015; 122: 6: 1139-1148.

The shifting tide of opinion on antibiotics

Articles published in the *Medical Journal of Australia* are encouraging health-care providers to stop antibiotic treatment when the patient feels better, rather than finish their full course of antibiotics.

Professor Gwendolyn Gilbert, of the Marie Bashir Institute for Infectious Diseases and Biosecurity at the University of Sydney, wrote that there was no risk, but 'every advantage' in stopping a course of an antibiotics once a bacterial infection had been excluded and 'minimal risk' if signs and symptoms of a mild infection had resolved.

For most infections, Professor Gilbert wrote, 'there was no solid evidence for the recommended duration of therapy, while for many syndromes associated with bacteraemia, studies showed no difference in outcome when shorter courses of antibiotics were used.'

Professor Chris Del Mar, professor of public health at the Centre for Research in Evidence-Based Practice at Bond University, Queensland, concurred, saying in an interview with *MJA InSight* 'the old mantra about finishing a course of antibiotics was based on an assumption that unless you eradicated the infection it could come back and you would need another course of antibiotics—but there is no evidence for this except in a few very specific illnesses such as tuberculosis.'

Professor Del Mar said he hoped that Australia would move towards a system where health-care practitioners prescribed the exact amount of antibiotic required, specific to the individual patient and their illness.

Greater co-operation was needed between GPs at the local level to agree on which antibiotics would

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NEWS of note

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be prescribed for which illnesses, to reduce the risk of antibiotic resistance developing in certain locales, he said.

'There is a common misconception that resistance will emerge if a prescribed antibiotic course is not completed,' Professor Gilbert wrote. 'However, premature cessation of antibiotic therapy will not increase the risk that resistance will emerge. For most infections, the recommended duration of therapy (5–14 days, depending on syndrome) is based on expert opinion and convention, rather than solid evidence.'

Gilbert G. Intrinsically photosensitive retinal ganglion cell activity is associated with decreased sleep quality in patients with glaucoma. *Med J Aust* 2015; 202: 3: 121-122.

Testing the Triggerfish

How good is a contact lens sensor (CLS) for 24-hour monitoring of IOP-related short-term patterns compared with IOP obtained by pneumatonometry? Pretty good.

In this prospective clinical trial, 31 healthy volunteers and two glaucoma patients were housed for 24 hours in a sleep laboratory. One randomly-selected eye was fitted with a CLS (Triggerfish, Sensimed, Switzerland), which measures changes in ocular circumference. In the contralateral eye, IOP measurements were taken using a pneumatonometer every two hours with subjects in the habitual body positions.

Performance of CLS was defined in two ways.

1. Recording the known pattern of IOP increase going from awake (sitting position) to sleep (recumbent), defined as the wake/sleep (W/S) slope.
2. Accuracy of the ocular pulse frequency (OPF) concurrent to that of the HR interval. Strength of association between overall CLS and pneumatonometer curves was assessed using coefficients of determination (R2).

The W/S slope was statistically significantly positive in both eyes of each subject (CLS, 57.0 ± 40.5 mVeq/h, $p < 0.001$ and 1.6 ± 0.9 mmHg/h, $p < 0.05$ in the contralateral eye). In all, 87 CLS plots concurrent to the HR interval were evaluated. Graders agreed on evaluability for OPF in 83.9 per cent of CLS plots. Accuracy of the CLS to detect the OPF was 86.5 per cent.

The researchers concluded that CLS measurements compare well to the pneumatonometer and may be of practical use for detection of sleep-induced IOP changes. The CLS also is able to detect ocular pulsations with good accuracy in a majority of eyes.

Mansouri K, Weinreb RN, Liu JH. Efficacy of a contact lens sensor for monitoring 24-h intraocular pressure related patterns. *PLoS One* 2015; 10: 5: e0125530. doi: 10.1371/journal.pone.0125530.

Metformin for pre-diabetic patients

Metformin, which was first synthesised in 1922 and shown to lower blood glucose, has become one of the most prescribed drugs in the world. Fresh debate on the use of the drug has flared following a study that suggested that the drug was still under-prescribed.

In the retrospective cohort study 'Metformin Prescription for Insured Adults with Prediabetes From 2010 to 2012',[1] researchers concluded that metformin was rarely prescribed for diabetes prevention in working age adults.

In the study, researchers examined health insurance claims data to assess metformin use among a national sample group of more than 17,000 adults (age range, 19-58) with pre-diabetes between 2010 and 2012. Researchers found that only 3.7 per cent of patients received metformin. They concluded that the barriers to wider adoption of metformin as a safe, tolerable, evidence-based and cost-effective pre-diabetes therapy should be scrutinised.

Reviewing the study in the *NEJM*, Dr Jamaluddin Moloo was openly sceptical of the finding. 'We don't know whether giving metformin to [pre-diabetic patients] will eventually pay off in clinically meaningful reductions in mircrovascular or macrovascular complications,' he wrote.

Dr Moloo cited a recent reanalysis of Diabetes Prevention Program data,[2] which suggested that metformin delayed progression to formal diagnoses of diabetes in a relatively small subgroup of prediabetic patients who were at highest baseline risk for progression.

In that study, researchers found that the benefit of metformin was seen almost entirely in patients in the top quarter of risk of diabetes. No benefit was seen in the lowest risk quarter.

1. Moin T et al. Metformin prescription for insured adults with prediabetes from 2010 to 2012: a retrospective cohort study. *Ann Intern Med* 2015; 162: 8: 542-548.
2. Sussman et al. Improving diabetes prevention with benefit based tailored treatment: risk based reanalysis of Diabetes Prevention Program. *BMJ* 2015; Feb 19; 350: h454. doi: 10.1136/bmj.h454.

Metformin for open angle glaucoma

According to a study online by *JAMA Ophthalmology*, Metformin may decrease the risk of open angle glaucoma (OAG) in people with diabetes.

To determine if medications that mimic caloric restriction—such as metformin—can reduce the risk of age-associated eye diseases, researchers from the University of Michigan examined metformin use and the risk of open-angle glaucoma (OAG) using data from a large US managed care network from 2001 through 2010.

Study results indicate that patients prescribed the highest amount of metformin (greater than 1,110 grams in two years) had a 25 per cent reduced risk of OAG risk compared with those who took no metformin. Every one gram increase in metformin was associated with a 0.16 per cent reduction in OAG risk, which means that taking a standard dose of two grams of metformin per day for two years would result in a 20.8 per cent reduction in risk of OAG.

Other diabetes medications did not confer a similar OAG risk reduction. The study authors concluded that these results illustrate the importance of understanding the potential impact of caloric restriction mimetic drugs such as metformin on the risk of developing medical conditions that affect older persons.

Lin H-Chang et al. Association of geroprotective effects of metformin and risk of open-angle glaucoma in persons with diabetes mellitus. *JAMA Ophthalmol.* Published online May 28 2015. doi:10.1001/jamaophthalmol.2015.1440

Intraretinal oedema the source of visual aberrations

A study has found that increased higher order (HO) wavefront aberrations are present in eyes with macular oedema.

In the prospective study, 33 eyes of patients with diabetic macular oedema were scanned with a ray-tracing wavefront device. As a control group, wavefront aberrometry was performed in 31 patients. Ocular and internal aberrations and visual quality metrics were evaluated separately to determine whether the source of aberrations was ocular or internal.

There was a statistically significant difference between the groups in internal higher order (HO) root mean square (0.34 +/- 0.24 vs 0.16 +/- 0.05), HO Strehl ratio (0.08 +/- 0.05 vs 0.18 +/- 0.09), and modulation transfer function (0.29 +/- 0.1 vs 0.4 +/- 0.1). There was no statistically significant difference in Strehl ratio and HO root mean square between phakic and pseudophakic patients. Height of cystoid spaces was a significant predictor ($p < 0.001$) of Strehl ratio.

The study authors concluded that in eyes with macular oedema, internal HO wavefront aberrations were greater than in control eyes. The authors suggested that the increase in HO wavefront error seemed visually relevant, and pointed to increased intraretinal oedema as the source of higher order aberrations.

Miháltz K et al. Ocular wavefront aberrations and optical quality in diabetic macular edema. *Retina* 2015; Jun 3. [Epub ahead of print].

First-in-class cholesterol-lowering drug recommended to FDA

An advisory committee has recommended that the Food and Drug Administration (FDA) approve two PCSK9 inhibitors for the reduction of low-density lipoprotein (LDL) in certain patient populations.

The panel voted to recommend approval of the monoclonal antibody alirocumab (Praluent), and evolocumab (Repatha) during the Endocrinologic and Metabolic Drugs Advisory Committee meeting on June 10, 2015.

Panel members recommended that both drugs initially be limited to patients with familial hypercholesterolaemia until more data are available on whether the drugs actually reduce cardiovascular events.

Studies have found that alirocumab reduces LDL cholesterol by 40 per cent to 60 per cent, compared with placebo, while evolocumab was associated with a roughly 60 per cent LDL reduction.

The FDA is not required to follow the recommendations of its advisory panels, but it usually does. If approved, the injectable drugs would be the first available proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, which help the liver remove LDL cholesterol from the blood.

Endocrinologic and Metabolic Drugs Advisory Committee, FDA Briefing Document [monograph on the Internet]. 2015 (cited 2015 July 24). Available from http://www.fda.gov/downloads.

IOP-lowering effect of SLT and ALT comparable

There is no difference between the IOP-lowering effect of selective laser trabeculoplasty (SLT) and argon laser trabeculoplasty (ALT), according to results of a systematic review published in *Eye*.

The investigator reviewed randomised controlled trials (RCTs) published in peer-reviewed journals comparing SLT to other glaucoma treatment options. The main outcome measure was the change in IOP from baseline.

According to the study, an initial search of PubMed identified 23 RCTs, with 17 meeting the inclusion criteria. Nine RCTs compared 180-degree SLT to 180-degree ALT, and one trial compared 360-degree SLT to 360-degree ALT; all reported no difference in terms of IOP reduction from baseline.

The author concluded that in terms of the IOP lowering effect, there is no difference between SLT and ALT. Three trials indicate no difference between 360-degree SLT and medical therapy, with one of the trials indicating greater IOP reduction with latanoprost over 90 degrees and 180 degrees SLT. Three trials indicate no difference between 180-degree SLT and 360-degree SLT. It is inconclusive whether 90 degrees is less efficacious than 180 degrees SLT. One trial reports greater IOP reduction with ELT over 180 degrees SLT in the long term.

McAlinden C. *Eye* (Lond). [published online ahead of print]. doi:10.1038/eye.2013.267.

Lucentis listed for DME and RVO

In July, Minister for Health Sussan Ley issued a statement that announced that the Australian government would expand the listing of the Pharmaceutical Benefits Scheme to include Lucentis to treat diabetic macular oedema and retinal vein occlusion.

'Patients with a range of serious eye conditions now have affordable access to life-changing medicines that normally cost up to $10,000 for treatment,' Ley said. 'Eighteen thousand Australian patients will now pay $6.10 (concessional) or $37.70 (general) for Lucentis.'

'Diabetic macular oedema is a complication of diabetes, and retinal vein occlusion is a blockage of the vessel which drains blood out of the retina, the light-sensitive tissue at the back of the eye, and if left untreated both conditions can lead to severe vision loss and blindness. Lucentis is effective in slowing or stopping the progression of these degenerative conditions,' Ley said. 'Without treatment for these conditions patients can suffer severe loss of vision and blindness and therefore lose their independence.'

This new listing will assist about 12,000 patients per year with diabetic macular oedema and 6,000 patients per year with retinal vein occlusion. ▲

Atropine as part of treatment protocols for amblyopia

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MANAGEMENT of amblyopia has progressed from largely conventional thinking to evidence-based practice in the past 15 years. Prior to this century, the vast majority of books, opinion pieces and guidelines from learned bodies included the conventional wisdom that amblyopia should be treated with all-day patching of the good eye from the time of diagnosis, and treatment should cease when a child turned six years of age because after that, it would not work.

Although long-standing principles of individualising and connecting with patient needs remain, new evidence should change the way we manage patients who have amblyopia.

Even the reasons for treating amblyopia have been better defined over the past 15 years. As eye-care practitioners, we have always been comfortable with the idea that improving vision is a reason unto itself, along with the positive reinforcement of individual patient anecdotes. More recently, there is evidence that treating amblyopia is important to the patients themselves, as well as economists, actuaries and policy-makers, among others. For example, treating amblyopia has been shown to measurably improve quality of life for patients,[1] and it provides a good return on health dollar investment.[2]

As practitioners, our primary aim in amblyopia therapy is to improve monocular function—to achieve normal visual acuity (VA) and fixation in each eye separately. This provides a 'spare tyre' for life, or 'vision insurance', along with a better quality of life and better health economics outcomes. Our secondary aim is to improve binocular function—to achieve normal fusion (all levels) and binocular correspondence measured with both eyes open. This provides insurance against or part treatment of uncosmetic strabismus, along with a better quality of life.

Amblyopia treatment protocols

The Monitored Occlusion Treatment of Amblyopia (MOTAS) group in the United Kingdom and the Paediatric Eye Disease Investigator Group (PEDIG) in the United States have been instrumental to the accumulation of new evidence for the treatment of amblyopia. For the first time, we can base amblyopia treatment protocols on solid evidence with flexible details. My interpretation of best evidence-based practice divides treatment into four stages, which will be elaborated on but can be summarised as:

Stage 1. Prescribe glasses only for three months or until vision of the amblyopic eye stops improving, whichever is longer.

Stage 2. Prescribe glasses and all-day patching of the non-amblyopic eye for preschool children, or glasses and two hour/day patching of the non-amblyopic eye for school children.

Stage 2. Modification 1: when compliance/resolve for patching wanes or if patching is unsuccessful, change to glasses with atropine penalisation of the non-amblyopic eye.

Stage 2. Modification 2: when approaching equal visual acuity between eyes, consider translucent or refractive penalisation, for example Bangerter Filter, or over-correcting hyperopia.

Stage 3. Use glasses, prisms, vision therapy and/or surgery to treat any strabismus.

Stage 4. Use vision therapy and/or glasses modifications to treat accommodation-vergence issues, particularly high lag of accommodation in the previously amblyopic eye.

Atropine penalisation has an important evidence-based role in treatment of amblyopia, within a framework such as this, with safe protocols such as those described below and with defined discharge criteria as described below.

First step

As a first step after amblyopia diagnosis, MOTAS and PEDIG have independently established that it is worthwhile to start with up to three months of treatment with glasses alone.[3-5] This stage in treatment provides equally clear retinal images by correcting anisometropia, with a bias towards fusion and supporting the impaired accommodation of the amblyopic eye.

It is also the practitioner's opportunity to set up a trusting relationship with the child, building rapport and understanding without doing anything that the child will strongly dislike. In this time, around 75 per cent of children with either anisometropic or strabismic amblyopia will gain approximately two lines of improvement in visual acuity.[3-5]

Occlusion and/or penalisation therapies

After refractive-only treatment for up to three months, MOTAS and PEDIG have shown that a variety of occlusion and/or penalisation therapies can be used to decrease the strength of the neural signals from the non-amblyopic eye. Practitioners can devise suitable treatments for individual patients within the following bounds:

- Opaque patching of the non-amblyopic eye achieves a faster initial treatment response (visual acuity improvement of the amblyopic eye) than penalisation.[6-9]
- More patching hours probably gains faster and sometimes fuller treatment response, but part-time patching works.[10-12]
- Weekend atropine penalisation of the non-amblyopic eye achieves results (visual acuity improvement in the amblyopic eye) similar to those of daily atropine.[13]
- Prescribing specific activities (concentrated, interactive near activities) to be done during part-time patching might not matter.[14,15]
- Atropine penalisation and opaque patching have different impacts (social, physical comfort, effort required) on children and families.[16]
- The younger that treatment can be started, the better, but there is no age limit to amblyopia treatment.[17-20]
- Amblyopia recurrence is always a risk as you finish active phases of treatment but tapering the treatment helps.[21-23]

Consider translucent penalisation (a Bangerter Filter applied to the spectacle lens of the non-amblyopic eye) if visual acuity is better than 6/30 in the amblyopic eye and compliance seems likely.[24]

Extra practitioner effort significantly improves compliance with amblyopia therapy.[25] For example, take the time to explain amblyopia to parents and children, and provide reward stickers, a log book and an information sheet.

The MOTAS group has done the most thorough work to model amblyopia treatment dose (hours of patching) versus therapeutic response (VA improvement).[19] The results provide evidence-based support for the concept of 'amblyopia treatment cycles', where one cycle = one week for every year of life. A four-year-old can achieve a two line improvement in VA in four weeks, while this takes six weeks for a six-year-old to achieve the same.[19]

Atropine penalisation

Atropine is a non-selective muscarinic antagonist, long known to cause mydriasis and cycloplegia by disrupting parasympathetic innervation to the pupillary sphincter and ciliary body muscles. Both of these mechanisms and outcomes of ophthalmic atropine use degrade the retinal image for the duration of effect, particularly in a hyperopic eye. This degradation of retinal image means it can be used to penalise a non-amblyopic eye, giving some competitive advantage in cortical image processing to information coming from the amblyopic eye.

If a practitioner decides that atropine penalisation of the non-amblyopic eye is the most appropriate way to treat amblyopia at some stage, they should:

- Note contra-indications for atropine—Down Syndrome, spastic paralysis, brain damage, narrow anterior chamber angles, hypersensitivity to any of the ingredients.
- Prescribe 1% Atropt for somewhere between once daily and twice weekly use in the non-amblyopic eye.
- Provide a patient information hand-out including critical information about complications.
- Advise wearing sunglasses and a hat when outside.
- Reiterate that the family should contact you or a hospital emergency department immediately if the child shows signs of adverse reactions—local allergic reactions, dry mouth, facial flushing, headaches, ataxia, tachycardia, fever, irritability, low blood pressure or difficulty breathing.
- In a very small minority of cases (I have never encountered reactions requiring these responses), adverse reactions might need to be controlled in the short term via supportive treatments for high fevers and dehydration or intramuscular physostigmine to counteract the muscarinic antagonist effect of atropine, in severe or life-threatening toxicity.
- In a small minority of cases, adverse reactions need to be controlled in the longer term by decreasing the dosage, for example, to 'weekend only', changing drug therapy to homatropine or ceasing drug therapy entirely.
- It is sensible to review after one week of atropine penalisation to assess distance visual acuity (although noting that treatment effect does not require reduced distance visual acuity in the atropined eye, and that we do not expect improved visual acuity in amblyopic eye at this stage), complications from atropine use, efficacy of atropine use (little to no pupil response to light, or accommodative response, in the non-amblyopic eye), and accommodation in the amblyopic eye (systemic absorption of atropine can lead to decreased accommodation in the eye that does not receive drops—consider a bifocal correction if this occurs).

It is then sensible to review after each amblyopia treatment cycle, in other words, one week for every year of the patient's life. The practitioner should have clear criteria for discharging from atropine penalisation. For example, no improvement over two cycles, or

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Atropine

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continuous compliance for six months, or another therapy becomes indicated.

What to do after atropine penalisation—the final stages of amblyopia therapy

The third stage of amblyopia therapy involves treating any strabismus. The motor aspects of strabismus may require surgery, prism, an altered refractive correction, vision therapy and/or a near addition. The sensory aspects of strabismus may require anti-suppression vision therapy.[26]

The fourth and final stage of amblyopia therapy involves the removal of any other impediments to efficient binocular vision. This may require further alterations of refractive correction, a near addition, prism or vision therapy. Particularly, accommodative dysfunction in a previously amblyopic eye can lead to treatment regression. Note that active vision therapy to improve accommodation vergence skills is only likely to be useful once visual acuities are equal or almost equal—it will not replace the other amblyopia therapy stages.

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Research update: LANDMark study

Longitudinal Assessment of Neuropathy in Diabetes using novel ophthalmic MARKers

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DIABETES IS ONE of the most common diseases world-wide and can lead to serious complications including nephropathy, retinopathy and neuropathy. Diabetic peripheral neuropathy (DPN) is a debilitating and prevalent complication of diabetes and affects up to 50 per cent of patients with diabetes. DPN leads to numbness, loss of sensation, tingling, and pain or weakness that often affects patients' feet and legs first, followed by their hands and arms. Lack of awareness of foot injury may lead to foot ulcers, which in advanced stages, can result in lower limb amputation.

Conventional measures of DPN such as skin or nerve biopsies, nerve electrophysiology and quantitative sensory tests have significant shortcomings. They are invasive and uncomfortable. They are unable to detect early, small nerve damage and repair, and they require specialised medical expertise and equipment.

It seems that lack of an early biomarker for nerve changes in diabetic neuropathy is one of the most notable obstacles of assessing treatment efficacy in clinical trials. There is an urgent need for a sensitive and reliable diagnostic marker for DPN.

The LANDMarK Study

The eye has been explored as a simple, non-invasive location for screening, diagnosis and follow-up of DPN. The LANDMark (Longitudinal Assessment of Neuropathy in Diabetes using novel ophthalmic MARKers) study is a two-site (Brisbane, Australia and Manchester, UK), four-year longitudinal observational study.

The LANDMark study has investigated the association between corneal confocal microscopy (CCM) (Figure 1), non-contact corneal aesthesiometry (NCCA), optical coherence tomography, and visual field perimetry and peripheral nerve morphology and function in individuals with type 1 and type 2 diabetes as well as healthy participants. The Brisbane site completed the four-year longitudinal study in July 2014 and the Manchester site is scheduled to finish this year.

The cross-sectional baseline findings of the LANDMark study were published in 2012 and demonstrated the utility of CCM and NCCA in diagnosis of DPN.[1,2] The results also demonstrated reduced visual sensitivity within the central 30 degrees of visual field in participants with DPN.[3]

We have recently also published the four-year longitudinal outcomes, revealing that corneal nerve structure is relatively stable over time in non-neuropathic individuals.[4] However, a significant linear decline of corneal nerve fibre density in neuropathic individuals was observed over four years with a decrease of approximately

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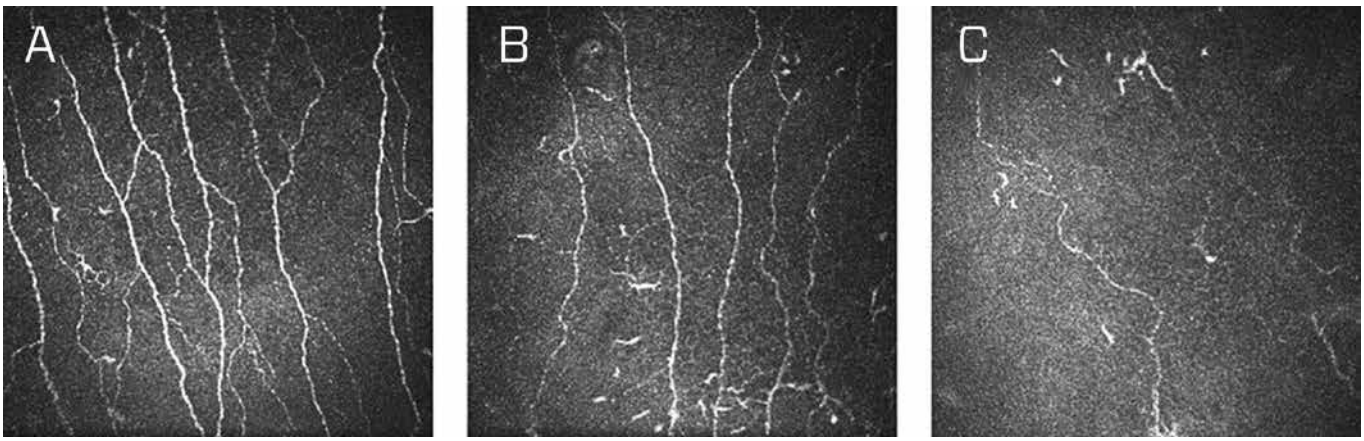

▲ Figure 1. Laser-scanning confocal microscopy images of central corneal sub-basal nerve plexus (A) healthy participant, (B) diabetic participant without DPN and (C) diabetic participant with severe DPN

Value of autofluorescence imaging in retinitis pigmentosa

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PHOTO CLINIC

RETINITIS PIGMENTOSA (RP) is a group of inherited disorders characterised by a progressive peripheral vision loss (tunnel vision) and poor vision in dim light. It can progress to total central vision loss.

Ocular examination includes visual acuity, perimetry, colour vision testing and retinal imaging. Ideally, electroretinogram assessment and dark adaptometry may be performed. Genetic subtyping may be indicated to identify the particular metabolic defect. Optical coherence tomography (OCT) is not required to diagnose RP, though it can be helpful in detecting cystoid macular oedema.

While there is no cure for RP, it is essential to help patients maximise their vision with a careful refraction and low vision assessment.

Medical management of RP may include prescribing fat-soluble vitamins (vitamin A, vitamin E, ascorbic acid), calcium-channel blockers (diltiazem) and carbonic anhydrase inhibitors (acetazolamide). Surgical management may involve cataract extraction. Experimental procedures for the long-term management of RP include transplantation of retinal pigment epithelial tissue, retinal prosthetic devices, for example a bionic eye, and subretinal gene therapy.

Fundus autofluorescence

Fundus autofluorescence (FAF) is an imaging technique that maps fluorophores of the ocular fundus. The main retinal fluorophore is A2-E found in lipofuscin that accumulates in the RPE during incomplete breakdown of photoreceptor outer segments. FAF imaging is useful in detecting alterations in RPE function in age-related macular degeneration and hereditary retinal disorders such as Stargardt's disease, vitelliform dystrophy, pattern dystrophy and RP. In RP, parafoveal hyperfluorescence rings may be seen before lesions are visible with ophthalmoscopy (Figures 1-4).

Case report

A 27-year-old Caucasian female presented for an ocular examination. She complained of 'spots' in one of her eyes and difficulty seeing at night. Her sister had an 'undiagnosed' eye condition. Best corrected visual acuity was RE 6/7.5 LE 6/9.5. Fundus examination showed bone-spicule pigmentation in both eyes (Figures 1 and 3). An updated prescription and daily living skills advice were provided. The patient was referred to ophthalmology for further tests to confirm the diagnosis.

Optos Daytona widefield retinal imaging was performed using standard and autofluorescence modes. FAF clearly indicates macula involvement in this case, which is not easily seen in the standard ocular image. FAF allows for early detection and clear documentation of RPE dysfunction in RP.

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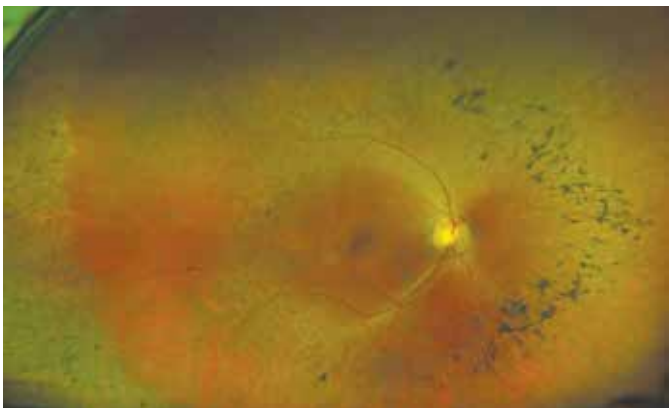
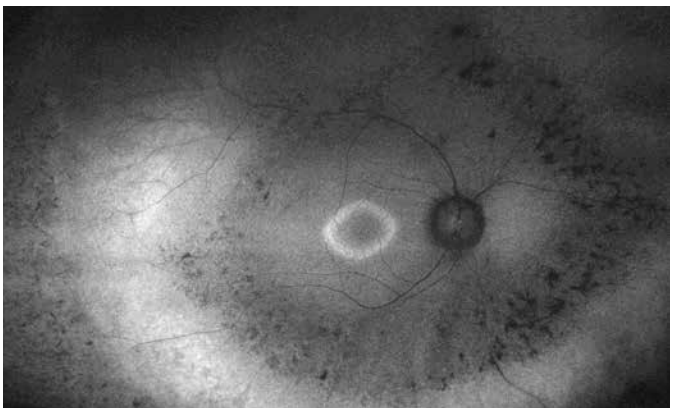
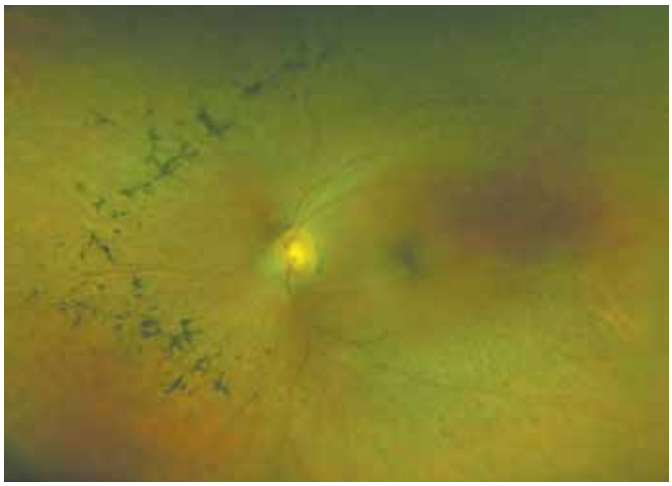


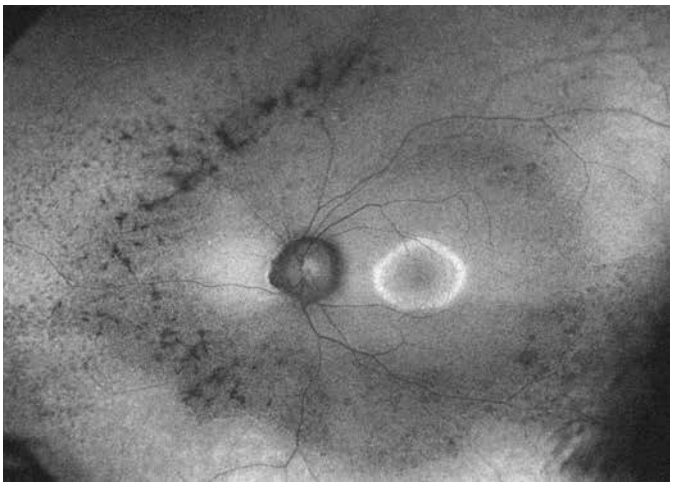
▲ Figure 1. Composite image of RE using Optos Daytona



▲ Figure 2. FAF image of RE using Optos Daytona



▲ Figure 3. Composite image of LE using Optos Daytona



▲ Figure 4. FAF image of LE using Optos Daytona

LANDMark study

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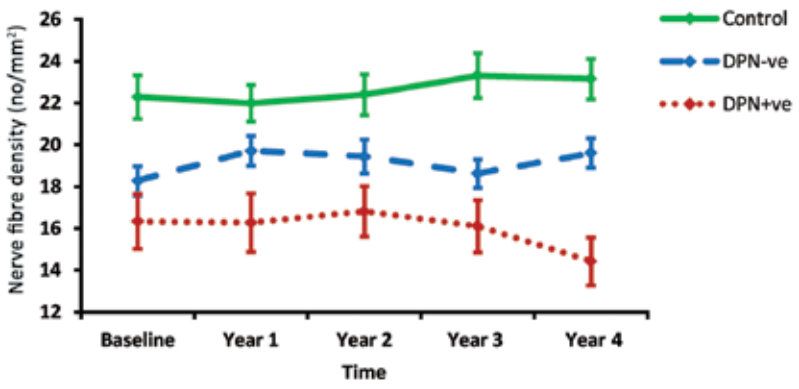
one nerve/mm^2 per year (Figure 2, below). The observed decline was associated with age and duration of diabetes of the participants. The study also demonstrated that the corneal nerve parameters did change in a pattern comparable with some conventional measures of neuropathy.[5]

Future directions

In 2014, the US National Institutes of Health funded a multinational collaborative study, of which the Brisbane-based LANDMark study is a part, with the aim of assessing CCM as a surrogate endpoint for the identification and prediction of diabetic neuropathy in type 1 and type 2 diabetes.

This dataset will ultimately include five to seven years of follow-up on over 500 participants with diabetes from Australia, Canada, the USA and the UK. Through the approach of the multinational pooled dataset, this project will derive and validate specific CCM parameter cut-offs for the identification of DPN and the identification of individuals at future risk of DPN onset.

These results will permit application of corneal nerve assessment as a diagnostic marker for DPN in clinical practice and more importantly, in intervention trials for therapeutic agents for DPN.



▲ Figure 2. Longitudinal course of corneal nerve fibre density over time in LANDMark study (Brisbane site). DPN-ve, diabetic participants without neuropathy; DPN+ve, diabetic participants with neuropathy.

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Reticular pseudodrusen

An often-missed risk factor in the early stages of age-related macular degeneration

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THE PRESENCE of drusen is considered the hallmark feature of age-related macular degeneration (AMD), with the presence of pigmentary abnormalities further contributing to the risk of developing advanced, vision-threatening complications including choroidal neovascularisation (CNV) and geographic atrophy (GA).

Drusen are focal deposits of extracellular debris that accumulate between the retinal pigment epithelium (RPE) and Bruch's membrane (BM), and are described clinically by their size and characteristics. For example, large, soft drusen typically have indistinct borders while cuticular or basal laminar drusen appear as a multitude of small (25-75 µm diameter) discrete and uniformly-sized yellow lesions.

However, another distinct clinical feature, termed 'reticular pseudodrusen' (RPD) was first recognised more than two decades ago. These lesions are uniquely characterised by their appearance as ill-defined networks of broad, interlacing ribbons on clinical examination and fundus photography. The significance of these lesions became increasingly important because they were often found in eyes with late AMD. It was therefore suggested that they were an important risk factor.

With the advent of multimodal imaging modalities including high-resolution, spectral domain optical coherence tomography (SD-OCT), several studies subsequently reported that the RPD observed clinically and on colour fundus photographs were actually deposits above the RPE, as opposed to accumulations below the RPE that are characteristic of drusen.[1] The term 'subretinal drusenoid deposits' was therefore proposed, and the localisation of these lesions to the subretinal space was subsequently confirmed in a histological study.[2]

The increasing use of SD-OCT along with near-infrared reflectance (NIR) and fundus autofluorescence (FAF) imaging in medical retina practice led to the recognition that RPD were present more often than had been previously thought because they are often not recognised on clinical examination and colour fundus photography.

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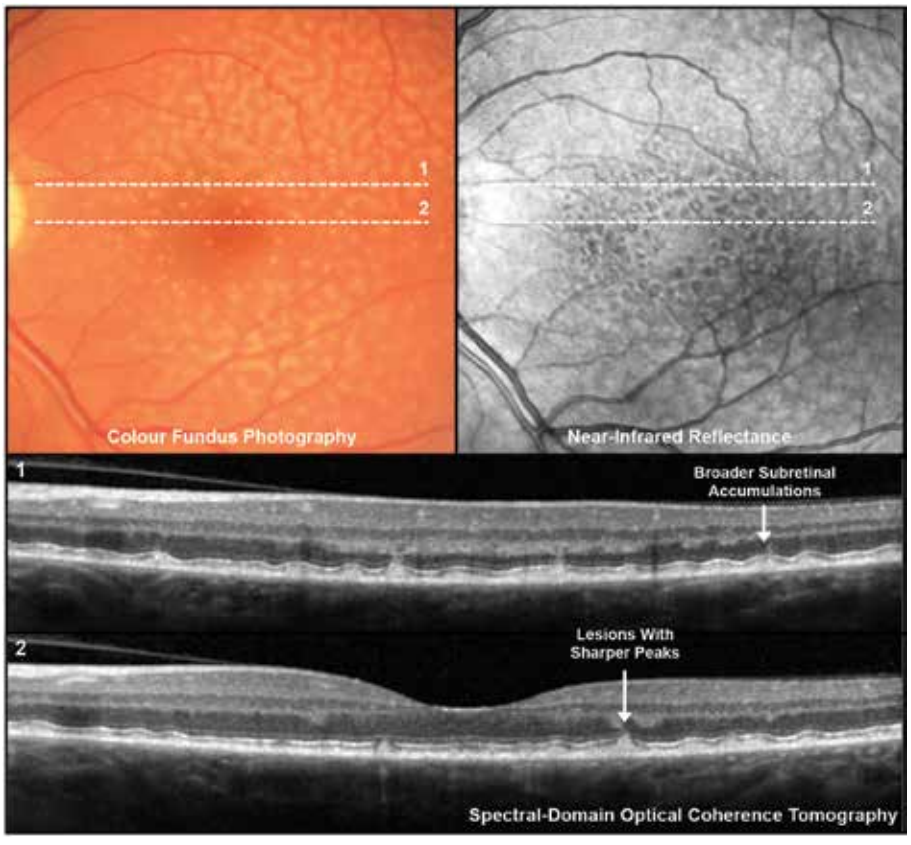
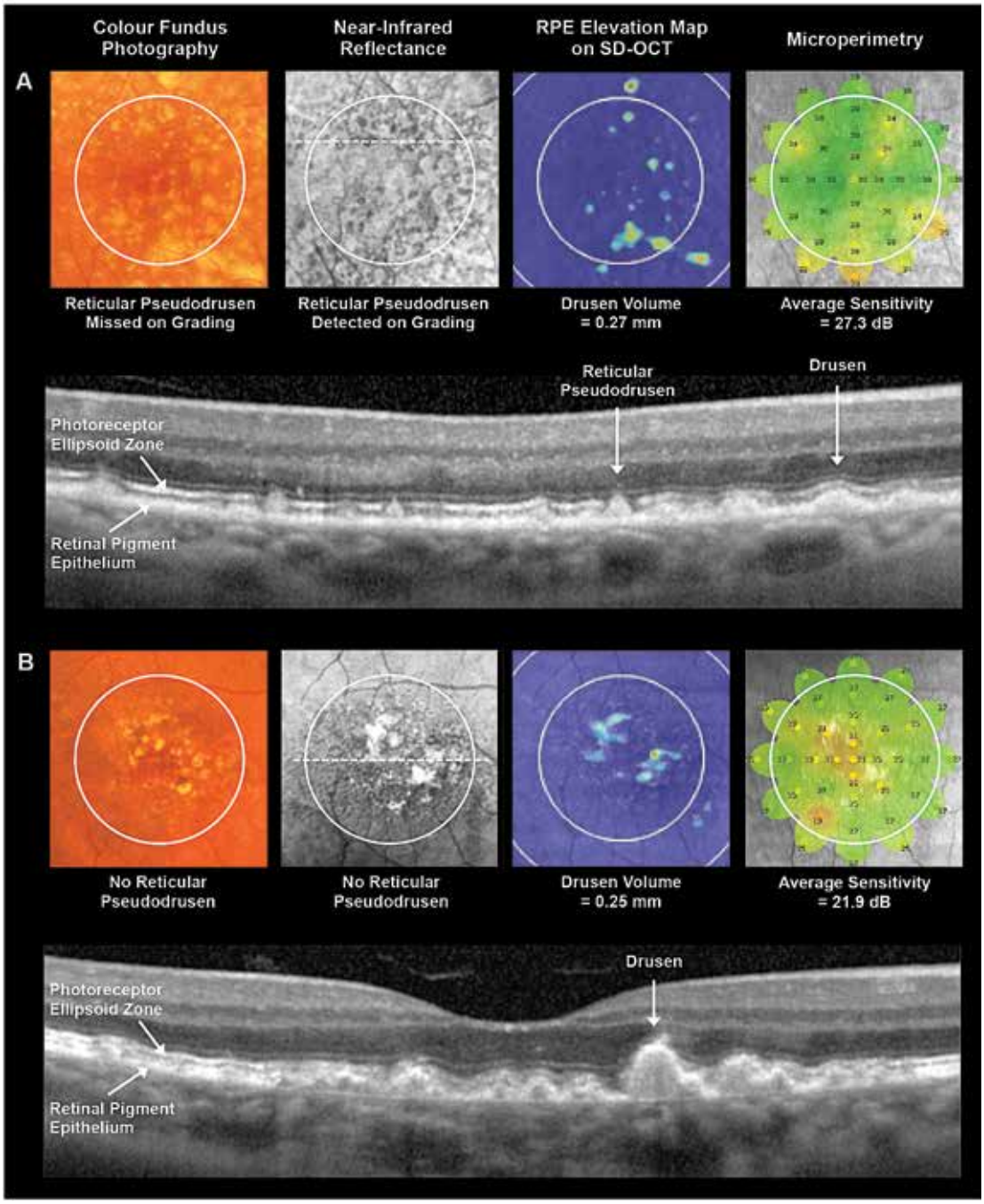


▲ Figure 1. Appearance of reticular pseudodrusen (RPD) on colour fundus photography, near-infrared reflectance (NIR) imaging and spectral-domain optical coherence tomography (SD-OCT) scans. Dashed lines indicate areas where the SD-OCT scans (numbered) were taken. On SD-OCT, RPD can appear as either broader subretinal accumulations or lesions with sharper peaks.



▲ Figure 2. Reticular pseudodrusen (RPD) distinguished from typical drusen

A: This figure illustrates how RPD can be missed on grading of a colour fundus photograph but detected on near-infrared reflectance (NIR) imaging and spectral-domain optical coherence tomography (SD-OCT) scans (shown at the bottom of each example). RPD are also missed when considering the retinal pigment epithelium (RPE) elevation maps generated by some SD-OCT devices.

B: An example showing an eye with typical drusen that appears to have groups of hypo-reflective lesions on NIR imaging but without any subretinal drusenoid deposits on SD-OCT imaging. While both examples are characterised by similar drusen volume, RPD are present in the first example (A) and pigmentary abnormalities are present in the second example (B), and the latter is associated with reduced mesopic microperimetric sensitivity.

Reticular pseudodrusen

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For example, RPD was detected in only 20 per cent of eyes on colour fundus photography when they were present on SD-OCT scans.[3]

With these imaging modalities, RPD has been reported to be present in as many as 62 per cent of eyes with GA.[4] For neovascular AMD, RPD has been reported to be present in 14 per cent of eyes with typical (classic or occult) CNV, but up to 39 per cent in eyes with retinal angiomatous proliferation (RAP).[5]

However, this prevalence is also likely to be underestimated because RPD have been observed to disappear with the development of CNV. This is most likely the reason that we and others have found that RPD were present in between 41 per cent and 58 per cent of fellow eyes of individuals with unilateral CNV.[6,7]

Identification of reticular pseudodrusen

The detection and identification of RPD can be most reliably performed using a combination of SD-OCT and NIR. NIR imaging is helpful at detecting these lesions because they appear most distinct in the near-infrared spectrum, but SD-OCT imaging is required to confirm the subretinal location of these lesions and distinguish them from other features similar in appearance.

On NIR, these lesions are often seen as groups of hypo-reflective lesions against a mildly hyper-reflective background, with a target appearance (slightly greater central reflectivity against the hypo-reflective lesion) often associated with subretinal accumulations with sharper peaks. On the other hand, lesions that appear as hypo-reflective ribbons on NIR imaging are often associated with broader subretinal accumulations on SD-OCT.[8] An example is shown in Figure 1 to illustrate these features.

It is important to note that most current analysis parameters on OCT imaging are not suitable for identifying RPD. For example, retinal thickness or RPE elevation maps will fail to identify these lesions due to their negligible influence on overall retinal thickness and because of their subretinal location, respectively. This is illustrated in Figure 2, where drusen-associated RPE elevation is detected but RPD are missed without looking carefully at the SD-OCT scans.

Clinical implications of reticular pseudodrusen

When monitoring eyes with the early stages of AMD, the presence of RPD is an important risk factor to note for patient management. The currently available evidence suggests that the presence of RPD is an independent risk factor for the development of GA in the fellow eye of patients with unilateral CNV, in addition to the presence of large drusen and pigmentary abnormalities.[6,7]

RPD have also been reported to confer an increased risk of progression to late AMD in patients without such advanced complications in either eye, but these findings stemmed from an epidemiological study that relied on detection of RPD on colour fundus photographs.[9] Prospective studies are now underway to better characterise the risk of progression when RPD are present in intermediate AMD.

The findings regarding the impact of RPD on visual function have also varied throughout literature, depending on the type of patients examined, the techniques used to evaluate visual function and analysis performed. Results also vary depending on whether other confounding factors such as drusen and pigmentary abnormalities were present.

A comprehensive discussion can be found in our recent publication. In short, we were unable to demonstrate a significant influence of RPD on mesopic microperimetric sensitivity, involving measurements of luminance increment using a method similar to conventional perimetry, but found that the presence and extent of drusen and pigmentary abnormalities had a detrimental effect on the sensitivity.[10]

A recent study reported scotopic microperimetry was reduced in areas with RPD,[11] consistent with suggestions from histological findings that rod photoreceptors may be preferentially affected in areas of RPD. This is an important finding when seeking to understand the impact of RPD on visual function, and further studies are now being carried out at the Centre for Eye Research Australia to investigate this. For now, optometrists should be aware of this new clinical entity and understand its implication as a risk factor for progression of AMD to vision loss.

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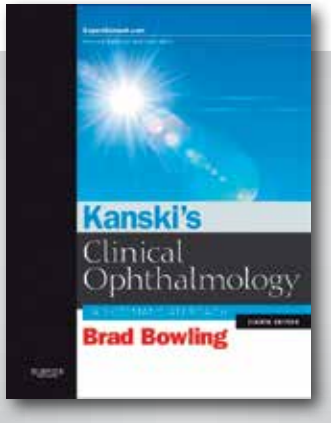

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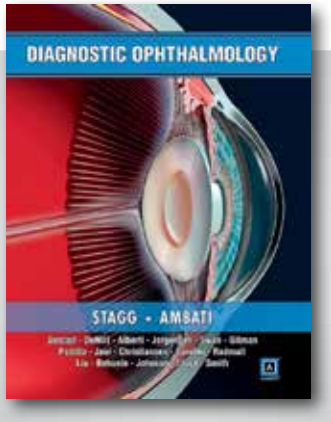

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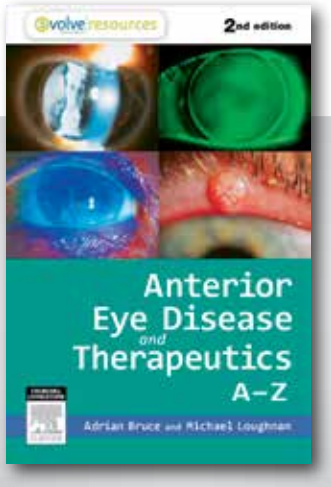

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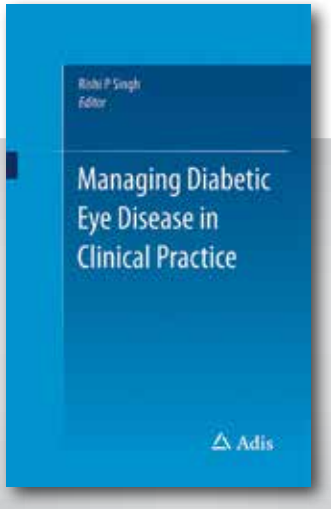

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Dive into the evidence

PBS Information: Authority Required. Refer to SINCE LAUNCH, MORE THAN 3 MILLION EYLEA® DOSES# Authority Required information for wet AMD. EYLEA is not PBS listed for CRVO and DME.

Before prescribing please review full Product Information.

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); diabetic macular oedema (DME)*. **CONTRAINDICATIONS:** Known hypersensitivity to aflibercept or excipients; ocular or periocular infection; active severe intraocular inflammation. **PRECAUTIONS:** Endophthalmitis, increase in intraocular pressure; immunogenicity*; arterial thromboembolic events; bilateral treatment*; risk factors for retinal pigment epithelial tears*; treatment should be withheld in case of rhegmatogenous retinal detachment, stage 3 or 4 macular holes, retinal break, decrease in best-corrected visual acuity of ≥ 30 letters, subretinal haemorrhage or intraocular surgery*; treatment not recommended in patients with irreversible ischemic visual function loss*; population with limited data (diabetic macular oedema due to type 1 diabetes, diabetic patients with HbA1c > 12 %, proliferative diabetic retinopathy, active systemic infections, concurrent eye conditions, uncontrolled hypertension)*; see full PI for effects on fertility, pregnancy, lactation, effects on ability to drive or use machines. **ADVERSE EFFECTS:** Very common: conjunctival haemorrhage, visual acuity reduced*, eye pain. Common: retinal pigment epithelial tear, detachment of retinal pigment epithelium, retinal degeneration*, vitreous haemorrhage*, cataract, cataract nuclear, cataract subcapsular, cataract cortical*, 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, punctate keratitis*, conjunctival hyperaemia, ocular hyperaemia. Others: see full PI. **DOSAGE AND ADMINISTRATION*:** Injection volume of 50 µL EYLEA (equivalent to 2 mg aflibercept). The interval between doses injected into the same eye should not be shorter than one month. Once optimal visual acuity is achieved and/or there are no signs of disease activity, treatment may then be continued with a treat-and-extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes. If disease activity persists or recurs, the treatment interval may be shortened accordingly. Monitoring should be done at injection visits. There is limited information on the optimal dosing interval and monitoring interval especially for long-term (e.g. > 12 months) treatment. The monitoring and treatment schedule should be determined by the treating ophthalmologist based on the individual patient's response. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, EYLEA should be discontinued. *For wet AMD:* Treatment is initiated with one injection per month for three consecutive months, followed by one injection every two months. Long term, it is recommended to continue EYLEA every 2 months. Generally, once optimal visual acuity is achieved and/or there are no signs of disease activity, the treatment interval may be adjusted based on visual and/or anatomic outcomes. The dosing interval can be extended up to every 3 months. *For CRVO:* Treatment is initiated with one injection per month for three consecutive months. After the first three monthly injections, the treatment interval may be adjusted based on visual and/or anatomic outcomes. *For DME:* Treatment is initiated with one injection per month for five consecutive months followed by one injection every two months. After the first 12 months, the treatment interval may be adjusted based on visual and/or anatomic outcomes. **DATE OF PREPARATION:** April 2015. Please review the full Product Information before prescribing. Approved PI available at https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2012-PI-01387-3 or upon request from Bayer Australia Ltd, ABN 22 000 138 714, 875 Pacific Highway, Pymble NSW 2073. #Data on file. Bayer HealthCare

*Please note changes in Product Information.

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