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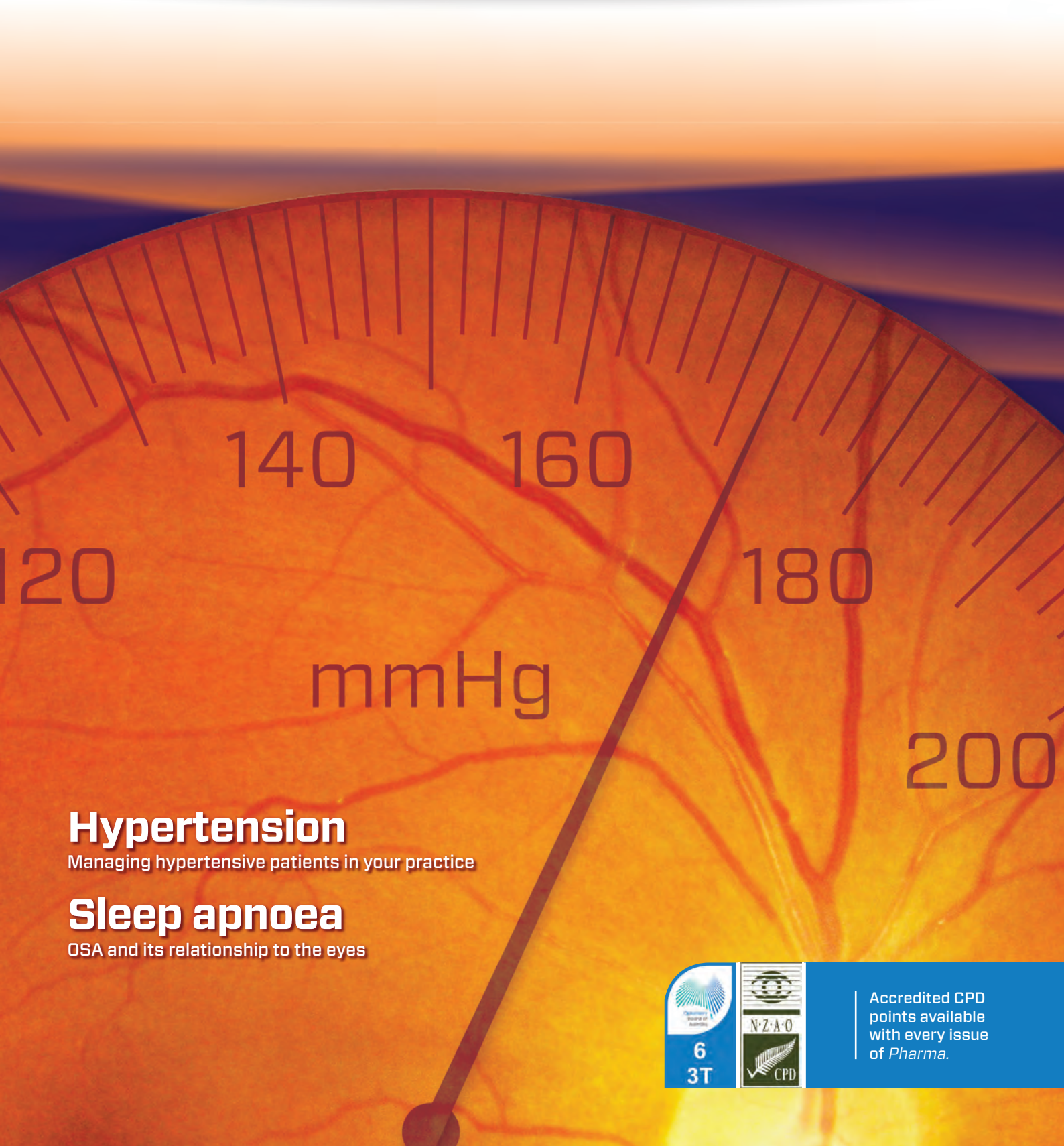


## Hypertension

Managing hypertensive patients in your practice

## Sleep apnoea

OSA and its relationship to the eyes

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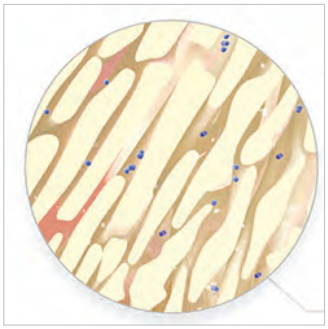

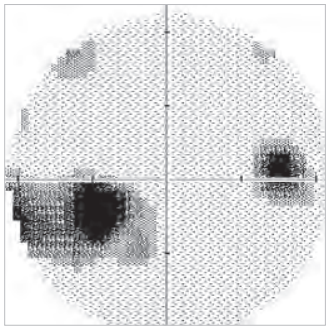





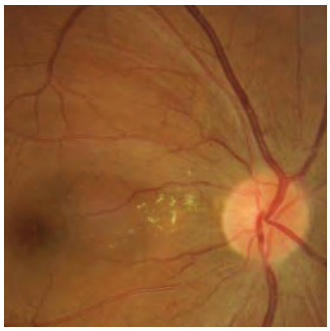




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# Cardiovascular Q and A

**Associate Professor Mark Roth**

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Associate Professor Mark Roth OAM, clinical editor of *Pharma* interviews Associate Professor Leo Hartley, one of Australia's most prominent optometrists who has also completed a medical degree. His dual qualifications and clinical experience provides a rare insight into the commonality of medicine and optometry.

**Roth:** Firstly, congratulations on your obstructive sleep apnoea (OSA) article, published in this issue of *Pharma*. It's a massive work and it covers the topic comprehensively. Why do you believe it's an important topic for optometrists?

**Hartley:** It's my opinion that optometrists, as primary care health professionals, should be aware of what ophthalmic conditions can signal systemic conditions in our patients. OSA has emerged as an important risk factor for many systemic associations.

**Roth:** I was surprised to read of the broad range of ophthalmic associations of sleep apnoea, such as non-arteritic ischaemic optic neuropathy and central serous chorio-retinopathy. Is there sufficient evidence to include glaucoma?

**Hartley:** The literature provides mounting evidence that, at the very least, OSA contributes to faster rates of progressive field loss and retinal ganglion cell loss. Obviously, larger studies will need to be conducted to reveal the mechanism of damage that may be exacerbating (or even causing) primary open-angle glaucoma (POAG) and normal tension glaucoma (NTG). We know that optic nerve dysfunction results from hypoxia, acidosis, hypercarbia and airway obstruction, frequently observed in patients with OSA. The mechanism I've reported on is reperfusion injury as a result of these factors.

**Roth:** I certainly will be including signs and symptoms of OSA in my history taking. This condition is yet another example of how optometry can work more closely with medicine. Do you think optometrists are under-recognised with their clinical skills and expertise and the part they can play in the health system?

**Hartley:** The increased use of the 'doctor' title by optometrists (in my opinion, rightly) reflects the increased role that optometrists play as true primary care health professionals. Optometrists have excellent undergraduate (and in some cases, postgraduate) training in basic sciences, medicinal systemic and eye health which form the important STEM knowledge needed to stay updated in this rapidly-expanding profession.

**Roth:** What would you suggest to early career optometrists who are interested in taking greater responsibilities in managing their patients? How can they build bridges with medical practitioners and specialists?

**Hartley:** Communication is the key. A routine eye examination report to GPs builds confidence that you know what you're talking about. Recognition by the government that optometrists can diagnose and expedite referrals for diabetic retinopathy has given optometry greater credibility in the eyes of GPs. Of course, there is no substitute for face-to-face visits when you're trying to establish yourself in an area. Visiting pharmacists is also very valuable, as they can refer patients to you and also feel comfortable calling you when they need advice.

Phoning the local ophthalmologist when you first refer a patient will help establish a good rapport.

**Roth:** Hypertension is also a focus of this edition of *Pharma*, which includes another excellent chair-side reference in a series from the Centre for Eye Health. As the introductory article from Paula Katalinic and Gonzalo Jacome states: 'hypertension significantly increases the risk of cardiovascular disease.' What is the front line General Practitioner perspective and main challenges of hypertension and cardiovascular health?

**Hartley:** Risk factors for cardio-vascular health should be determined. These can be modifiable and non-modifiable. Risk calculators have been developed for this purpose.

The first challenge GPs often have is getting patients to take care of themselves (and that means taking responsibility for their diet, exercise, alcohol intake and of course, smoking).

Brief interventions and referrals to allied health professionals (exercise physiologists, nutritionists) with GP follow-up, can really help to get patients to change. A healthy diet (with minimal salt and an emphasis on unprocessed foods, particularly vegetables and some lower-fructose fruits) can go a long way to decrease body fat and minimise reliance on antihypertensive drugs. Cutting down on established drinking and smoking habits (which are, effectively, self-medications) takes considerable commitment from patients.

As you know, depression is a significant risk factor for heart disease, so a healthy diet leading to a healthy gut biome has been shown to decrease reliance on medication for depression.

*Pharma* clinical editor Associate Professor Mark Roth and Associate Professor Leo Hartley discuss the role of optometrists and general practitioners in the management of the cardiovascular system

It can be frustrating (albeit essential, in many cases) having to rely on medications to control patients' blood pressure. Also, of course, several studies have shown (as with glaucoma) quite poor medication adherence 12 months after initiation.

**Roth:** On the positive side, there is strong evidence that controlling hypertension leads to reduced cardiovascular disease-related morbidity and mortality. Is it as simple as that?

**Hartley:** Obesity, and dietary salt intake of course, lead to hypertension, cardiovascular disease and diabetes. These conditions, if left untreated, lead to a cascade of events that include renal disease, stroke and heart attack.

My emphasis is on the whole patient. That is: encouraging the patient to work with me to take charge of their health as a whole and to see me as their health coach (who has a wide armamentarium of advice, other health professionals and medications to help in that process). Just as optometrists do when helping patients make appropriate lens choices, I try not to just prescribe treatments without the patient's involvement in the decision-making. Although, sometimes in cases where patients refuse to be actively involved in their own care ('just fix me doc') that is necessary.

**Roth:** Hypertension is not like a dial where you can turn pressure up and down accurately. What drugs are mainly used and are there new advances in medical therapy?

**Hartley:** Firstly, just as in glaucoma, we want to assess the risk of morbidity before commencing treatment. See Table 1 below for a list of hypertension drugs.

**Roth:** All drugs come with potential side-effects. This is why an initial case history of ALL the drugs a patient is taking is so vital. Several vascular medications come with significant ocular effects. For example: Digoxin for atrial fibrillation can cause xanthopsia, or yellowing vision. What are the main CV drugs for optometrists to look out for?

**Hartley:** Digoxin is fortunately not used that often these days. Most of the beta-blockers will have an effect on IOP and may cause dry eye (so may need tear lubricants concomitantly). I usually don't start a glaucoma patient on a topical beta-blocker if they're on a systemic beta-blocker already. That's not to say it won't have an additive effect, because it may.

**Roth:** What are your views regarding optometrists measuring their patients' blood pressure? Perhaps using a digital sphygmomanometer?

| Medication | Features |
|---|---|
| ACE inhibitor | Relaxes blood vessels, lowers blood pressure and prevents diabetes-related kidney damage |
| Diuretic | Increases urine production to get rid of excess salt and water |
| Beta blocker | Slows heart rate and decreases blood pressure |
| Antihypertensive drug | Lowers blood pressure |
| Calcium channel blocker | Relaxes blood vessels |
| Vasodilator | Widens blood vessels |

Table 1. List of hypertension drugs

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**Hartley:** I believe there is certainly no harm in checking blood pressure and doing a random blood sugar test. In some cases where the patient has never consulted a GP, it can be a game changer. For others, the more times a patient is reminded that they need to look after themselves, the better.

Before starting patients on antihypertensive medication, I usually encourage them to buy a digital sphygmomanometer and measure their BP twice daily (just after waking and before dinner) for at least five days. That is far more accurate than doing it in our rooms.

As I mentioned, having the patient really involved in their care increases the chance of adherence to the health measures we are trying to achieve (taking medication, better weight management, ceasing smoking or cutting down on alcohol).

**Roth:** Professor Hartley, thanks again for your great article and contribution to our discussion. ▲

# Obstructive sleep apnoea's effect on

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Obstructive sleep apnoea (OSA) is characterised by repetitive pharyngeal collapse during sleep, resulting in episodes of hypoxia leading to a cascade of neurological, ophthalmic and systemic consequences. Increasingly, it is recognised as a significant cause of morbidity and mortality.[1]

Pharyngeal patency is dependent on the competence of the dilator muscles and the bulk of the soft tissues of the throat. With the onset of sleep, the dilator muscles relax and, combined with the weight of the tongue, pharyngeal collapse occurs (Figure 1). This leads to cessation of breathing, resultant hypoxia and hypercapnia (build-up of CO2 in the blood) triggering the pons to arouse the sufferer. This temporarily restores normal oxygen levels and allows sleep restoration. The cycle continuously repeats, leading to neurological, ophthalmic and systemic sequelae.[2]

## Epidemiology

In most populations, about 50 per cent of middle-aged men and 23 per cent of middle-aged women have moderate-to-severe sleep apnoea.[3] As with eye disease, the incidence and prevalence of sleep apnoea increases with age.

## Signs and Symptoms

Typical signs of obstructive sleep apnoea in an adult follow a pattern. The patient initiates sleep followed by a shallowing of breathing and/or snoring or loud breathing, then cessation of breathing for several seconds (associated with occlusion of the nasopharyngeal airway) and then sudden arousal (usually with a typical gasping sound). Sleep is re-established, followed by snoring and the cycle repeats.[4]

Symptoms of sleep apnoea include somnolence, insomnia, nocturia, waking suddenly during the night,

| STOP-BANG questionnaire | |
|---|---|
| STOP | BANG |
| **S**noring | **B**MI> 35 kg/m2 |
| **T**ired | **A**ge > 50 |
| **O**bserved apnoea | **N**eck circumference > 40 cm |
| High blood **P**ressure | **G**ender: male |
| High risk of OSA: answering yes to three or more items<br>Low risk of OSA: answering yes to fewer than three items | |

Table 1. STOP-BANG screening test

# the eyes

## Associated ocular conditions resulting from long-term OSA

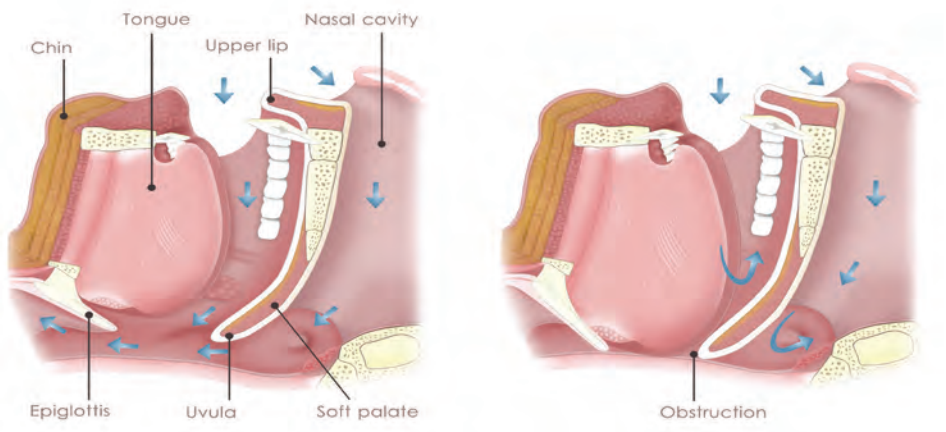


Figure 1. Sleep apnoea. As the patient sinks into a deep sleep, the muscle tone of the surrounding throat tissues relax, allowing the patient's throat to occlude. This is followed by a rapid decrease in saturated oxygen and a corresponding increase in carbon dioxide (and a concomitant increase in heart rate and blood pressure) which eventually stimulates the pons, causing arousal. Saturated oxygen increases and the patient again falls into a deep sleep. The cycle repeats several times a night.

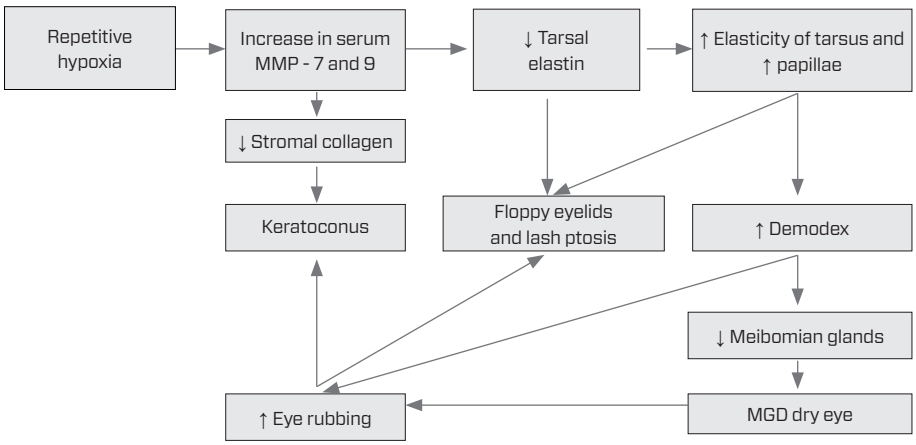


Figure 2. Keratoconus and floppy eyelid syndrome. Repetitive hypoxia may lead to an increase in corneal and tarsal matrix metalloproteinases 7 and 9 (MMP) as well as a decrease in corneal collagen and tarsal elastin. Floppy eyelids are often attributed to side sleeping. However this doesn't explain why everyone who side-sleeps doesn't have floppy eyelid syndrome (FES). Floppy eyelids, lash ptosis, papillary conjunctivitis and keratoconus result. Demodex infestation and meibomian gland dysfunction (MGD) often ensue. Resultant eye rubbing can contribute to floppy eyelids and keratoconus.

inability to get back to sleep, nightmares, mouth breathing, morning headaches, dry mouth, sore throat, migraine exacerbation, irritability, mood swings, so-called 'brain fog' due to decreased mentation, daytime sleepiness, increased risk of car crashes due to micro-sleeps, aching muscles and weight gain.[4]

### Long term effects of sleep apnoea

Sleep apnoea causes intermittent hypoxia, intermittent hypercapnia, sympathetic activation,[2] intrathoracic pressure changes,[5,6] systemic and neurological inflammation,[5,6] cerebrovascular disease,[2] metabolic dysregulation, endothelial dysfunction,[2] oxidative stress and hypercoagulation,[5,6] neurohumoral changes,[5,6] systemic hypertension,[7] ischaemic heart disease,[5–7] pulmonary hypertension,[8–10] congestive heart failure,[7] portal hypertension and liver disease,[11] arrhythmias,[5, 6, 12] metabolic syndrome and insulin resistance.[4]

### Ophthalmic associations of sleep apnoea

Sleep apnoea has been implicated with several ophthalmic conditions including floppy eyelid syndrome and lash ptosis,[13–28] non arteritic ischaemic optic neuropathy (NAION),[15,16, 29,30] idiopathic intracranial hypertension (IIH),[30–42] central serous chorioretinopathy (CSCR),[15,16,43–57] retinal vein occlusion (RVO),[16,50,58] keratoconus[15,20,21] and glaucoma (POAG, NTG).[15,16,59–69] However, some studies have not found a correlation of glaucoma with OSA.[61,67,70]

Possible or proposed mechanisms of cause of these conditions are outlined

**Continued page 6**

# Sleep apnoea

**From page 5**

in Figures 2 to 7.

### Screening tests for sleep apnoea

There have been a number of screening tests for OSA. The Berlin Sleep questionnaire,[71,72] the Epworth Sleepiness Scales[73,74] and the STOP-BANG questionnaire[59,73–75] are often used. While the Berlin Sleep questionnaire is often preferred by many Australian sleep physicians, the STOP-BANG test is very fast to administer for the busy optometric clinician. See Table 1 for an example of the STOP BANG questionnaire. Figure 8 shows suggested decision-making regarding OSA for a busy optometrist.

### Assessment of sleep apnoea

The gold standard in assessment for obstructive sleep apnoea is polysomnography.[76–78] During this test, the patient has several functions monitored simultaneously. These include oxygen saturation, heart rate and rhythm (ECG), breathing rate and depth as well as leg movements (EMG) and eye movements (EOG) and electroencephalography (EEG). These functions are monitored while the patient sleeps. Snoring may be measured with a sound probe.

The tests can be administered in a sleep laboratory (overnight stay) or at home using an ambulatory unit which is fitted to the patient before he/she goes home. The patient removes the sensors in the morning. A sleep physician reviews the recordings.

### Treatment of sleep apnoea

Treatment is recommended based on the severity of the OSA. Mild-to-moderate OSA responds well to oral appliances which move the jaw forward, relieving the obstruction. These have been found to be mostly well tolerated with a good compliance rate after 30 months of use.[4,79–81]

The mainstay of treatment is continuous positive airway pressure (CPAP) devices.[81,82] These devices use continuous positive pressure to keep the airways open. The patient

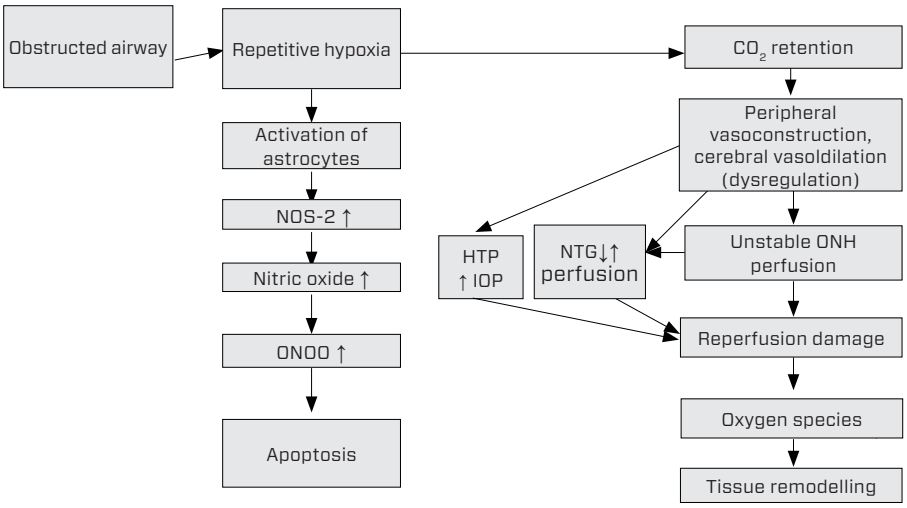


Figure 3. Normal tension and high tension glaucoma. Repetitive hypoxia and reperfusion damage at the level of the optic nerve head causes an increase in nitric oxide and peroxynitrite leading to apoptosis. Reperfusion damage leads to tissue remodelling (increase in cupping). $CO_2$ = carbon dioxide, NOS-2 = nitric oxide synthase 2, ONOO = peroxynitrite, HTG = high tension glaucoma, NTG = normal tension glaucoma, ONH = optic nerve head.

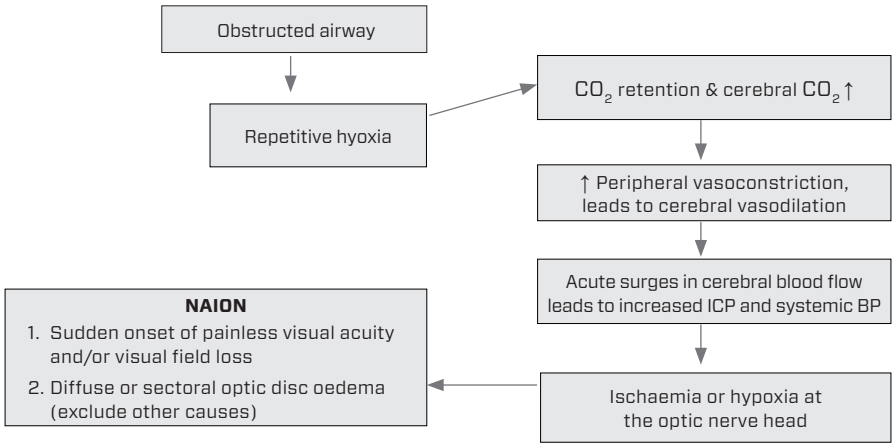


Figure 4. Non-arteritic anterior ischaemic optic neuropathy (NAION). Repetitive hypoxia and cerebral hypercapnia lead to intracerebral surges in intracranial pressure resulting in ischaemia or hypoxia of the optic nerve head causing optic neuropathy.

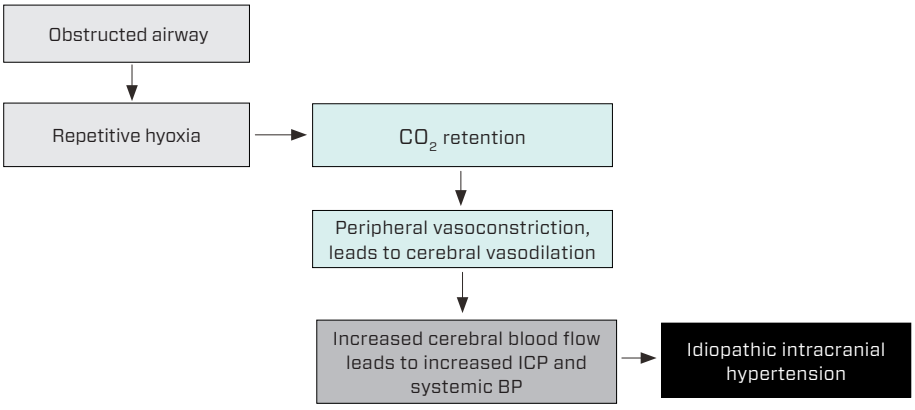


Figure 5. Idiopathic intracranial hypertension (benign intracranial hypertension). Sleep apnoea leads to raised intracranial pressure, most frequently seen in females between ages 20 and 30 with morbid obesity. $Co_2$ = carbon dioxide, BP = blood pressure, BMI = body mass index.

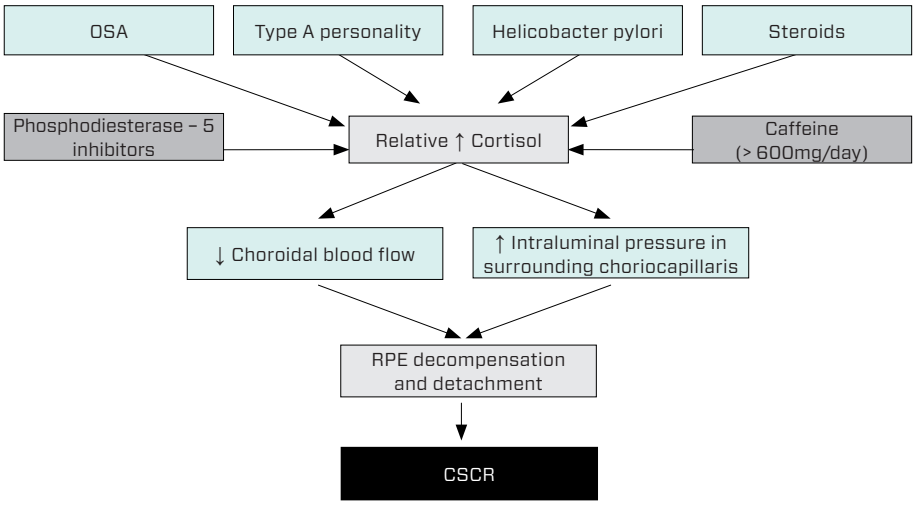


Figure 6. Central serous chorioretinopathy (CSCR). Sleep apnoea, Type A Personality, H. Pylori, systemic steroids, Phosphodiesterase-5 inhibitors, and caffeine have all been implicated in causing relative hypercortisolism which leads to a decrease in choroidal blood flow and increased intraluminal pressure in the surrounding choriocapillaris. This leads to retinal pigment epithelial decompensation and detachment and central serous chorioretinopathy. OSA = sleep apnoea, RPE = retinal pigment epithelium, CSCR = central serous chorioretinopathy.

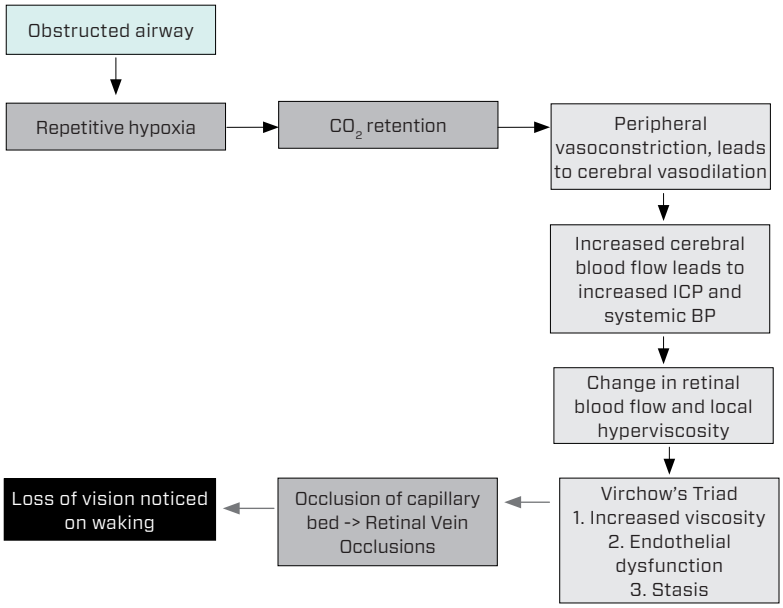


Figure 7. Retinal vein occlusion. Obstructive sleep apnoea leads to hypercapnia and cerebral vasodilation causing raised intracranial hypertension, hyperviscosity of retinal vasculature and ultimately venous occlusion.

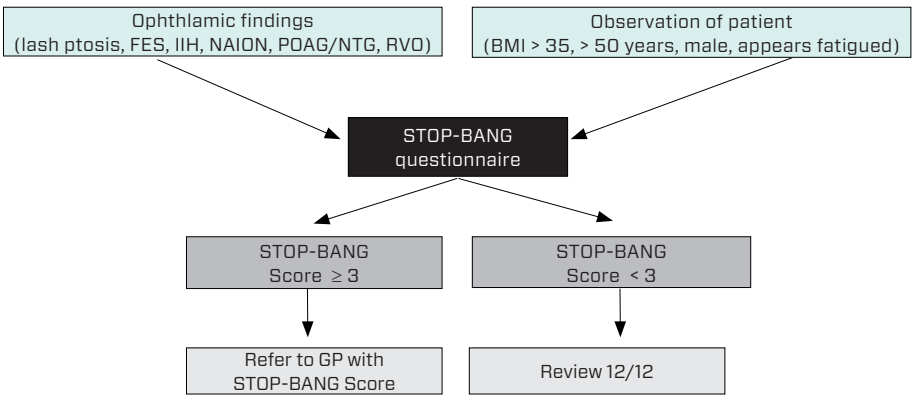


Figure 8. Suggested decision making in OSA in optometry practice

must exhale against this pressure. The pressure can be set based on titration in an overnight test, or set using an automatic sensing CPAP machine which detects occlusions and increases pressure to overcome these occlusions. Automatic titration CPAP devices have been found to be non-inferior to pre-set pressure devices.

Many CPAP devices feature humidifiers and warmed tubing to improve comfort and decrease the likelihood of damage to susceptible airways.

CPAP has a disappointing compliance rate with up to 30 per cent of patients refusing to continue past an initial trial. Only 50 per cent of starting patients comply after 12 months.[82] However, a number of studies have shown a significant improvement in compliance of greater than four hours a night to 70 per cent of participants.[83]

Surgery has been largely unsuccessful, probably because the actual mechanisms of occlusion are complex and multifactorial.[84] Techniques to improve compliance include brief intervention, phone coaching, partner coaching, upper airway assessment and alcohol consumption as well as a smart phone application.[85–90]

## Conclusion

Obstructive sleep apnoea has been linked to several ophthalmic conditions including floppy eyelid syndrome, lash ptosis, non-arteritic anterior ischaemic optic neuropathy, central serous chorioretinopathy, glaucoma, idiopathic intracranial hypertension and keratoconus.

Sleep apnoea is a serious health condition that is mostly undiagnosed in Australia and the western world. It is commonly seen in obese males who are over the age of 50 years. It has been associated with neurodegenerative and cardiovascular disease (including hypertension and heart failure), type 2 diabetes, obesity and, if left untreated, it can lead to multiple organ failure. ▲

**Continued page 8**

# Sleep apnoea

**From page 7**


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# Self-monitoring leads to lower blood pressure

A new study suggests that having patients monitor their own blood pressure may help lower it.

The TASMINH4 trial aimed to assess the efficacy of self-monitored blood pressure, with or without telemonitoring, for antihypertensive titration in primary care, compared with usual care.

The study was a parallel randomised controlled trial done in 142 general practices in the UK, and included hypertensive patients older than 35 years, with blood pressure higher than 140/90 mmHg, who were willing to self-monitor their blood pressure.

Patients were randomly assigned to self-monitoring blood pressure (self-monitoring group), to self-monitoring blood pressure with telemonitoring (telemonitoring group), or to usual care (clinic blood pressure; usual care group).

After 12 months, systolic blood pressure was lower in the self-monitoring and telemonitoring groups compared with the group in usual care (137.0, 136.0, and 140.4 mmHg, respectively).

The study authors concluded that self-monitoring when used by general practitioners to titrate antihypertensive medication in individuals with poorly controlled blood pressure, leads to significantly lower blood pressure than titration guided by clinic readings.

They suggested that, with most general practitioners and many patients using self-monitoring, it could become the cornerstone of hypertension management in primary care.

*Lancet*. Mar 2018 doi: 10.1016/S0140-6736(18)30309-X

# Brain injury assessments

## A systemic history and testing symptoms and signs and lead

**Steven Leslie**

BOptom FACBO FCOVD GradCertOcTher

Eyes on Oxford, Perth, WA

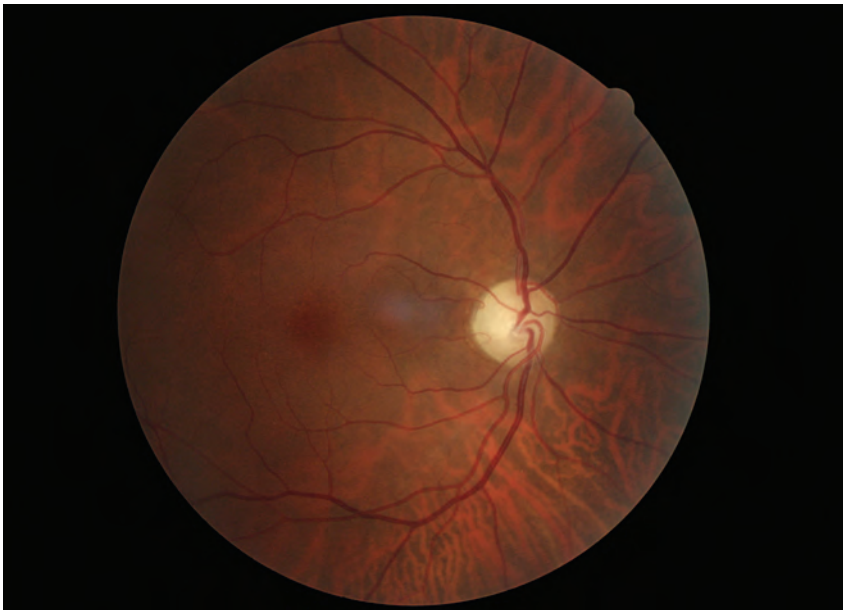

Figure 1. Right eye optic nerve temporal pallor

It is not uncommon to have patients who report a history of a head injury, whiplash or concussion, stroke, or neurological conditions such as Parkinson's disease or multiple sclerosis. Or you may have a patient whose symptoms or signs suggest the possibility of, or at least the need to reasonably rule out, neurological issues.

You could refer the patient and wait a few months for an assessment, or you could make a probably-unnecessary urgent referral; or you could work through a measured process of assessment and testing to determine the best options for professional care.

Rather than attempting to guess what the problem might be, or trying to remember a myriad of symptoms and signs associated with neurological issues, the best approach is:

- Taking a careful history
- Conducting a systematic visual and ocular assessment

Be wary of any previous diagnoses, as it is very easy to prejudice the outcome of your own assessment in the light of previous diagnoses.[1,2] Start afresh.

### History

If you ask enough targeted questions, in many cases the patient will tell you their diagnosis. We routinely use a two-page 'Welcome to the Office Form,' which can be filled out online and sent back before the exam, or done on arrival, alerting you to symptoms and history, and suggesting possible further questions and tests. Importantly, it can be saved to the patient's record, providing evidence of the questions asked and answered, which is sometimes helpful when there is pathology discovered by you or someone else later.

If there is a suggestion of neurological issues, I then move to an expanded questionnaire. It saves having to remember them. It is vitally important that you record negative answers and test results, such as 'no headaches/double vision/pain/…'. Do not make the dangerous mistake of only recording abnormal symptoms and results. A good history allows you to:

- Define presenting complaints
- List pertinent health history and medications
- List diagnosis or differentials
- Plan further investigations

Age is important. For instance, giant cell arteritis typically occurs in people older than 50; stroke in a younger woman can be due to a combination of smoking and contraceptive pills.

Ask about the time course of presenting symptoms: when first noticed, any progression, any previous episodes, frequency, duration, any triggering factors, previous investigations and treatment, any eye pain (particularly if worse with eye movement) any transient loss of or double vision, or 'migraines' (ask more questions about migraine features).

If there is a history of a brain injury or stroke, ask about the details and effects at the time.Was there loss of consciousness and for how long?

Were there effects on speech or motor function, cognition, memory, emotional behaviour (often suggests frontal lobe effects), depression or epilepsy? Then explore the visual and ocular history regarding spectacles, eye turn or surgery, diagnosis or

regime can elucidate to appropriate management

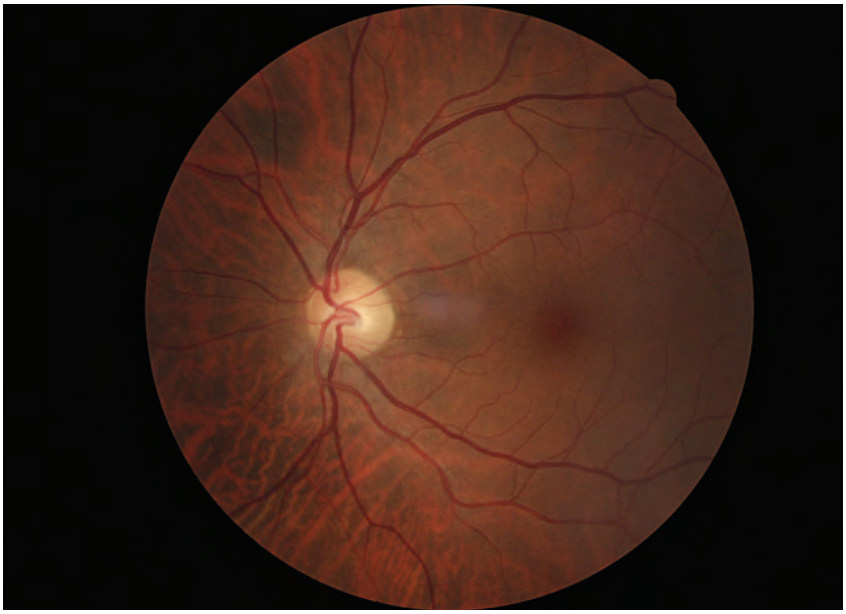

Figure 2. Left eye healthy optic nerve

treatment of a 'lazy' eye such as patching, eye drops, laser surgery or any history of eye disease.

Medical history can be reasonably covered by asking about unusual fatigue, any history of cancer or auto-immune disease; any issues of heart, diabetes, hypertension, cholesterol or head or neck trauma; or any history of surgery.

Medications need to be questioned, particularly steroids, heart, erectile dysfunction, oral contraceptives, cancer treatment (tamoxifen, radiation, chemotherapy) and any medications for depression, anxiety or psychosis.

Sometimes it is necessary to carefully ask about smoking and alcohol use, or ask: 'Have you used any recreational drugs, such as marijuana, ice, speed, or coke?'—you may be surpised at the answer.

Anyone over 50 with a history of transient or sustained visual loss or diplopia, should be asked about symptoms of giant cell arteritis: new or severe headaches, scalp or temple tenderness, difficulty or pain chewing, ear pain, fevers, fatigue, weight loss, or reduced appetite.

### Comprehensive visual and ocular assessment

If you systematically work through a comprehensive sequence of tests of visual function and ocular health, you will record many normal results (ruling out some issues), and gather all the abnormal results into a pattern which helps to guide further action. Always assume results are abnormal until proven otherwise.

Visual function tests should include:

- VA distance and near, BCVA, pinhole, VA refraction
- Colour vision of each eye, red cap comparison
- Eye movements for normal movement, or signs of strabismus or cranial nerve palsy, or nystagmus; pursuit and saccadic eye movements, both horizontal and vertical; convergence
- Confrontation visual fields, perimetry
- Pupil size in light and dark, direct response, near response, RAPD testing
- External eye health from front to back: lids
- Any ptosis or proptosis
- Cornea and lens
- IOP
- Ophthalmoscopy of optic nerve, macula and retina

In my experience, many patients have significant ocular and neurological symptoms and yet:

- They have no diagnosis despite other assessments
- They have a diagnosis which does not fit the signs and symptoms
- They do not understand their diagnosis and effects
- They do not connect their vision problems with neurological or other health issues

A systematic history and testing regime frequently elucidates symptoms and signs which were not obvious, and can lead to further testing, referral, discovery of unknown and potentially-significant issues and appropriate management.

## CASE REPORT

'M' is a 57 year-old male teacher with good general health other than slightly high cholesterol levels. He had unaided VA of R 6/12- L 6/7.5, improving to 6/5 each eye with correction of moderate bilateral hyperopic astigmatism. Pupil reaction testing suggested a trace weaker direct reaction of the right eye, and a trace right eye RAPD. Assessment of his binocular vision function was unremarkable, with normal

**Continued page 12**

# Brain injury

**From page 11**

convergence and a full range of eye movements.

His anterior eye health was normal, he had IOPs of R and L 16 mm Hg, no significant lens changes and normal maculas, but moderate sectoral temporal pallor of his right optic nerve, with the superior rim very pale, shelved and sloping towards the cup, with cup to disc ratios of R 0.4, L 0.3 (see Figures 1 and 2).

Medmont visual fields revealed an inferior arcuate scotoma (see Figure 3). OCT showed significant temporal (superior and inferior) retinal nerve fibre layer thinning (Figure 4). He had central corneal thicknesses of 615 microns R and L with open angles.

A recent CT scan was reported as unremarkable. Monocular colour vision Ishihara testing was equal and normal for both eyes.

He described slight memory changes over the last six months, but no specific neurological symptoms were elicited on comprehensive questioning. Specifically, he denied any recent acute and severe headache.

In view of the right eye optic nerve temporal pallor and associated inferior arcuate scotoma, without associated disc excavation or notching, he was referred for urgent ophthalmological assessment of other possible optic neuropathic aetiologies, including ischaemic optic neuropathy (unlikely due to age and good health) and multiple sclerosis or inflammatory vascular disease.

MRI showed thinning of the right side of the optic chiasm, and thinning of the pituitary gland, with the sella mainly filled with cerebrospinal fluid (empty sella syndrome).

The most likely explanations include a previous pituitary apoplexy (haemorrhage into, or reduced blood supply of the pituitary), or tumour. Pituitary function was normal.

The unilateral visual field defect argues against a post-chiasmal neurological insult, which would produce bilateral visual field defects. It could be due to impaired optic nerve head perfusion, or a lesion or mass effect anterior to, or adjacent, to the right anterior optic chiasm.

The anterior chiasmal pathology over time has probably caused either mild papilloedema which has resolved, or transneuronal degeneration along the right optic nerve, appearing as sectoral optic atrophy. Medical review three months later showed no change, with no specific aetiology identified, but it is considered unlikely to progress. ▲

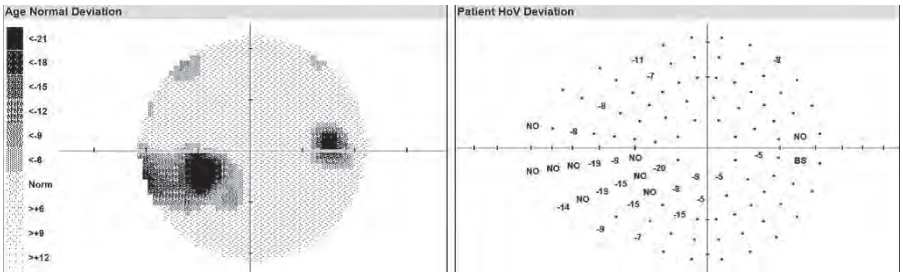


Figure 3. Right eye Medmont glaucoma visual field with inferior nasal step defect

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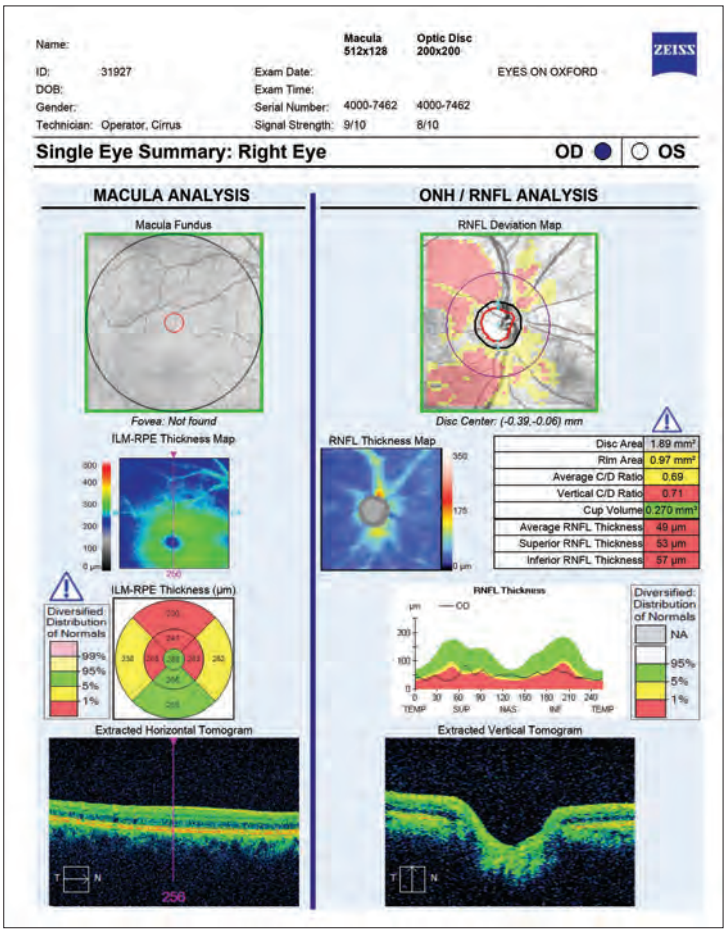


Figure 4. OCT of right eye shows significant temporal (superior and inferior) retinal nerve fibre layer thinning.

GUIDE

HYPERTENSION CHAIR-SIDE REFERENCE GUIDE PAGES 14–16

# The ocular effects of hypertension

## Managing hypertensive patients in your practice

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Centre for Eye Health

High blood pressure (HBP) or hypertension is a significant public health burden. In Australia, nearly six million people are affected by hypertension with potentially 68 per cent of hypertension remaining undiagnosed.[1,2] The condition affects more than a billion people worldwide, increasing in prevalence with age. The complications of hypertension account for more than 9.4 million deaths worldwide every year.[3] In 2014–15, approximately 34 per cent of Australians aged 18 years or older had high blood pressure.

Most importantly, hypertension significantly increases the risk of cardiovascular disease (specifically: ischaemic and haemorrhagic stroke, myocardial infarction and heart failure), chronic kidney disease and premature death.[2] Increased risk of cardiovascular disease (CVD) begins at 115/75 mmHg and doubles with each increment of 20/10 mmHg.[4]

There is strong evidence that controlling hypertension leads to reduced CVD-related morbidity and mortality, including incident stroke (by 35 to 40 per cent), myocardial infarction (by 15 to 25 per cent) and heart failure (by up to 64 per cent).[5-7] Furthermore, the randomised, controlled SPRINT trial showed that intensive blood pressure control (systolic pressure of < 120 mmHg) reduces the risk of heart attacks, stroke and death as compared to systolic pressure > 130 mmHg.[5] CVD disease is associated with the highest level of Australian health care expenditure of any disease group, with a direct cost of approximately $7.7 billion in 2008–2009.[2]

### Definitions of hypertension

The National Heart Foundation (NHF) Guidelines for the diagnosis and management of hypertension in adults 2016 assists practitioners in making diagnosis and management decisions by categorising blood pressure into a number of categories.[2] Normal blood pressure is defined as a systolic reading of 120–129 mmHg and diastolic reading of 80–84 mmHg and mild hypertension as 140–159 mmHg (systolic) or 90–99 mmHg (diastolic). The decision about when to start anti-hypertensive treatment depends on both the degree of hypertension and the patient's cardiovascular risk profile.

Risk factors for CVD include diabetes, elevated blood lipids, smoking, male sex, ethnicity and age > 45 years, or > 35 years in Aboriginal and Torres Strait Islander peoples. For patients with a low cardiovascular disease risk, NHF and the Royal Australian College of General Practitioners recommend that anti-hypertensive therapy be instigated with persistent blood pressure ≥ 160/100 mmHg to achieve a normal range.[2,8] However, an optimal target blood pressure (< 120/80) may be more appropriate in patients with existing cardiovascular disease.[8]

Urgent referral is required in cases of severe HBP (> 180/110 mmHg) associated with symptoms or moderate target organ damage (nephropathy or retinopathy).[2] Oral anti-hypertensive treatment should be instigated within 24–72 hours and hospitalisation may be required in some cases.[2] A medical emergency exists when blood pressure is very high (> 220/140 mmHg) and acute target organ damage or dysfunction is present (papilloedema, haemorrhagic stroke or heart failure). Hospitalisation is indicated in these cases.

### Ocular effects of hypertension

Elevated blood pressure can induce a series of pathophysiological changes to the retinal, choroidal and optic nerve circulations resulting in a constellation of clinical signs referred to as hypertensive retinopathy, hypertensive choroidopathy and hypertensive optic neuropathy.[9] Hypertension also increases the risk of developing retinal vein and artery occlusion, diabetic retinopathy, retinal macroaneurysm and ischaemic optic neuropathy, and may be associated with glaucoma and AMD.[9-11]

In early hypertension, local autoregulatory mechanisms lead to vasospasm and increased retinal arteriolar tone resulting in generalised arteriolar narrowing. Subsequent thickening and degeneration of the blood vessel wall leads to severe generalised and focal areas of arteriolar narrowing, arteriovenous nipping and copper wiring. As the condition progresses, disruption of the blood-retina barrier manifests as retinal

**Continued page 17**

Chair-side Reference

# Hypertension

## Hypertension is a chronic medical condition in which arterial blood pressure is elevated.

**It affects over 1 billion people worldwide, increasing in prevalence with age.**

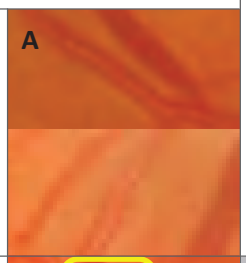
## Lesions of hypertensive retinopathy

### Vascular calibre changes
(Mild retinopathy)

- Thickening and loss of elasticity of the arterial wall
- Broadening of light reflex masking the blood vessel column, represents chronic arterial changes

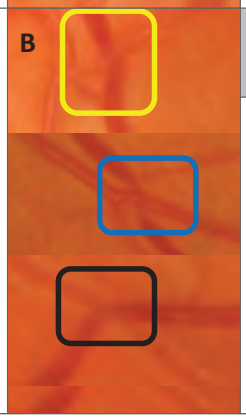
**Copper vs. silver wiring (A)**

- Changes start off as 'copper wiring' (slight broadening of light reflex) (top) 'Silver wiring', represents greater broadening of reflex (more 'silver' within the vessel) (bottom)
- May be more useful to quantify broadening
- Can be focal or generalised




**A/V 'nicking' (US) or 'nipping' (UK) (B)**

- Thickened arteriole can impinge upon the underlying retinal veins, leading to potential vein occlusions (below)
- Salus's sign: Vein deflected by arteriole (**yellow**)
- Bonnet sign: Vein banked (course changed) (**blue**)
- Gunn sign: 90 degree vein banked and tapered (**black**)
- Note: arterial tortuosity is not expected due to stiffening, but banking may cause venous tortuosity




### Retinal haemorrhages
(Moderate retinopathy)

**Flame haemorrhage**

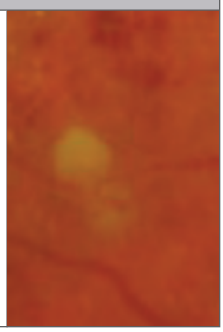
- Originates from superficial capillary bed or radial parapapillary capillaries
- Appearance due to RNFL orientation
- Typically resolves in around six weeks

**Dot/blot haemorrhage**

- Originates from deep capillary bed (INL, ONL, or OPL)
- Displaces retinal structures, takes longer to resolve

### Cotton wool spots
(Moderate retinopathy)

- Ischaemia of the RNFL results in disruption of axoplasmic flow which manifests as a grey-white lesion along RNFL bundles
- Usually appears within 3 disc diameters of the ONH
- Typically resolves in 5–7 weeks
- May result in loss of retinal tissue and visual field changes



| Heart Foundation Classification (adults) | Systolic, mmHg | | Diastolic, mmHg |
|---|---|---|---|
| **Optimal** | < 120 | and | < 80 |
| **Normal** | 120–129 | or | 80–84 |
| **High normal** | 130–139 | or | 85–89 |
| **Grade 1 (mild)** | 140–159 | or | 90–99 |
| **Grade 2 (moderate)** | 160–179 | or | 100–109 |
| **Grade 3 (severe)** *Requires emergency referral to the patient's general practitioner and/or local hospital, whichever can provide the most urgent care.* | ≥ 180 | or | ≥ 110 |
| **Isolated systolic hypertension (may be normal in elderly)** | ≥ 140 | or | < 90 |

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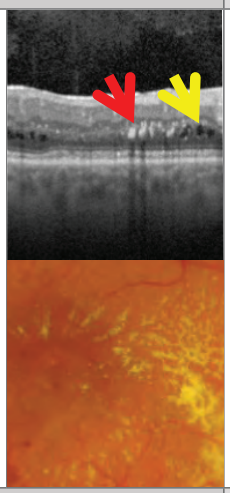
Hypertension is one of the most important preventable risk factors for premature death, as it increases the risk of ischaemic heart disease, stroke, peripheral vascular disease, other cardiovascular disease and nephropathy. The presence of moderate hypertensive retinopathy correlates strongly with acute hypertension. The Mitchell-Wong classification scheme for hypertensive retinopathy is detailed below (Wong & Mitchell, New England Journal of Medicine, 2004; 351 (22): 2310-7.

# Sequelae of hypertension in the eye

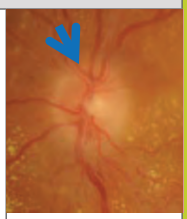
## Hard exudates and macular oedema
(Moderate retinopathy)

- Compromised vessels in the macula leak lipids (hard exudates; hyper-reflective on OCT, **red arrow**) from the deep capillary bed, depositing in the OPL. Deposition within Henle's fibre layer forms a 'macular star'
- Appears white-yellow waxy, with a glitter due to cholesterol
- Leakage also produces macular oedema (hyporeflective on OCT, **yellow arrow**)



## Optic neuropathy 'hypertensive papillopathy' (malignant retinopathy)

- In severe acute hypertension, optic neuropathy and oedema (blue arrow) results from vasoconstriction and poor choroidal autoregulation leading to choroidal ischaemia and axoplasmic flow stasis. This is because the ONH blood supply is through the short posterior ciliary arteries
- In the chronic phase, the oedema resolves, leaving ONH pallor/atrophy
- Strongly associated with hypertensive emergency (BP: systolic ≥ 180 or diastolic ≥ 110, and should be managed as such)



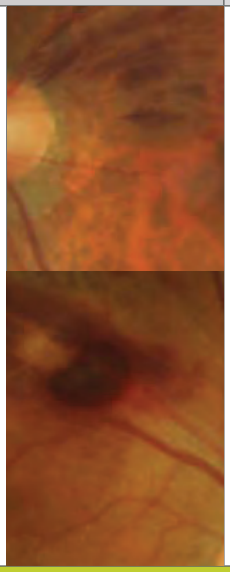
## Vascular occlusions/macroaneurysms

**Vascular occlusions (right)**

- Venous: due to impingement by thickened artery, intraretinally (branch occlusion) or posterior to lamina (central occlusion)
- May be associated with macula oedema

**Macroaneurysm (right)**

- A localised dilatation of a retinal arteriole (saccular appearance)
- Gradual leakage of vessels compromises vision
- Appears as deep red haemorrhage +/-exudates



## Choroidopathy
(Rare; follows acute hypertensive crisis: systolic ≥ 180 mmHg)

**Elschnig spots**

- Changes in RPE due to choriocapillaris infarcts
- Appear as small, black atrophic spots, surrounded by yellow haloes
- Accelerated hypertension causes choroidal ischaemia

**Siegrist streaks**

- Linear hyper-pigmented streaks over choroidal arteries
- Indicative of fibrinoid necrosis, which then leads to fibrinous exudation

*Images unavailable, though note that the presence of these are typically accompanied by systemic symptoms and signs*

Centre for Eye Health

Optometry NEW SOUTH WALES AUSTRALIAN CAPITAL TERRITORY

Hypertension is a commonly seen and self-reported condition in optometric practice. In cases where there are signs of retinopathy, an optometrist would ideally have the capacity to screen blood pressure in their office.

The information below is intended as a guide for measurement of blood pressure status in an optometric practice, and should not be used as a replacement for cardiovascular assessment by a suitably-trained general physician and/or cardiologist.

## Establishing blood pressure status in your office

**Entering medical history:**

- +/- hypertension (past or present)
- Anti-hypertensive medications
- Cardiovascular co-morbidities (for example DM, cholesterol, stroke, heart disease)
- Obesity (BMI ≥ 30 kg/m$^2$)

**Entering family history:**

- FHx of hypertension and/or cardiovascular co-morbidities
- Cause of death of family members? (esp. if premature [< 60 years] death)

**Entering ocular history:**

- Vascular diseases of the eye
- Previous intraocular injections

**NOTE:**

- Optometric office screening of blood pressure should not be a replacement for evaluation by a trained general physician and/or cardiologist
- Blood pressure taken at the arm is just one method for determining blood pressure, and does not exclude other cardiovascular diseases or peripheral vascular disease.
- Ongoing communication and co-management with the patient's general physician is recommended

**Cut-off blood pressure levels for referral to GP:**

- 140–159/90–99: routine referral
- 160–179/100–109: within two weeks
- ≥ 180/110: emergency referral

## Tips for measuring blood pressure in office

**Equipment:**

- Check to make sure equipment working properly
- Check against another model for accuracy
- Check cuff size appropriate (bladder length should be approximately 80% of arm circumference [note manufacturer recommendation], especially if circumference > 30cm)

**Patient:**

- Patient should be well-rested and comfortable prior to exam
- Patient should be seated straight, feet on the ground, with arm supported at heart level
- Similar to blink rate, consider performing blood pressure while engaging in relaxing activities


- Good tightness
- Sensors correct
- No/loose sleeve
- 2-3cm above elbow

- Too loose
- Upside down
- Sensor not on vessel
- Thick clothes

**Measurement:**

- An average of three readings should be taken, each two minutes apart
- Sleeves should not be rolled tightly; if thin clothing, screening blood pressure can be taken over the top, otherwise, removal of sleeved clothing should be considered

# Effects of Hypertension

**From page 13**

haemorrhages (flame-shaped, dot or blot), microaneurysms, cotton wool spots, hard exudates and/or retinal oedema.[9]

Acute blood pressure elevations can lead to optic disc swelling from vasoconstriction, choroidal ischaemia and axoplasmic flow stasis, concurrent with other clinical signs of hypertensive retinopathy. Once the condition has become chronic, disc oedema resolves and ONH atrophy can develop.

Clinically, generalised arteriolar narrowing and AV nipping typically indicates damage from more chronic hypertension (Figure 1), whereas haemorrhages, cotton wool spots and hard exudates are likely to indicate more recent severe hypertension (Figure 2).[12] As detailed in the CFEH chairside reference, and summarised in Table 1 below, hypertensive retinopathy can be graded as mild, moderate or malignant using the Mitchell-Wong simplified classification scheme.[12] This grading scale has been found to have similar sensitivity to the older Keith-Wagener-Barker grading scale.[13]

The presence of hypertensive retinopathy is thought to be a marker of other target-organ damage.[4] Accelerated hypertension (severe HBP associated with retinal haemorrhages and exudates) and malignant hypertension (accelerated hypertension with papilloedema) both have poor prognoses without treatment and require urgent referral for treatment by experienced practitioners.[2]

Hypertensive choroidopathy is most frequently seen in cases of acute hypertension such as in younger women with pre-eclampsia.[14,15] Signs of choroidopathy include serous retinal detachment, Elschnig spots (ischaemic infarcts of the choriocapillaris and RPE), and Siegrist streaks (linear hyperpigmentation over choroidal arteries).

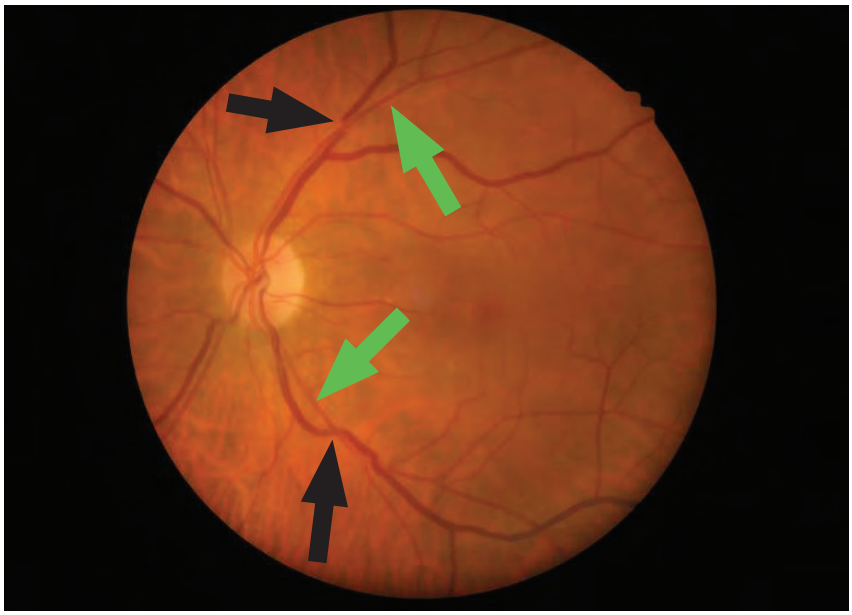


Figure 1. A 68 year-old male with chronic hypertension, now normalised on treatment, demonstrating features of mild hypertensive retinopathy including arteriolar narrowing (green arrow) and arteriovenous nipping (black arrows).

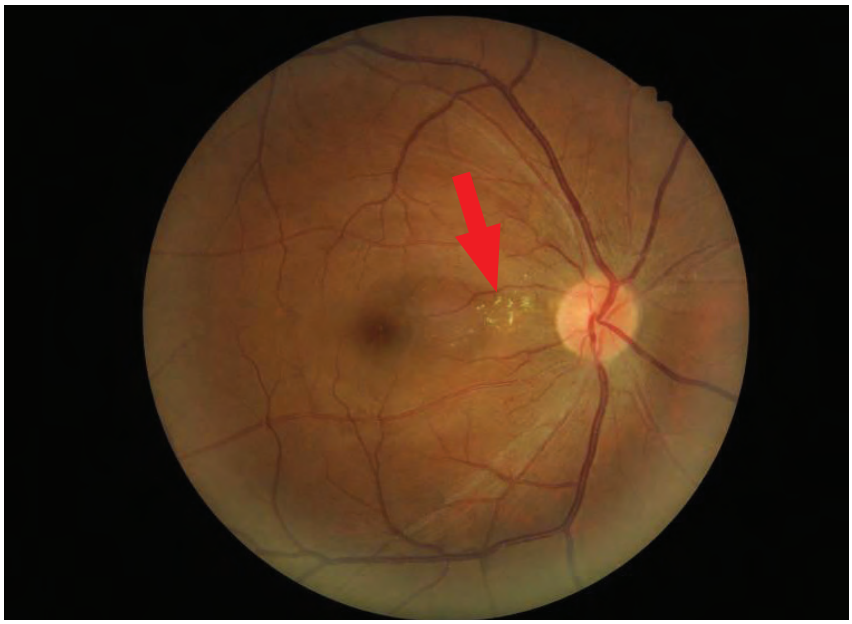


Figure 2. A 50 year-old male with acute hypertension, measuring 174/110 mmHg at the time of visit, who had been hospitalised with systolic blood pressure > 200mmHg a week earlier. The retinal photograph shows signs of moderate hypertensive retinopathy including hard exudates (red arrow), microaneurysms and dot haemorrhages, arteriolar narrowing and arteriovenous nipping.

### The role of the optometrist

A comprehensive optometric eye examination typically includes direct visualisation of the retinal vasculature for signs of hypertensive retinopathy. Fundus photography may be a useful adjunct to detect more subtle changes in the vasculature. It also provides a valuable baseline for future monitoring. In cases where hypertensive retinopathy is detected, measuring in-office blood pressure may assist the optometrist in determining if retinal changes are due to acute or chronic hypertension.

While optometrists routinely ask their diabetic patients about risk factors for developing diabetic retinopathy

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# Hypertension

**From page 17**

(for example: HbA1c to gauge the level of glycaemic control), it is commonly assumed that a patient with previously-diagnosed hypertension is well controlled. To complicate matters, patients will frequently deny having 'high blood pressure' as they believe their blood pressure to be normalised on treatment. As a result, using targeted questions – such as: 'are you on treatment to control high blood pressure?' and 'is your GP happy with your blood pressure control?' – along with a careful exploration of the individual's medication list, may provide a more accurate hypertension history.

It is important to note that adults with presbyopia or refractive error who perceive themselves to be in good general health may visit their optometrist more regularly than their general practitioner (GP).

In the absence of vascular changes, early diagnosis of hypertension may be challenging, particularly as patients are often asymptomatic. Red flags are raised when the medical history uncovers that an adult patient has not recently seen a GP or is not taking any medications despite having apparent risk factors for hypertension. In these cases, referral to a GP may be indicated and measuring blood pressure at the time of the eye examination can assist with determining the urgency of triage.

A Saudi Arabian-based study found that introducing routine measurement of blood pressure into optometry practices identified 93 of 443 patients (21 per cent) with hypertension; of those, 68 per cent were unaware of their HBP. Overall, one previously undiagnosed hypertensive patient was identified for every eight adults tested and poor control was found in approximately 29 per cent of previously-diagnosed patients.[16] While routine in-office measurement of blood pressure is not generally indicated within optometric practice, the CFEH chair-side reference in this issue of *Pharma* provides a succinct guide on when to consider taking blood pressure measurement in practice, how to correctly use an automated blood pressure cuff, and interpret and

## Management tree when seeing signs suggestive of hypertensive retinopathy

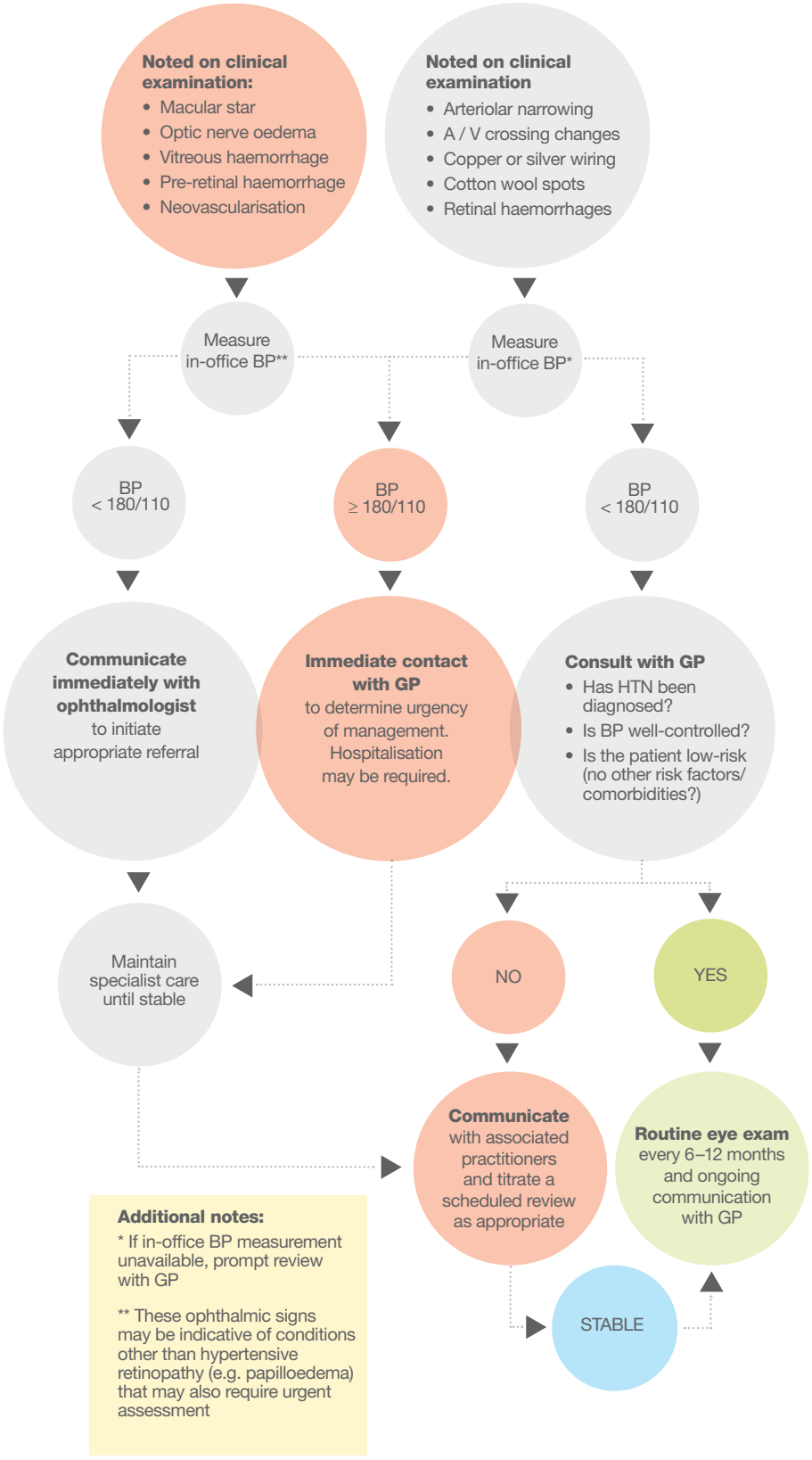


Figure 3. Acknowledgements: Dr Katherine Kalloniatis and Dr Chris Gilbert for their advice regarding measuring blood pressure and medical review periods.

| Grade | Features |
|---|---|
| None | No detectable signs |
| Mild | Generalised arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking (nipping), copper wiring (opacity of arteriolar wall) or a combination of these signs |
| Moderate | Retinal haemorrhages (blot-shaped, dot-shaped or flame-shaped), microaneurysm, cotton wool spot, hard exudate or a combination of these signs |
| Malignant | Signs of moderate retinopathy plus swelling of the optic disc |

Table 1. Mitchell-Wong Simplified Hypertensive Retinopathy Grading Scale[12]

manage the results.

As members of the multidisciplinary health care team, optometrists can make a valuable contribution to patient education. Optometrists are likely to have access to a retinal camera and images can be a powerful tool in reinforcing the benefits of compliance to treatment, lifestyle modification and the importance of regular GP visits for those at risk of chronic diseases such as hypertension and diabetes.

## Measuring blood pressure and initiating referral

Blood pressure measurements in an optometry practice will typically be obtained with an automated sphygmomanometer. As further expanded on in the CFEH chair-side reference, the patient should relax for several minutes in a quiet environment (at room temperature with legs uncrossed) before measurements are taken. Factors that can adversely affect blood pressure measurements include: drinking caffeine and smoking within two hours of measurement, incorrect cuff size or positioning, presence of peripheral arterial disease, or the presence of a pulse irregularity (for example: atrial fibrillation). NHF guidelines state that a comprehensive assessment of blood pressure should be based on at least two measurements one or more weeks apart. For additional information on the procedure itself and common errors, clinicians may wish to familiarise themselves with appropriate guidelines such as the NHF.[2]

Figure 3 ('Management tree when seeing signs of hypertensive retinopathy') is part of the CFEH chair-side reference; it was developed in collaboration with two GPs and an ophthalmologist to assist optometrists in managing patients with signs of hypertensive retinopathy and determining the urgency and type of referral required.

In urgent cases, consider speaking directly with the patient's GP (and ophthalmologist as necessary) to determine the most appropriate course of action. In less urgent cases, written communication to the GP may be more appropriate.

## Conclusion

Optometrists are skilled at detecting vascular changes suggestive of hypertensive retinopathy, however they may overlook their potential role in screening for hypertension and reinforcing the importance of regular GP visits and compliance to treatment. The CFEH chair-side reference aims to provide a practical tool to assist busy optometrists in managing hypertensive patients in their practice. ▲


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CLINICAL AND EXPERIMENTAL OPTOMETRY

*Pharma* and Optometry Australia's official journal *Clinical and Experimental Optometry (CXO)* are collaborating to bring our readers up to date with some of the most interesting articles, reviews and original research available in the latest issue of *CXO.*

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# Patient-reported outcome measures in amblyopia and strabismus: a systematic review

**Summary and comment provided by Maria Markoulli PhD MOptom GradCertOcTher FBCLA FAAO**
**Deputy Editor,** *Clinical and Experimental Optometry*

*Starting with this issue,* Pharma *and Optometry Australia's official journal* Clinical and Experimental Optometry *will collaborate to bring our readers up to date with some of the most interesting articles, reviews and original research available in the pages of CXO.*

*Published in Australia since 1919, CXO is the leading peer-reviewed journal of original optometric and vision science research and reviews in the Asia-Pacific region. In each new issue of* Pharma, CXO *Deputy Editor Maria Markoulli will confer with* Pharma *Clinical Editor Mark Roth to select a stand-out article from a recently-published issue of* CXO. *An overview of the article and a discussion on its relevance to the practice of optometry will be provided by Dr Markoulli.*

**Patient-reported outcome measures in amblyopia and strabismus: a systematic review**

*CXO.* July 2018 doi: 10.1111/cxo.12553

Amblyopia and strabismus are two conditions commonly encountered in clinical practice that can have a significant impact on an individual's quality of life. When identified early on, treatment can be initiated to minimise the impact of these developmental conditions. The resulting functional deficits of impaired stereoscopic depth perception and defective sensory, motor and visual cognition translate to difficulties in activities such as reading, grasping and driving as well as the psycho-social and emotional well-being of those affected, for example, in the case of perceivable strabismus. Understandably, this can significantly impact on quality of life. In order to determine if the screening and treatment regimens that we implement are effective relative to the cost and inconvenience, we need to have a robust and validated tool to measure quality of life.

Ms Sheela Kumaran and colleagues from Flinders University undertook a systematic review which aimed to identify the patient-reported outcome measures currently used to determine the impact of amblyopia and/or strabismus on quality of life and to determine the robustness of existing questionnaires.

In order to do this, they conducted a systematic search of electronic databases such as PubMed and Cochrane and assessed the quality of all patient-reported outcome measures identified and their comprehensiveness in terms of the eight ophthalmic quality of life domains: activity limitation, concerns, emotional well-being, social well-being, economic, convenience, symptoms and mobility.

They identified both non-disease and disease specific questionnaires that have been used to assess amblyopia and strabismus impact. Non-disease specific questionnaires identified include the Short Form (SF-36) and the Paediatric Quality of Life Inventory (PedsQL) which are widely used in adults and children respectively; both assess quality of life domains such as physical functioning, role limitations and social functioning. These questionnaires offer a superficial understanding of a person's well-being as they are not specific to a disease, lacking the sensitivity to evaluate the impact of amblyopia and/or strabismus.

When the authors explored disease specific questionnaires, 32 patient-reported outcome measures were identified that were specific to amblyopia and/or strabismus, 12 were specific to amblyopia and 18 were strabismus specific, while two addressed both conditions. Of the 12 amblyopia questionnaires, only two assessed the impact of amblyopia itself

**Continued page 21**

# Outer retinal tubulations

## AMD management requires a collaborative approach

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**CASE REPORT**

Medical management of wet macular degeneration has vastly improved with intravitreal injections of anti-VEGF agents.

In Australia, we are in an enviable position where our government provides specialists with access to these medications.

However, quoting Spider-Man's Uncle Ben: 'With great [injecting] power, comes great responsibility', and not all nails respond to the same hammer. As retinal specialists, we commonly receive referrals for second opinions regarding patients who have not responded to multiple injections with different agents for macular degeneration.

One such patient, an active 74-year-old, had been fitting in her monthly injections for the past two years between her yoga, local community work and overseas travelling. The frequent injections were cramping her style and there was a three-month cruise trip planned for winter with her group of friends. She was referred for a second opinion to see whether there was an alternative treatment for her wet macular degeneration.

At her appointment, she mentioned that vision had stabilised in her treated eye for the past year, at 6/24 in

**Continued page 22**

## *CXO* review

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(Amblyopia Survey and the Socio-Professional Integration Questionnaire, while the other 10 assessed the impact of treatment.

Most of the amblyopia instruments measured the impact on children; only the Amblyopia Survey targeted the psychosocial impact on adults. Of these 12 questionnaires, only one has been validated via modern psychometric tests (Children's Vision for Living Scale). These questionnaires predominantly measure activity limitation and emotional impact as a result of treatment.

Of the 18 strabismus surveys identified, six were developed to determine the impact of strabismus on quality of life and the remaining 12 measured the impact of strabismus surgery. The Effect of Diplopia Questionnaire was the only tool identified to measure the impact of post-operative diplopia. The Intermittent Exotropia Questionnaire was the only questionnaire validated for child-specific strabismus, with most of the strabismus instruments measuring the impact of strabismus on appearance in adults. These questionnaires generally measured concerns relating to appearance and treatment outcome.

Kumaran and colleagues conclude that none of the questionnaires summarised address quality of life comprehensively based on the eight identified ophthalmic domains. Although there are many questionnaires available, all current instruments used to measure quality of life in those with amblyopia and/or strabismus are flawed in some way.

### Discussion

As clinicians we need to be selective about which questionnaire we wish to use based on the presenting patient and the overall question we wish to have answered. If we are interested to know how their condition is impacting their psychosocial well-being as an adult, we will choose a questionnaire that differs from one we would select if we were interested in following up on the impact of patching on an amblyopic child.

Future work needs to be done to develop appropriate questionnaires to enable us to assess all eight ophthalmic domains of quality of life and to track the impact of our treatment on the overall well-being of our patients. ▲

Each quarter, *CXO*'s Deputy Editor Maria Markoulli and *Pharma*'s Clinical Editor Mark Roth select a stand-out article from a recently-published issue of CXO to appear in *Pharma*.

To access *CXO*, please go to: www.optometry.org.au/cxo-journal/

# AMD management

**From page 21**

her left pseudophakic eye. Intravitreal treatment had been extended at one stage but had returned to monthly injections due to her OCT scans, with no recent change in vision. She was otherwise healthy, did not smoke and took her AREDS2 vitamin pills religiously, along with some other herbal therapies.

The fundus examination showed areas of geographic atrophy and some disciform scar changes, but there was no acute haemorrhage. Her OCT scan demonstrated a significant cystic-looking structure but no signs of subretinal fluid. The fluorescein angiogram also did not reveal an active choroidal neovascular membrane. Her findings were consistent with outer retinal tubulations, which was nicely demonstrated on our OCT.

Outer retinal tubulations were first described in very similar scenarios: patients who had long-term injections with no apparent resolution of cystic fluid. Outer retinal tubulations are formed due to chronic retinal injury, damaging the inner and outer segments of photoreceptors, in the ellipsoid zone on the OCT.

Over a period of time the damaged cells form a circular rearrangement. On OCT, this appears as a hyper-reflective outer ring and a hypo-reflective core, which is not consistent with a cyst. The tubulations are in the outer nuclear layer. Outer retinal tubulations do not respond to anti-VEGF injections; however, these patients still require long-term monitoring for occurrence of new subretinal fluid and new wet AMD signs.

After another couple of visits with no new changes on her OCT scans and no further injections, I sent her back to her referring optometrist, requesting regular OCT scans. This collaborative approach is important in providing our patients with the best treatment pathways, minimising unnecessary interventions, and should be encouraged in both the public and private systems. It allows several minds to attack a problem, especially when a condition is not changing or improving and through collaboration we entertain other diagnoses.

Although we could not improve her vision, our patient was happy that she could be monitored locally by her optometrist, and if there was ever a concern about new wet AMD changes, she would be sent to us for a retinal assessment straight away. Her next goal is to rustle up an OCT scanner on her cruise ship, for a year-long cruise. ▲

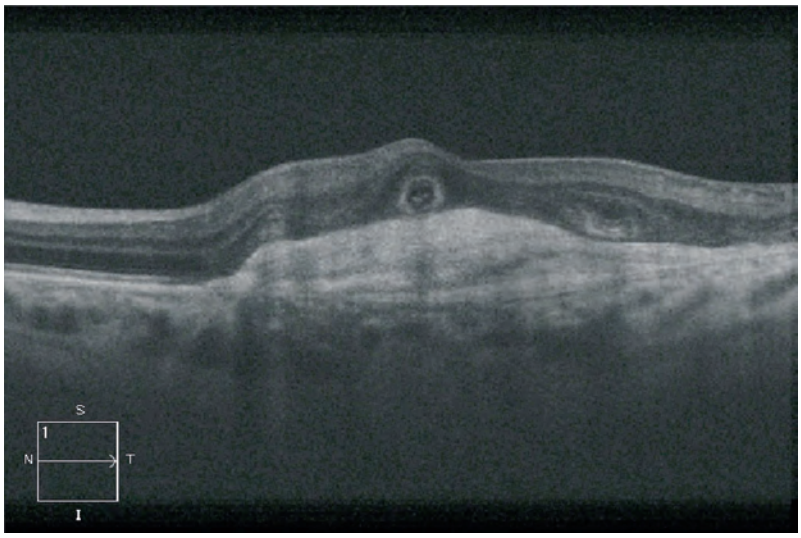


Figure 1. Defining features of outer retinal tubulations on OCT: hyper-reflective border, hypo-reflective core, in outer nuclear layer

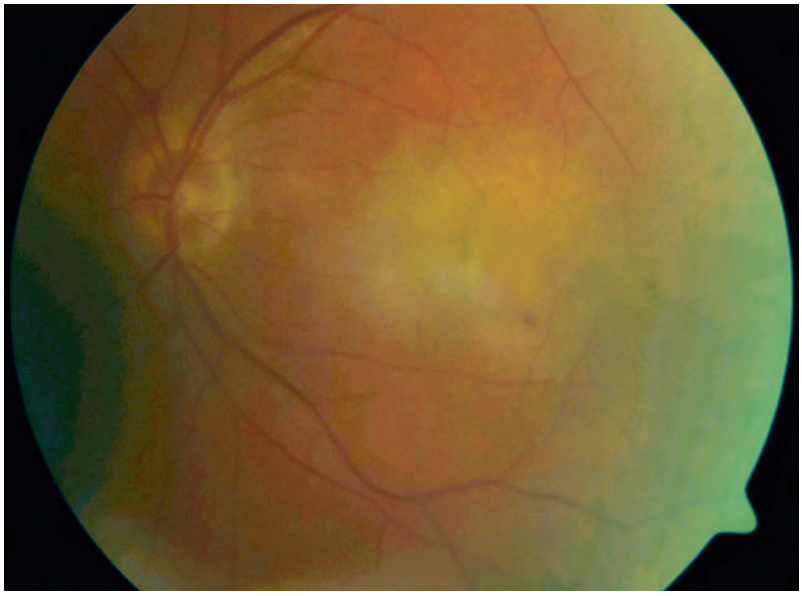

Figure 2. On fundus examination, there was no sign of an active choroidal neovascular membrane

# Therapeutic NEWS of note

**Associate Professor Mark Roth**

BSc(Pharmacology)
BAppSc(Optom) PGCertOcTher
NEWENCO FAAO OAM

### The retinal signs of cognitive decline

Researchers from the Atherosclerosis Risk in Communities (ARIC) study have found that vascular changes are associated with an increased risk for cognitive decline and dementia.

Drawing on data from a 20-year period among 12,313 men and women between ages 50 and 73 at baseline, researchers calculated composite cognitive scores that included memory, language and executive function/attention tasks. Participants were classified as having no, mild or moderate/severe retinopathy based on the presence of microaneurysms, retinal haemorrhages, or soft exudates on retinal fundus photography at visit 3 (4–8 years after baseline).

The study authors found that all retinopathy components, especially retinal haemorrhages, were associated with greater 20-year cognitive decline. Arteriolar changes were not associated with significant 20-year cognitive decline in fully adjusted models. Estimated rates of cognitive decline were similar between those with and those without diabetes mellitus and between blacks and whites.

The authors wrote that their study's findings support the exploration of more sensitive measures in the eye such as optical coherence tomography angiography, which may provide surrogate indexes of microvascular lesions relevant to cognitive decline in older adults. The results also draw attention to the importance of routine funduscopic examinations in optometric clinical practices.

*Neurology*. Feb 2018. doi.org/10.1212/WNL.0000000000005205

### The impact of supplemental antioxidants on patients with non-advanced AMD

Researchers at the Waterford Institute of Technology, Ireland conducted a two-year study to evaluate the impact of supplemental macular carotenoids (including versus not including meso-zeaxanthin) in combination with co-antioxidants on visual function in patients with non-advanced age-related macular degeneration.

The study involved 121 participants, randomly divided into two groups. (Group 1: Age-Related Eye Disease Study 2 formulation with a low dose [25 mg] of zinc and an addition of 10 mg meso-zeaxanthin; n = 60). Group 2: Age-Related Eye Disease Study 2 formulation with a low dose [25 mg] of zinc; n = 61).

Visual function was assessed using best-corrected visual acuity, contrast sensitivity (CS), glare disability, retinal straylight, photostress recovery time, reading performance, and the National Eye Institute Visual Function Questionnaire-25. Macular pigment was measured using customised heterochromatic flicker photometry.

Statistically-significant improvements in the primary and several secondary outcome measures were observed. Also statistically significant increases in macular pigment at all eccentricities were observed over time, and the degree of augmentation was statistically comparable between interventions.

The study authors concluded that supplementation with a formulation that contains the macular carotenoids (with or without meso-zeaxanthin), in combination with co-antioxidants, results in improvements in contrast sensitivity and other measures of visual function in patients with non-advanced AMD.

*Invest Ophthalmol Vis Sci*. Oct 2017. doi: 10.1167/iovs.16-21192

### Progression from unilateral to bilateral AMD

One in four to one in five unilateral AMD cases progress to bilateral in five years, and up to one in two late unilateral AMD cases progressed to bilateral in the same time span.

To assess the five-year progression from unilateral to bilateral age-related macular degeneration (AMD) and associated risk factors, researchers conducted pooled data analyses of three prospective population-based cohorts, the Blue Mountains Eye Study, Beaver Dam Eye Study and Rotterdam Study.

Retinal photography and interview with comprehensive questionnaires were conducted at each visit of three studies. AMD was assessed following the modified Wisconsin AMD grading protocol. Progression to bilateral any (early and late) or late AMD was assessed among participants with unilateral involvement only.

The researchers found that, in any five-year duration, 19–28 per cent of any unilateral AMD cases became bilateral and 27–68 per cent of late unilateral AMD became bilateral.

The authors concluded that one in four to one in five unilateral any AMD cases, and up to one in two unilateral late AMD cases progressed to bilateral in five years. Known AMD risk factors, including smoking, are significantly associated with the progression to bilateral involvement.

*Br J Ophthalmol*. Sept 2017 doi: 10.1136/bjophthalmol-2016-309729.

### Should there be only two types of diabetes?

According to a study published in *The Lancet: Diabetes & Endocrinology*: no. In fact, they propose classifying five types of diabetes.

In the introduction to their study, 'Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables,' the team of international researchers wrote that they believe that the two existing variations of diabetes (type 1 and type 2) is overly simplistic. They argue that 'a refined classification could provide a powerful tool to individualise treatment regimens and identify individuals with increased risk

**Continued page 24**

# TNoN

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of complications at diagnosis.'

Analysing data from the records of 15,000 people across five patient registries, the researchers behind the study found that the disease can actually be grouped into five distinct clusters, according to variables such as Body Mass Index (BMI), age of diagnosis and degree of insulin resistance:

Cluster 1: severe autoimmune diabetes, which overlaps with type 1 diabetes, and is 'characterised by early-onset disease, relatively low BMI, poor metabolic control, insulin deficiency, and presence of antibodies.'

Cluster 2: severe insulin-deficient diabetes (SIDD), which is similar to the first cluster (people were relatively young at diagnosis and were not overweight) without the presence of antibodies. 'People in this cluster looked for all the world like [they had] type 1 diabetes, but they didn't have "autoantibodies" that indicate type 1.'

Cluster 3: severe insulin-resistant diabetes (SIRD), marked by insulin resistance and high BMI. (Their bodies were making insulin, but the cells were not responding to it).

Cluster 4: mild obesity-related diabetes (MOD), characterised by obesity but not by insulin resistance.

Cluster 5: mild age-related diabetes (MARD): which is similar to diabetes of the fourth cluster (MOD), but found in patients older than those in other categories. The most common form of diabetes, affecting 40 per cent of the people in the study.

The authors acknowledged that their study can't confirm whether all five clusters of diabetes have different causes or whether the classifications will change over time. Future research, they suggested, is required.

*The Lancet*. March 2018 doi: 10.1016/S2213-8587(18)30051-2

### New guidelines for type 2 diabetics

Most patients with type 2 diabetes should aim for an HbA1c target between seven and eight per cent, rather than 6.5–7 per cent according to the recently-released evidence-based guidance statement from the American College of Physicians (ACP).

Published in March in the *Annals of Internal Medicine*, the guidance statement was based on a search of the literature for English-language national guidelines that addressed HbA1c targets for type 2 diabetes in non-pregnant outpatient adults.

Based on their review, the ACP put forward four major recommendations for clinicians:

Personalise goals for glycaemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.

Aim to achieve an HbA1c level between seven and eight per cent in most patients with type 2 diabetes.

Consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA1c levels less than 6.5 per cent.

Treat patients with type 2 diabetes to minimise symptoms related to hyperglycemia and avoid targeting an HbA1c level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residing in a nursing home, or with other chronic conditions.

*Ann Intern Med*. March 2018 doi: 10.7326/M17-0939

### A-scan and OCT to differentiate papilloedema from pseudopapilloedema

Researchers conducted a retrospective cross-sectional analysis on papilloedema and pseudopapilloedema patients to determine the utility of A-scan ultrasound and spectral domain OCT retinal nerve fibre layer (RNFL) thickness in differentiating papilloedema from pseudopapilloedema.

The study found that compared with pseudopapilloedema, papilloedema eyes showed larger mean optic nerve sheath diameter (ONSD), greater change of ONSD at lateral gaze and thicker retinal nerve fibre layer.

The researchers concluded that retinal nerve fibre layer thickness can potentially be used to detect moderate-to-severe papilloedema. A-scan may further assist differentiation of mild papilloedema from pseudopapilloedema.

*Optom Vis Sci*. Dec 2017 doi: 10.1097/OPX.0000000000001148.

### New guidelines for hay fever

US-based publication *Annals of Internal Medicine* convened a work group of representatives of the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI), to provide specific guidance on pharmacologic treatment for seasonal allergic rhinitis, including for initial therapy.

Following a systemic review, the workgroup made two 'strong' and one 'weak' recommendations.

1. For initial treatment of seasonal allergic rhinitis in persons aged 12 years or older, monotherapy with an intranasal corticosteroid is preferred; combining it with an oral antihistamine confers no additional benefit. (Strong recommendation).

2. For initial treatment of seasonal allergic rhinitis in persons aged 15 years or older, an intranasal corticosteroid should be chosen over a leukotriene-receptor antagonist such as montelukast. (Strong recommendation).

3. For treatment of moderate-to-severe seasonal allergic rhinitis in persons aged 12 years or older, the clinician may recommend the combination of an intranasal corticosteroid and an intranasal antihistamine for initial treatment. (Weak recommendation).

Finally, the work group suggested that although patients tend to prefer oral medications over nasal sprays, if an intranasal corticosteroid is used regularly, it is the most effective medication for addressing all allergic rhinitis symptoms, with no need to add an oral antihistamine.

*Ann Intern Med*. Nov 2017 doi: 10.7326/M17-2203

# Looking into the future: the biological contact lens bandage

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The ProKera bandage contact lens[1] is a therapeutic device used to promote healing of a damaged corneal or conjunctival surface.[2] It is used widely in The United States of America, with FDA approval,[3] to treat diseases such as severe dry eye, chemical injury, keratitis, herpetic ulcers and recurrent corneal erosions.[2]

The device works by inserting a small portion of amniotic membrane* onto the posterior surface of a ProKera conformer between two polycarbonate rings. This is then applied to the patient's eye, where the amniotic membrane interacts with the anterior surface to promote healing and regeneration. The amniotic membrane eventually dissolves, usually in about one week, and the ProKera device can be removed by the optometrist.

## Clinical Findings

Unaided visual acuity (VA): right eye (OD) 20/60, pin-hole (PH) 20/40+ and OS 20/200 (with bandage contact lens), PH 20/40. Anterior slitlamp examination revealed OS superior recurrent corneal erosion and inferior corneal neovascularisation. Diagnosis was a REE of the OS. A ProKera Amniotic bandage contact lens was placed on the patient's eye. Artificial tears as needed, both eyes and Besivance for the left eye every night before dinner was chosen as the most beneficial treatment strategy.

Figure 1A-1F. Biological contact lens insertion. (Images courtesy of Bio-tissue, Inc.)

Figure 1A. Apply topical anesthesia

Figure 1B. The clinician prepares the bandage lens for insertion by removal from protective packaging and rinsing vigorously with sterile saline. The superior eyelid is held.

Figure 1C. Ask the patient to look down. The superior eyelid is held by the clinician.

Figure 1D. Insert the bandage lens into the superior bulbar conjunctiva.

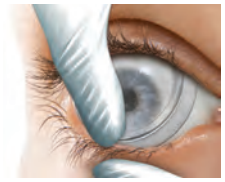

Figure 1D. Gently hold the inferior eyelid surface and insert the inferior portion of the bandage lens onto the ocular surface. Ask patient to close close their eyes, allowing the bandage to rest on the ocular surface.

Figure 1F. Confirm centration with slitlamp. Review the patient in approximately one week to confirm wound healing and bandage contact lens removal.

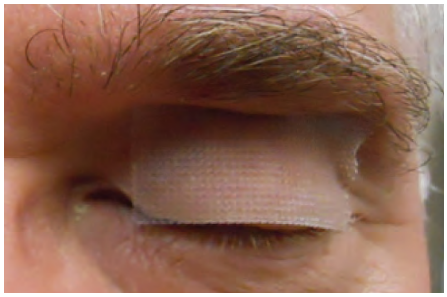

Figure 2. A temporary tape-tarsorrhaphy over the lid crease, narrows the eye opening, keeps the bandage lens centered and minimises discomfort. Exposure may also cause undesirable thinning of the amniotic membrane tissue.

The convenience and efficiency of the biological contact lens makes it desirable to use in clinical practise and has been shown to work successfully in managing recurrent corneal erosions.

## Case study

A 56-year old Caucasian female presented at Ophthalmic Consultants of Connecticut for review of a persistent corneal ulcer left eye (OS), managed with a bandage contact lens. On this occasion she reported waking with her 'lids were glued shut,' with discharge and swelling around her eyes. She has a previous ocular history of microbial keratitis after sleeping in her coloured contact lenses, and OS recurrent corneal erosion (REE).

## Discussion

ProKera is an alternative treatment option to increase the rate and healing of the corneal surface in recurrent corneal erosion. This patient was slow to respond to previous treatment regimens of artificial tears, antibiotics, steroids and rigid contact lenses, therefore this strategy was employed.

An amniotic membrane is an avascular, sterile, fetal membrane

**Continued page 26**

Figure 3A-F. Biological contact lens removal. (Images courtesy of Bio-tissue, Inc.)

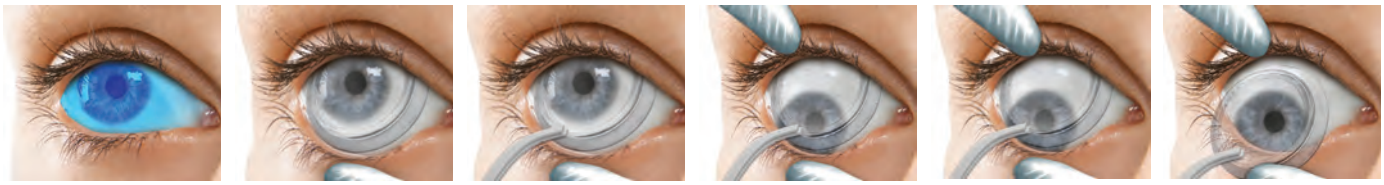

Figure 3A. Apply topical anesthesia

Figure 3B. Pull the lower eyelid down

Figure 3C. Lift the lower edge of the bandage lens using a cotton swab or blunt-tipped tweezers

Figure 3D. Ask the patient to look down

Figure 3E. Apply gentle pressure on the upper eyelid

Figure 3F. Slide the bandage lens out

# Lens bandage

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found deep within the placental tissues during embryological development. It contains an epithelium, stroma and basement membrane. The basement membrane contains collagen, including collagen type VII,[2] which is common to the corneal basement membrane and conjunctiva. Amniotic membranes are extracted from donors undergoing caesarean delivery and are analysed for any transmissible diseases and treated with broad-spectrum antibiotics prior to ocular application.[2]

When applied to the cornea, the amniotic membrane – either cryogenic or dehydrated – interacts with the surface to promote epithelial growth through cell migration, differentiation and adhesion to the ocular surface.[2,4] It also promotes limbal stem cell regeneration and repair of the corneal epithelium.

The stromal portion of the amniotic membrane contains hyaluronic acid which is effective in inhibiting fibroblast growth, decreasing cytokine expression and therefore decreasing inflammation[4] and angiogenesis.[2] It is also believed that the amniotic membrane displays antimicrobial properties which is useful in decreasing the chance of corneal infection.

How the amniotic membrane provides anti-microbial defence is still a topic of controversy, but it is suggested that it is due to components within the tissue and the bandage contact lens itself acting a physical barrier between the eye and the environment.[2,4]

Implantation of the ProKera from a donor to recipient does not mount an immune response as it lacks major histocompatibility antigens HLA-A, B and/or DR.[2,4] Despite this, with inefficient sterilising of the amniotic membrane prior, there is still a possibility of transmitting a viral or bacterial infection to the host if the donor amniotic membrane is not accurately screened or stored correctly.[4]

In 2009, a study investigated the safety and efficacy of ProKera for patients with anterior eye disease. Out of the twenty participants (twenty eyes), 60 per cent recovered visual acuity over an average of twenty-five days. Possible side effects were recurrence of the eye conditions in 20 per cent and 30 per cent reported ocular discomfort and headache. Discomfort is most likely due to the ProKera polycarbonate ring, especially from the superior eyelid.[2,5] Researchers suggest that the application of a softer ring may be a way to improve ocular comfort.[5]

Although currently unavailable in Australia, the use of biologic corneal bandage devices in the US have provided safe and effective healing to corneas with less scarring and inflammation, less pain and improved clinical outcomes.

ProKera offers clinicians a safe and effective alternative approach to manage ocular surface disorders such as RCE. It may be useful for patients with chronic eye diseases where traditional therapeutic approaches are not enough. ▲

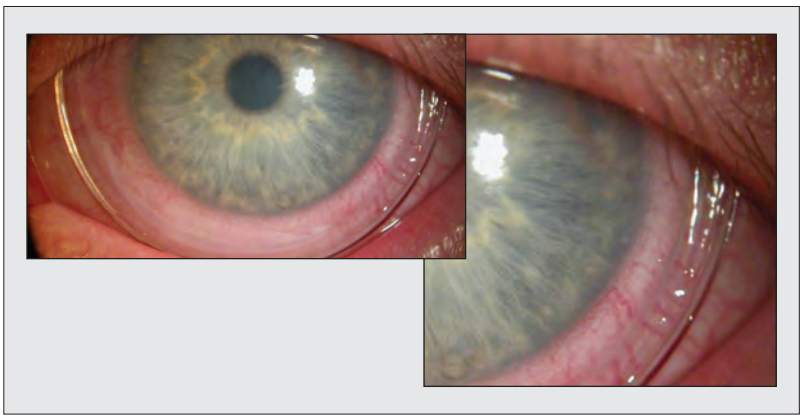

Figure 4. Biological contact lens in place. (Image courtesy of Bio-tissue, Inc.)


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*Amniotic membranes currently do not have widespread, private practice, commercial availability in Australia compared with the USA. Access in some states is via the cornea bank or major eye hospitals.

# A new glaucoma treatment

## Latanoprostene bunod and the trabecular meshwork

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Lowering intraocular pressure (IOP) has been the mainstay of glaucoma and ocular hypertension management for decades. The Centre for Eye Health recommends beginning with the simplest topical strategy, a prostaglandin analogue (PGA) or beta-blocker (BB).[1] This recommendation follows setting a target pressure based on a number of clinical findings that are beyond the scope of this article.

Four specific PGAs are available for use by optometrists in Australia. Latanoprost became commercially-available over 20 years ago. An emerging chemical modification of the latanoprost molecule includes the addition of a nitric-oxide (NO) moiety. Vyzulta (latanaprostene bunod 0.024% ophthalmic solution) was approved by the US Food and Drug Administration in November 2017.[2] The mechanism and site of action are both interesting and will be detailed below.

### NO

Nitric oxide (NO) was named 'molecule of the year' in 1992.[3] Its history, however, begins well over 200 years earlier. NO was discovered in the 1770s by Joseph Priestly, in England.[4] Until the culmination of research into NO's capacity for vasodilation, it was regarded as a reactive free radical and air pollutant. Although nitroglycerin was synthesised and found to have a vasodilatory effect in the 1840s, and, by the 1870s, had been widely used along with related nitrate compounds to treat patients with angina and hypertension, no one connected these chemicals' effects on vascular tissues with NO for the next century.[5]

In 1977, Murad found that it was, in fact, NO release that accounts for the vasodilatory effect of nitroglycerin and related compounds.[6,7] NO is also a biologically active molecule at the cellular level during metabolic processes. The discovery of exogenous NO's vasodilatory effect raised, for the first time, the question about endogenous NO's potential role in cardiovascular physiology.

Several years later, while studying vasodilation in response to acetylcholine, Robert Furchgott observed that, in the absence of the endothelial lining, the smooth muscle cells of vessels were unable to relax in response to acetylcholine.[8]

He postulated that some substance produced by the endothelium was required for the relaxation of vessels, setting off an intense search to identify this substance, known then as endothelium-derived relaxing factor (EDRF). This designation remained for the rest of the decade.

In 1987, nearly a decade after the elucidation of NO's role in nitrate-induced vasodilation, Moncada and Ignarro discovered independently that NO is in fact the mystery EDRF that had long been sought after by researchers.[9,10] To honour their pioneering work 'concerning nitric oxide as a signaling molecule in the cardiovascular system', the 1998 Nobel Prize in Physiology of Medicine was awarded to Furchgott, Ignarro, and Murad.[11] The discovery of endothelial-cell-derived NO's critical role in vasodilation marked a major advancement in the history of physiology.

Thereafter, researchers began to explore the messenger molecule's functions beyond the vessel wall, and they soon recognised that NO was a remarkably versatile messenger playing a complex role in physiological activities of multiple human body systems.[3] This then became the focus of the application of NO-donating compounds in glaucoma management.

### Latanoprostene bunod

A new focus for the management of glaucoma has become the trabecular meshwork. The hypothesis is that impaired aqueous drainage is the initiation of the cascade of glaucomatous damage. It is thought that this then results in increased intraocular pressure. While this hypothesis appears contrary to much of the conventional concept of glaucoma, the primary risk factor for glaucoma remains elevated IOP. In fact, the only means to minimise glaucomatous damage is to reduce that primary risk factor. The 2015 version of the American Academy of Ophthalmology's Preferred Practice Pattern does not even include elevated IOP as part of the definition.[12] This leads to newer thinking, suggesting that there may be some non-IOP related insult that occurs to raise IOP. This is what has pinpointed the trabecular meshwork as that potential site and has brought about the development of latanoprostene bunod.

Development of the specific molecule included clinical trials that resulted in FDA-approval in the United States. The mechanism of action to lower IOP for latanoprost is well known as enhancing uveoscleral outflow.[13] Addition of the NO moiety to the latanoprost chain is thought to bolster IOP reduction by two means. First, enlarging pores of the trabecular meshwork as well as activity at the endothelial-cell level of the trabecular vasculature to enhance blood flow.[2,14] These combined actions are thought to be responsible for enhanced IOP-lowering compared to latanoprost alone.[15]

The side-effect profile of latanoprostene bunod is similar to that of the latanoprost formulation alone. These include predominantly reversible eyelash growth and largely permanent increased iris and periocular pigmentation.[2] The adverse events reported from the initial clinical trials are also familiar—conjunctival hyperemia, eye irritation and pain and

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# Glaucoma

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pain at the instillation site.[2,16,17] These occurred at rates greater than two per cent but all were observed to occur in fewer than 10 per cent of patients enrolled in the clinical trials.

Non-IOP related factors continue to emerge as components of the glaucoma risk spectrum. Looking to the future, we may find ourselves investigating blood flow to the optic nerve, inner retina and perhaps even the trabecular meshwork. These directions may also include the larger sphere of systemic blood flow as well as such extrinsic factors such as cerebrospinal fluid pressure.[18] We have known that systemic absorption of topically applied medications has systemic implications. Specifically, the beta-blockers slow heart rate and have the potential for significant adverse pulmonary effects.[19,22] So we should exercise caution in those scenarios and recognise that these effects can be identified and minimised.[23,24] Newer compounds such as latanoprostene bunod may offer alternatives.

The prevalence of glaucoma continues to be underestimated. In fact, a greater proportion of high-risk patients may be overlooked than previously thought.[25]

As optometrists on the front line of primary eye care, we can work together to lessen the vision- and sight-threatening burden of glaucoma. Now we will have new weapons in that fight. ▲

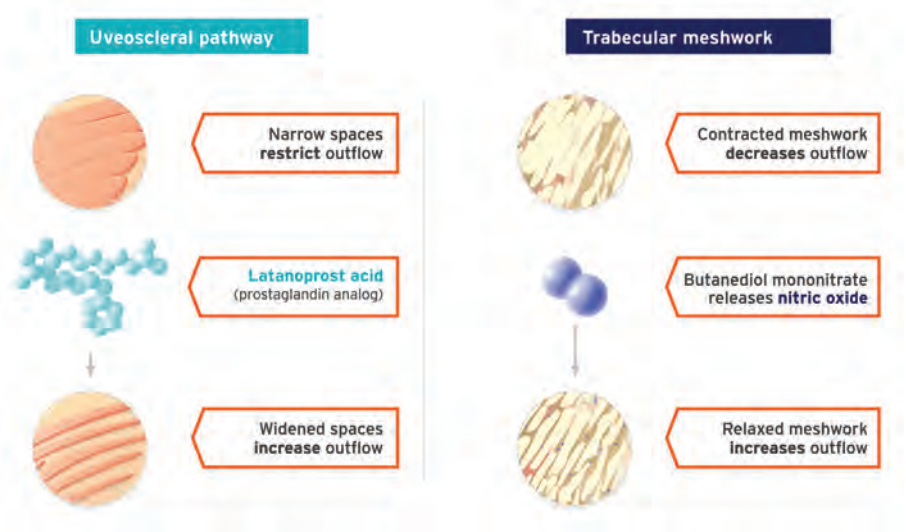


Figure 1. Latanoprost acid works within the uveoscleral pathway to increase aqueous humor outflow. Butanediol mononitrate releases NO to increase outflow through the trabecular meshwork and Schlemm's canal. (Image courtesy of B+L)


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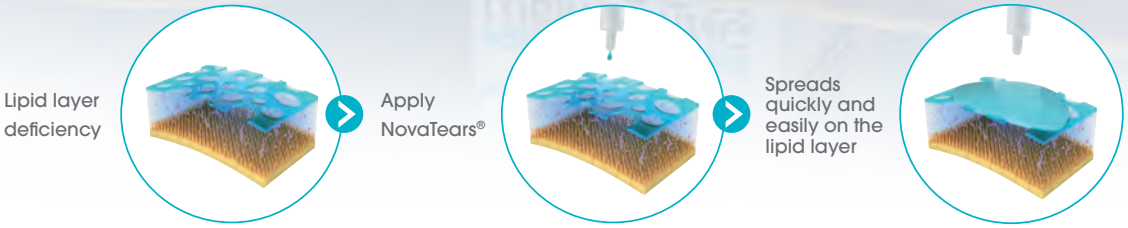


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