Supplement to
AUSTRALIAN OPTOMETRY

Special issue
• AMD • DRY EYE

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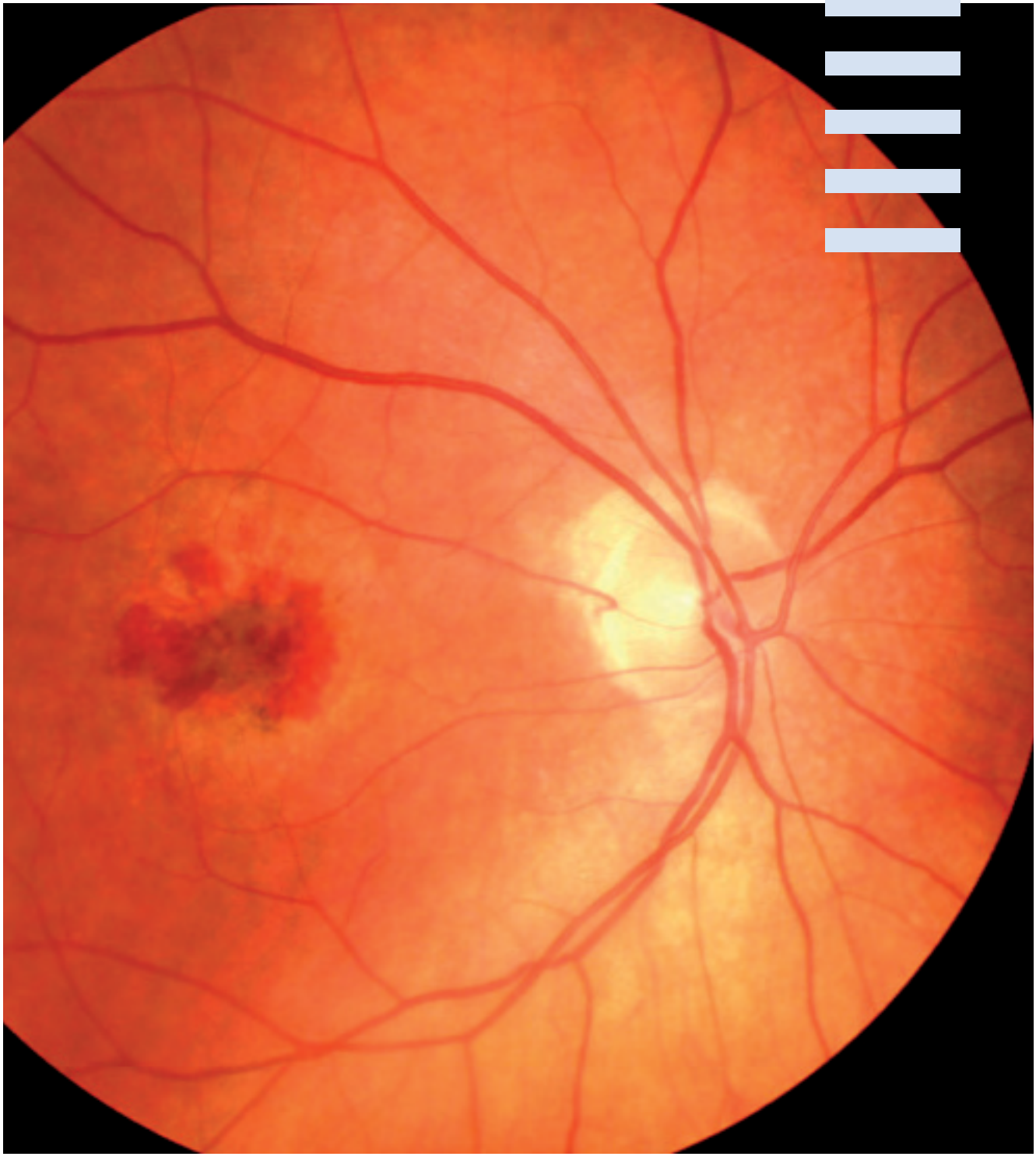
June 2010



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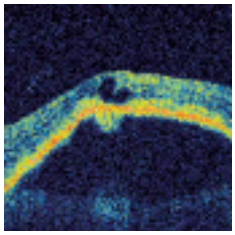
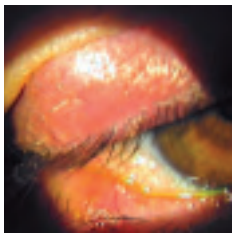
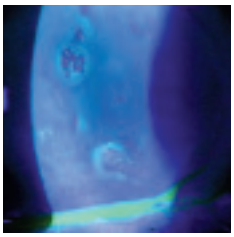
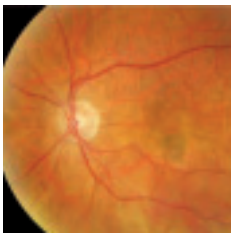
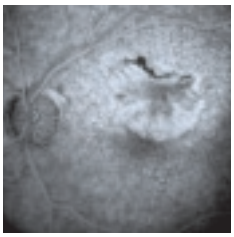

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COVER
Neovascular AMD with a subretinal haemorrhage

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Slow the progression

With an ageing population and the number of AMD sufferers set to double in the next 40 years, timely diagnosis and providing effective treatment have become more critical

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Age-related macular degeneration is the most common cause of irreversible vision loss in the developed world in people over 50 years of age.[1] **The Australian Government's Intergenerational Report (IGR) projects that over the next 40 years the proportion of the population aged over 65 years with the disease will almost double. The number of Australians aged 65 years and older is expected to increase rapidly from around 2.5 million or 13 per cent of the population in 2002, to 6.2 million or about 25 per cent in 2042.**

AMD affects the central portion of the retina responsible for acute, fine vision. Patients usually present when they experience difficulty performing activities where central vision is involved, such as driving, reading or watching television.[2] Distortion of straight lines—which may appear waxy or curvy—is another common complaint.

Risk factors for AMD increase with age (particularly once a person reaches 50 years of age),[3,4] female gender, Caucasian race, blue irides, age-related maculopathy, positive family history,[5] cataract and the presence of biomarkers for cardiovascular disease such as a history of cardiovascular disease[6,7] and smoking.[8,9,10,11,12] About 15 genes have been linked with MD and the strongest associated genes are complement factor H and ARMS 2. There is conflicting evidence on whether cataract surgery accelerates the development of AMD.

AMD can be classified in two ways.

- **Dry (atrophic)**

This is the most common form of the disease. It progresses slowly and affects about 90 per cent of people over 60 years of age. Ocular indications of dry AMD include subretinal drusen deposits, which are essentially hyaline products of the retinal pigment epithelium (RPE). There may be also RPE atrophy in a focused or geographic pattern as well as subretinal pigment epithelial clumping. The size and number of soft drusen deposits are predictors of progression to wet AMD, making it essential for regular dilated funduscopic examination to detect these changes.

- **Wet (neovascular)**

This is the less common but more acute form of AMD and accounts for 90 per cent of the blindness from AMD. Clinical signs may include retinal, subretinal or sub-RPE haemorrhage, retinal thickening, pigment epithelial detachment, and hard exudate. It involves proliferation of new leaky blood vessels from the choroid into the retina, known as choroidal neovascularisation.[13] Vascular endothelial growth factor (VEGF) is a potent mitogenic and vascular permeability factor, which is produced in response to retinal hypoxia.[14,15,16,17,18] VEGF is thought to play a pivotal role in neovascularisation. Optical coherence tomography (OCT) and angiography—both fluorescein and indocyanine green—can form an integral part in the diagnosis and management of macular pathologies.[19,20]

Diagnosis

Fundus fluorescein angiography and OCT are used to complement the clinical examination. An ICG can be used to look for retinal angiomatous proliferation (RAP) or polypoidal choroidal vaculopathy (PCV) if indicated. Fundus fluorescein autofluorescence can also assist in assessing disease progression.

Treatment options

There is currently no proven effective treatment for dry AMD and this is largely attributed to the poorly understood pathogenesis of the disease. The current emphasis is on reducing the progression of the disease by controlling modifiable risk factors and performing close surveillance. The Age-Related Eye Disease Study (AREDS) demonstrates the benefits of nutritional supplementation with anti-oxidants such as beta-carotene,

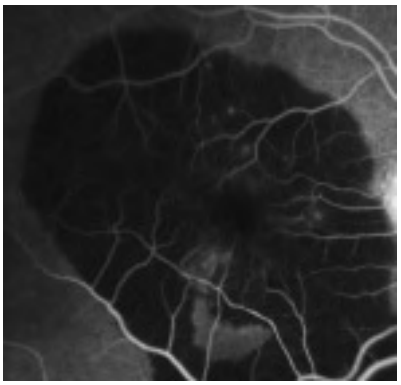


Figure 1. FFA image with blood obscuring the lesion

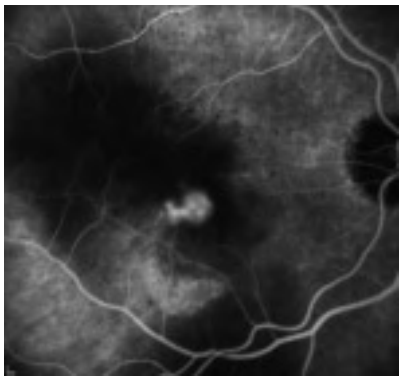


Figure 2. ICG image shows the CNV clearly

zinc, vitamin C and vitamin E to reduce RPE free radical damage, which is thought to be responsible for the formation of drusen.[21] This is of benefit for intermediate AMD, defined as the presence of several medium-sized drusen (125 microns) or larger drusen in one or both eyes, or advanced AMD, defined as either central GA or wet AMD in one eye only.

Beta-carotene supplementation has been linked to an increased risk of lung cancer and coronary heart disease. Therefore, AREDS supplementation–involving 500 mg vitamin C, 400 IU vitamin E, 15 mg beta-carotene, 80 mg zinc oxide and 2 mg of cupric oxide–is recommended for non-smokers with moderate to advanced AMD.[22] For smokers with moderate to advanced AMD, treatment with zinc alone, or the AREDS formula without beta-carotene, is recommended. A second AREDS study is assessing the effects of lutein, zeaxanthin and omega 3 fatty acids on AMD and is expected to be completed in December 2012.[23,24]

Studies involving laser therapy for prevention of progression in patients with high risk drusen provided inconsistent results and a systematic review of these trials has found that laser photocoagulation did not decrease the risk of choridal neovascularisation, geographic atrophy or loss of visual acuity.[25]

The current frontline treatments for wet AMD are vascular endothelial growth factor inhibitors, as VEGF has been found to be a potent stimulant for choroidal neovascularisation. Most treatments are targeted toward VEGF-A which is most strongly associated with angiogenesis. VEGF inhibitors currently on the market are ranibizumab (Lucentis), bevacizumab (Avastin) and pegaptanib (Macugen). These are delivered via intravitreal injections, allowing for good penetration of the retina. Ranibizumab has been extensively tested in clinical trials[26,27] as opposed to bevacizumab, which has been marketed only for its role in anticancer treatments such as colorectal cancer. There are several trials comparing Lucentis and Avastin; in the United States (CATT), United Kingdom (IVAN), France (GEFAL), Germany (VIBERA), Austria (MANTA) and Norway (LUCAS). CATT is the largest trial, is funded by the National Eye Institute and is expected to be finished in early 2011. Other studies are due for completion in 2011 and 2012.

Photodynamic therapy with verteporfin is another AMD treatment, involving a verteporfin dye being injected into the eye. Activated by a laser in the presence of oxygen, it forms highly reactive, short-lived oxygen radicals, which damage the vascular endothelium, causing thrombosis of the neovascular tissue. This tissue retains the dye more effectively than the normal vessels. The treatment has been shown in randomised controlled studies to be effective for patients with certain types of choroidal neovascularisation (CNV) secondary to AMD.[28,29]

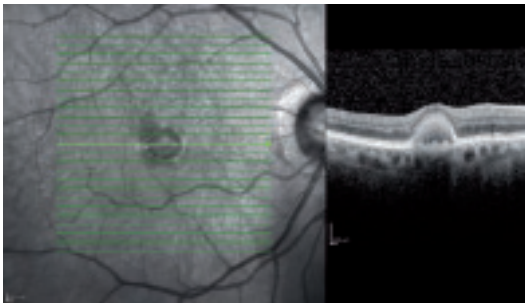
Thermal laser photocoagulation uses a thermal laser that is generated at a high energy to coagulate abnormal new choroidal blood vessels. This modality has been shown to cause focal damage to the overlying retina,[30] limiting its use to lesions outside of the central macula, for example, in patients with small extrafoveal choridal neovascularisation.[31]

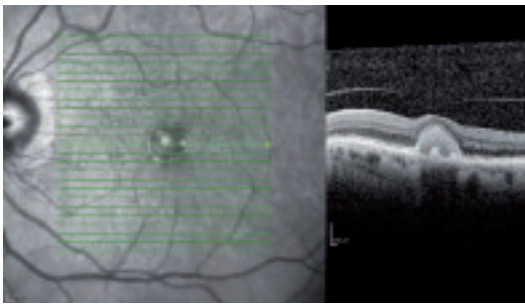
Submacular surgery has not been shown to have a positive risk-benefit ratio with higher rates of cataract and retinal detachment post surgery.[32] Macular translocation surgery, which also has insufficient evidence to support it, may be reserved for specific situations where pharmacological therapy has failed.[33] Statins have not been shown in recent RCTs to play a role in preventing or delaying the onset or progression of AMD.[34]

There are further treatments on the horizon for wet AMD, among which are topical antioxidant eye-drops, implantation of encapsulated human cells genetically modified to secrete ciliary neurotrophic factor, fetal cell transplantation,[35,36,37] topical angiogenesis inhibitor eye-drops such as pazopanib (tyrosine kinase inhibitor), VEGF trap and epimacular brachytherapy, implantable miniature telescopes for those with advanced AMD, and retinal prosthesis devices (known as bionic eyes). These are all still subject to clinical trials and there should be more outcome data available in the next few years.

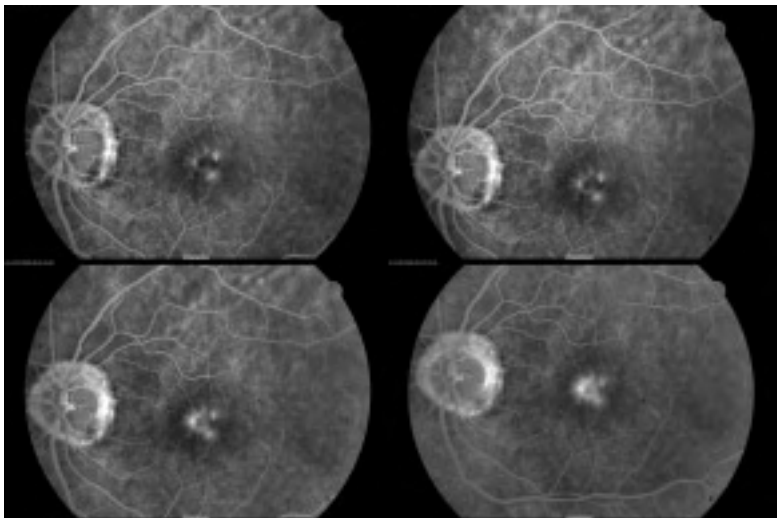
AMD prevention has a huge role to play in reducing the burden of this disease.

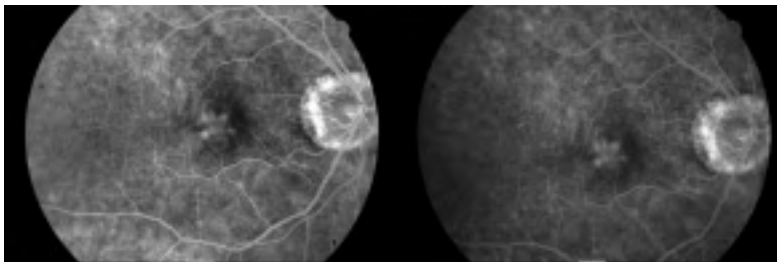
Modifiable risk factors such as smoking–which is known to increase the risk





Figures 3 and 4. Adult vitelliform mimicking a CNV: FFA of the left eye and right eye showing hyper fluorescence





Figures 5 and 6. OCT images show that the retina is dry in both left and right eyes

Slow the progression

From page 3

of progression from dry AMD to wet AMD–should be reduced. AMD costs Australia $2.6 billion a year and this figure is expected to grow to $6.5 billion in 2025.[38] People with AMD have an increased rate of hip fracture and depression.

Patients over the age of 50 years should be encouraged to have regular funduscopic examinations to detect early signs of this disease and thus prevent its progression. Appropriate and timely evaluation of patients suitable for treatment should follow. This should be a collaborative effort between the optometrist and ophthalmologist.

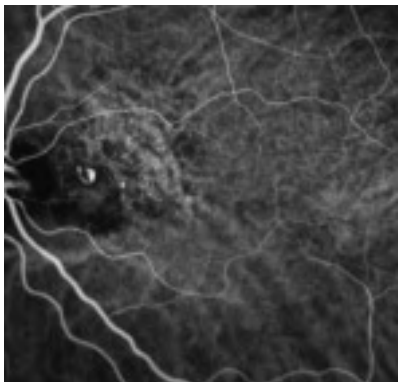
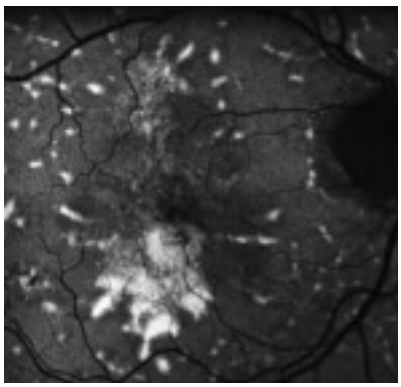
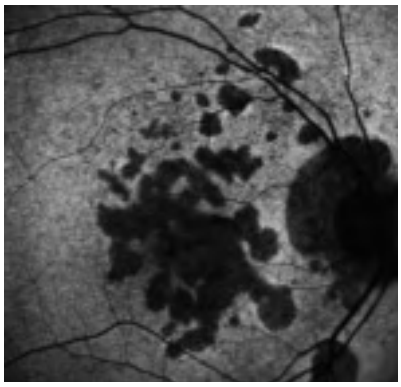


Figure 7. ICG of the left eye shows PCV





Figures 8 and 9. Fundus autofluorescence shows the lesion of (A) fundus flavimaculatis (pisciform lesions where the RPE is full of lipofuscin and thus lights up) (B) area of geographic atrophy (the areas that appear dark)

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Although the jury may still be out on whether bevacizumab is as effective as ranibizumab for treating neovascular AMD, physicians continue to use the drug off-label to good effect

Is there a difference?

Comparison of Lucentis and Avastin

Ashley Olson, BS
Leonid Skorin Jr
DO, OD, FAAO, FAOCO

Age-related macular degeneration is the leading cause of vision loss among the elderly in developed countries around the world. It is estimated that 30 per cent of adults over the age of 75 years have signs of the disease.[1] **The World Health Organization estimates that there are 14 million people worldwide suffering from blindness or severe vision loss due to AMD.**[2] **As the elderly population continues to grow in the coming years, these numbers will increase. There have been many advances in understanding AMD and determining how to treat it. A cure has not been discovered but options to slow its progression have improved dramatically within the past few years.**

There are two categories of AMD: non-exudative and exudative. Non-exudative AMD is more common, making up about 85 per cent of all cases. It is characterised by small hard drusen, large soft drusen, geographic atrophy of the retinal pigment epithelium (RPE), RPE clumping, decreased acuity, and an abnormal Amsler grid with central/paracentral scotomas or metamorphopsia.[3] Geographic atrophy within the foveal region causes the most vision loss with dry AMD.[2]

Exudative AMD is less common but has more serious visual consequences. Clinical manifestations include a subretinal or intraretinal haemorrhage, subretinal or intraretinal fluid, a pigment epithelial detachment, fibrovascular disciform scars, or macular edema[2,3] (Figure 1). The hallmark feature is the presence of a choroidal neovascular membrane (CNV) within the macula. This membrane often takes on a grey or yellow-green discoloration.

A CNV lesion is classified in two ways: classic or occult. A fluorescein angiogram is used to confirm the presence of CNV and any associated leakage that may be present[2] (Figure 2). A classic lesion demonstrates intense fluorescence during early stages with leakage in the late phase. Occult lesions exhibit less intense leakage during later stages of the fluorescein angiogram.[1,3]

Treatment options

Patients who are diagnosed with early dry AMD are encouraged to try lifestyle modifications to slow the progression of the disease. These modifications include taking vitamin and mineral supplements, smoking cessation, dietary changes and ultraviolet protection of the eyes. The Age Related Eye Disease Study (AREDS) concluded that taking vitamin and mineral supplements results in a 25 per cent reduction of progression to late AMD over five years.

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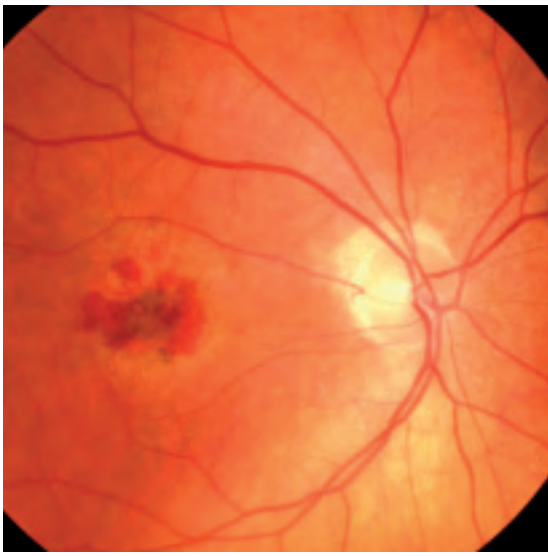

Figure 1. Neovascular AMD with a subretinal haemorrhage

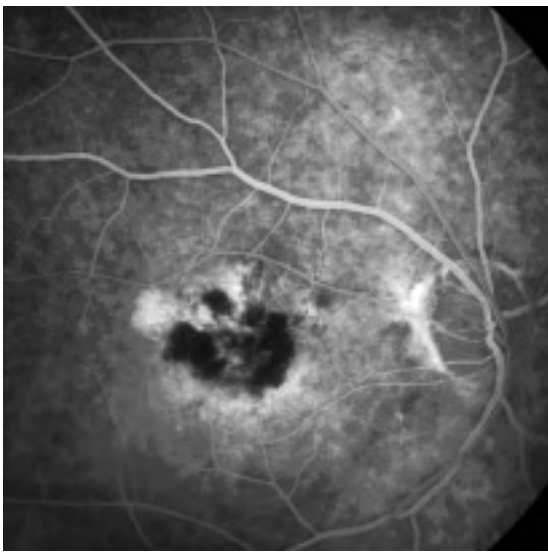

Figure 2. Fluorescein angiogram of neovascular AMD; blockage of fluorescence indicates a subretinal haemorrhage; hyperfluorescence signifies leakage of a CNV

Comparison of Lucentis and Avastin

From page 5

Antioxidants such as beta-carotene, vitamin C and vitamin E prove to be beneficial, along with zinc. A follow-up study titled AREDS II is evaluating the possible advantage of adding lutein, zeaxanthin and omega-3 fatty acids to the recommended vitamins and minerals.[1,2] The risk of progression to neovascular AMD intensifies as the severity of dry AMD increases, therefore slowing its progression is important.[2] If neovascular AMD develops, treatment options to prevent significant vision loss become more invasive.

Over the years there has been much improvement in the treatment of neovascular ARMD. In 2000, the United States Food and Drug Administration (FDA) approved photodynamic treatment (PDT) with verteporfin. Verteporfin is given intravenously and accumulates in the blood vessels. A non-thermal laser is then used to activate the drug, leading to localised damage to the endothelial cells of the CNV. This process occludes the CNV and prevents further vision loss. However, only about 16 per cent of patients showed an improvement in visual acuity from the treatment. This was a slight improvement from the previous thermal laser treatment.[1]

Further research has led to the current use of anti-angiogenic drugs for treatment of wet ARMD. Angiogenesis is the formation of new blood vessels, as seen in CNV. It is now known that the biologic modulator vascular endothelial growth factor A (VEGF-A) plays a critical role in the angiogenic process and pathological neovascularisation.[4] This correlation has led to the development of VEGF inhibitors to treat neovascular ARMD.

The first anti-VEGF drug approved for intravitreal injection by the FDA in 2004 for the treatment of neovascular ARMD was pegaptanib (Macugen).[1] This medication specifically targets one isotype of VEGF, VEGF-165, which is the most prevalent form of VEGF.[2]

One large-scale study evaluating the efficacy of pegaptanib was conducted by the VEGF Inhibition Study in Ocular Neovascularization (VISION) clinical trial group. Patients received intravitreal injections of pegaptanib or a sham injection at six-week intervals for 48 weeks. The majority of patients receiving pegaptanib injections had no further vision loss. Only six per cent had improved visual acuity.[5] There continues to be new developments in anti-VEGF drug therapy showing better efficacy in the treatment of wet ARMD.

The risk of progression to neovascular AMD intensifies as the severity of dry AMD increases, therefore slowing its progression is important. If neovascular AMD develops, treatment options to prevent significant vision loss become more invasive.

Ranibizumab

Ranibizumab (Lucentis) is a recombinant humanised monoclonal antibody fragment that neutralises all active forms of VEGF-A. It was approved by the FDA in 2006 for treatment of CNV in neovascular ARMD.[6] The advantage of ranibizumab over pegaptanib is its ability to target all of the active forms of VEGF-A, instead of targeting only VEGF-165.[1]

The Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) study was a large-scale study performed to evaluate the usefulness of ranibizumab for the treatment of minimally classic or occult CNV lesions. Patients were given intravitreal injections of 0.3 mg or 0.5 mg on a monthly basis for one year. The study showed a prevention of further vision loss in 95 per cent of patients. The main advantage of ranibizumab was that visual acuity improved in 25 per cent of the 0.3 mg cohort, and 34 per cent of the 0.5 mg cohort. This was the first treatment to show a significant amount of acuity improvement after one year of treatment.[6]

Another major clinical trial was performed to compare ranibizumab to verteporfin in the treatment of classic CNV. The Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) study group performed a randomised, double-blind, multicenter trial. Treatment with ranibizumab in this study was superior to the results of verteporfin therapy. Visual acuity increased by eight to 11 letters in patients receiving 0.3 or 0.5 mg injections of ranibizumab, whereas those receiving verteporfin lost over nine letters of visual acuity.[7]

Bevacizumab

Bevacizumab (Avastin) is also a humanised monoclonal antibody that targets all active forms of VEGF-A. It was the first anti-VEGF drug to be approved by the FDA in 2004 for the intravenous treatment of metastatic colorectal cancer.[8] Ranibizumab is an antibody binding site fragment derived from the same anti-VEGF antibody as bevacizumab. This similarity has led physicians to use bevacizumab off-label for the treatment of neovascular AMD. It has become the

leading treatment choice for neovascular AMD in certain countries, even as an off-label medication.[9]

The first patient treated in the United States with intravitreal bevacizumab for neovascular AMD responded well to the treatment, showing similar results to those of previous reports of systemic use of bevacizumab and intravitreal ranibizumab for neovascular AMD.[1] Since that initial report, many smaller studies have shown the benefits of using bevacizumab.[2]

Ranibizumab or bevacizumab?

There is no doubt that the current standard of care to treat neovascular AMD is intravitreal injections of ranibizumab or bevacizumab.[2] The debate lies in which drug is more beneficial to use based on safety, efficacy and frequency of administration.

The National Eye Institute in the United States is conducting the Comparison of Age-Related Macular Degneration Treatment Trial (CATT), a large head-to-head clinical trial evaluating the efficacy of ranibizumab and bevacizumab.

A study is also being conducted in Germany to evaluate the same concept. This is the Prevention of Vision Loss in Patient With Age-Related Macular Degeneration (AMD) by Intravitreal Injection of Bevacizumab and Ranibizumab (VIBERA) study. These studies aim to determine if there is a difference between the two medications being used to treat all forms of neovascular AMD. The results of the trials will not be available for at least two years.[11] In the meantime, physicians will continue to use bevacizumab off-label for treatment, making it important to appreciate that results have been obtained in smaller, retrospective and prospective studies.

A recent study published in 2009 directly compared two similar cohorts treated with ranibizumab and bevacizumab. The patients were given three intravitreal injections over a set period of time and evaluated one month after the third injection. They were then evaluated with an optical coherence tomographer to determine the central foveal thickness. Patients treated with three doses of ranibizumab had a greater reduction in macular volume compared to three doses of bevacizumab. Visual acuity was not measured directly in this study.[11]

Another study published in 2009 evaluated patients who had been started with three intravitreal injections of bevacizumab and switched to ranibizumab. The patients were evaluated after finishing bevacizumab and again when finishing ranibizumab. There was not an apparent difference in visual acuity outcome after the switch. Neither drug showed a strong advantage over the other.[12]

Two smaller studies looking at the short-term effectiveness of bevacizumab and ranibizumab showed no statistically significant difference between visual outcomes of either treatment option.

Gamulescu and colleagues did a retrospective study on 30 patients receiving a series of three injections every four weeks of 1.25 mg bevacizumab and 30 patients receiving 0.5 mg ranibizumab. Patients were evaluated from two to four months after the last injection. Similar improvement of visual acuity and reduction in central retinal thickness was seen in both groups.[13]

Subramanian and co-workers performed a randomised treatment of bevacizumab or ranibizumab. Patients were also given one injection every month for three months. They were then evaluated by optical coherence tomography to determine if further treatment was necessary. After six months, visual acuity and central macular thickness were evaluated. The treatment groups showed similar improvements and stabilisation in visual acuity.[14]

Conclusion

With the large treatment trials underway, smaller studies such as these present the best ideas available about the effectiveness of bevacizumab and ranibizumab. They do not definitively offer the clear answers that the CATT and VIBERA studies will provide concerning the comparison of safety and efficacy of the two treatments. Although the results of these studies are still a couple of years away, the current research can guide physicians to make better clinical decisions right now.

It is not uncommon for physicians to use medications such as bevacizumab off-label. Considering the comparable results of both treatment options, it is likely that off-label bevacizumab will continue to be used as treatment protocol for neovascular AMD.

Note: the treatments mentioned have been used in the management of AMD in Australia. Avastin is currently being used off-label.

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Early detection, prompt referral, timely treatment and regular follow-up for wet AMD are essential to achieve and maintain good visual outcomes with modern anti-VEGF therapy

Amsler grid distortion raises alarm

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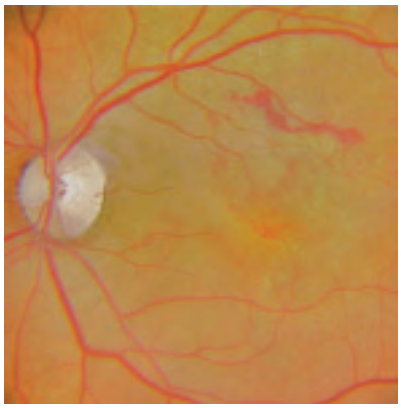

Figure 1. Left fundus photo showing wet AMD with macular haemorrhage, drusen and oedema

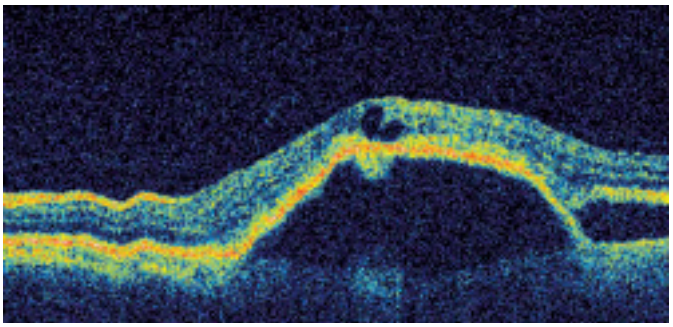

Figure 2. Left macular optical coherence tomography scan showing subfoveal pigment epithelial detachment with intraretinal and subretinal fluid

Anti-vascular endothelial growth factor (anti-VEGF) agents have revolutionised the treatment of wet age-related macular degeneration. The following case illustrates some important issues in the modern treatment of wet AMD.

Case history

Gwen, a 72-year-old female, consulted her optometrist after her sister had been diagnosed with AMD. Although she had no visual complaints, she was concerned about her risk of developing AMD. Her general health was excellent and she did not smoke. Gwen's visual acuity was 6/6 OU. Fundus examination revealed bilateral macular drusen and retinal pigment epithelial changes. The optometrist diagnosed dry AMD and instructed Gwen to monitor her vision every week with an Amsler grid. She was also advised to take supplements as recommended by the Age Related Eye Disease Study (AREDS) Research Group.[1]

Three months later, Gwen returned to her optometrist, reporting a two-week history of blurred left vision with distortion on the Amsler grid. Examination demonstrated VA of 6/6 OD, 6/60 OS and a left macular haemorrhage (Figure 1). Gwen was referred urgently to my practice on the same day.

Optical coherence tomography scanning showed a left pigment epithelial detachment (PED) (Figure 2). Fluorescein angiography revealed subfoveal choroidal neovascularisation (CNV) secondary to exudative AMD (Figure 3).

I initiated immediate treatment with intravitreal Lucentis (ranibizumab). Four weeks later, the PED was reduced and VA had improved to 6/36 OS. Intravitreal Lucentis was administered on a monthly basis over the subsequent 10 months, leading to progressive shrinkage and eventual disappearance of the PED with an improvement in VA to 6/6 OS (Figure 4). Gwen's VA had stabilised and she declined further treatment.

Six months later, Gwen returned complaining of a one-week history of reduced left vision. VA was 6/6 OD, 6/18 OS with a recurrent right macular haemorrhage, PED and CNV. Monthly left intravitreal Lucentis treatment was restarted, leading to an incomplete recovery of VA to 6/12 OS.

Three months later, Gwen reported a four-day history of reduced right vision. Assessment revealed VA of 6/12 OD, 6/12 OS with fluorescein angiographic evidence of right subfoveal CNV due to wet AMD. Treatment with right intravitreal Lucentis was commenced and VA improved to 6/9 OD.

Gwen is currently receiving monthly bilateral intravitreal Lucentis injections. To date, her VA has been maintained at 6/9 OD, 6/12 OS with a total of seven Lucentis injections in the right eye and 20 in the left eye.

This case highlights the following issues in the modern management of wet AMD.

- Optometrists play a vital role in the early detection and monitoring of AMD, as well as patient education regarding the condition.

Optometrists are ideally placed to counsel patients regarding lifestyle modification to minimise progression of AMD. Patients should be advised to avoid smoking and eat a diet rich in antioxidants and omega 3 fatty acids. Supplements such as those recommended by the AREDS Research Group should be recommended for patients with intermediate level AMD.[1]

- Patients with AMD can use the Amsler grid for self-monitoring of central vision.

Visual loss from wet AMD results from CNV. Regular monitoring with an Amsler grid can lead to early detection of CNV, which enables earlier treatment and better visual outcomes. Patients should be advised to seek urgent attention if they notice distortion on Amsler grid testing.

- Patients with wet AMD should be referred urgently to a retinal specialist for assessment and treatment.

Early treatment of wet AMD is vital to achieve optimal visual outcomes. CNV can cause permanent visual loss within days of onset, so referral of new patients with wet AMD to retinal specialists should be made urgently. Fluorescein angiography is required to diagnose CNV associated with wet AMD and is a mandatory investigation required for obtaining government funding of Lucentis treatment in Australia.

- Intravitreal anti-VEGF is effective for treatment of wet AMD.

The landmark MARINA and ANCHOR trials confirmed that treatment with the intravitreal anti-VEGF agent Lucentis is effective for wet AMD.[2,3] Lucentis stabilised vision in over 90 per cent of patients. About one in three patients gained three or more lines of vision with Lucentis treatment.

- Wet AMD may return following anti-VEGF therapy cessation.

Intravitreal anti-VEGF treatment is effective at reducing the activity of CNV but when treatment is stopped, CNV frequently becomes active again, often leading to further loss of vision. This is why it is important that all patients with wet AMD are monitored closely over the long term.

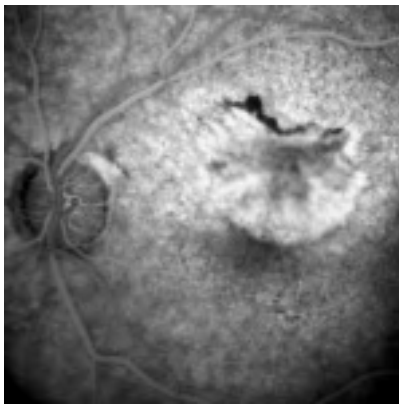

Figure 3. Left fluorescein angiogram showing subfoveal choroidal neovascularisation

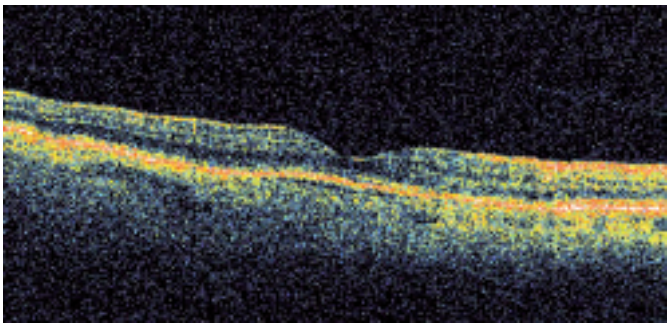

Figure 4. Left macular optical coherence tomography scan showing resolution of pigment epithelial detachment following 11 intravitreal Lucentis injections

- Repeated anti-VEGF treatment is needed to control CNV and maintain VA.

The sub-optimal visual results seen in many wet AMD patients treated with brief courses of intravitreal anti-VEGF agents has led many retinal specialists to favour regular monthly injections over short-term treatment regimes. A monthly treatment approach is considered to be the gold standard of treatment because it is the only regime supported by evidence from large randomised controlled clinical trials.

- Bilateral wet AMD occurs frequently.

The occurrence of CNV in one eye with wet AMD is a major risk factor for the development of CNV in the fellow eye, with a five-year risk of about 30 per cent. This is another reason why patients need careful long-term follow-up monitoring.

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AMD a complex

Genetic technology may enable you to counsel potential AMD patients and tailor treatment strategies based on their predicted response to medication

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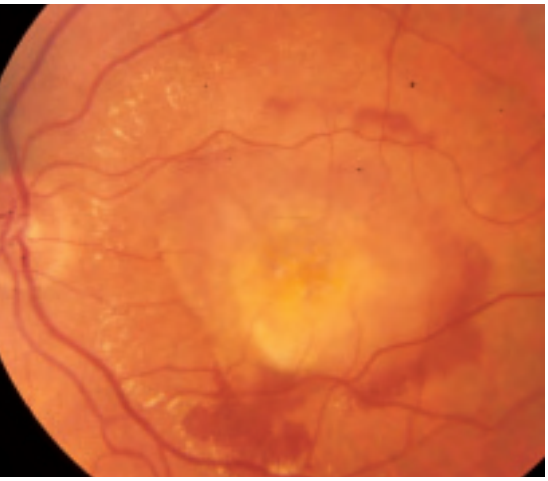

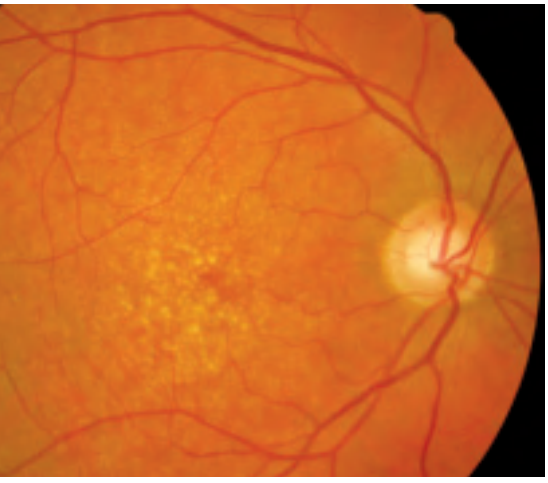

Photos: Khin Zaw Aung, CERA

Age-related macular degeneration is a progressive neurodegenerative disease primarily affecting the macular region of the retina.

It is now the most common cause of blindness in the elderly population in developed countries. The appearance of drusen—extracellular deposits of proteins and lipids under the retinal pigment epithelium (RPE)—is an early risk factor associated with AMD. As the disease progresses, drusen increase in size and number and become more confluent. In late stages of AMD, atrophy of the RPE (geographic atrophy) and/or development of new blood vessels (neovascularisation) result in photoreceptor cell death and central vision loss. Identification of the factors that drive disease progression and the reasons for a patient developing either geographic atrophy or neovascular disease are still not clearly understood.

Complex genetic diseases

AMD is a multifactorial or complex genetic disease in which both a genetic component and environmental influences such as age, smoking and diet will influence the development of the disease.[1] Most common diseases in our society such as heart disease, dementia and diabetes follow this pattern, in contrast to a disease with an established mendelian or 'monogenic' mode of inheritance such as cystic fibrosis or some inherited retinal dystrophies. A definitive measure of the heritability of a complex disease is unattainable, as the precise extent to which genes determine inter-individual differences in risk varies between populations and over time.

While early studies attempting to identify AMD genes came from the examination of families, it became apparent that the lack of large families consisting of multiple generations limited this approach. As a consequence, 'candidate gene approaches' were used based on the likely biological role of a gene as well as its gene expression within the retina. While this approach led to the identification of several genes causing other rare retinal disease such as Malattia Leventinese and Doynes honeycomb dystrophy, the implicated genes did not appear to be responsible for any significant proportion of AMD.[2] Some success was achieved with looking at genes that had been identified in causing other chronic ageing diseases with the apolipoprotein gene (APOE) being identified as an AMD risk gene.[3,4]

Recent rapid advances in genetic technology have now taken this a step further in allowing the interrogation of the entire genome through the use of genome wide-association studies (GWAS). These studies are based on the use of up to one million genetic variants—also known as single nucleotide polymorphisms (SNPs)—and examine whether there is an increased or decreased frequency of specific genetic markers in disease cases compared to control individuals (no disease).[5]

Success in gene discovery

To date, GWAS have identified a number of variants associated with complex diseases but typically these explain only a very small fraction of the heritability of most of these disorders. AMD on the other hand stands alone as a relative success where it is now estimated that SNPs in a handful of genes account for about 76 per cent of attributable risk of the development of AMD.[6]

Probably the most studied gene in AMD is CFH (complement factor H) located on chromosome 1q31. Identification of this gene confirmed the complement pathway's involvement in the aetiology of AMD. The complement system performs an essential role in the interplay between adaptive and innate immunity and contributes to overall physiological homeostasis by eliminating damaged, necrotic and apoptotic cells. Abnormalities in the structures and functions of complement pathway regulatory proteins can lead to an imbalance in normal homeostasis of the complement system, often resulting in 'bystander' damage to healthy

genetic disease

cells and tissues. This phenomenon accounts for substantial tissue damage in a variety of complement-mediated disease, including Alzheimer's disease and atherosclerosis.[7]

The hypothesis that immunity and inflammation have important roles in AMD formed following in vitro immunocytochemical analyses on drusen, which were found to contain several components of inflammatory processes, particularly the complement pathway. It was strengthened by five genetic studies published concurrently in 2005[8,9,10,11,12] which identified that a polymorphism rs1061170 (representing a tyrosine → histidine change at amino acid 402, that is, Y402H) in the CFH gene was associated with an increased risk of AMD.

The subsequent consistent replication of CFH risk in diverse studies prompted studies examining the role of other related genes in the complement pathway. Variants in genes coding for complement factor B (CFB), complement component 2 (C2), and complement component 3 (C3) proteins have been discovered and also shown to be associated with AMD risk as well as protection. Other studies have documented a large, common deletion encompassing the complement factor H–related 1(CFHR1) and complement factor H–related 3 (CFHR3) genes.[13]

Not all AMD associated genes are complement related. Two genes (LOC387715/ARMS2 and PRS11/HTRA1) on chromosome10q26 also appear strongly associated with AMD but their role in AMD is not yet fully understood.[6] Another gene not associated with the complement pathway is APOE, which has been found to have modest associations with both prevalent AMD as well as progression.[3,4]

Using genetic knowledge to help patients

A study in America demonstrated that having the high risk genotype at the three loci CFH, ARMS2 and C3 increases the risk of disease by 14 times when compared to the general population. Another study looking at these three genes and an additional gene (CFB/C2) showed that the predictive testing for these genes was 86 per cent, and having no high risk alleles at any of these genes reduced the risk of developing late-stage AMD by the age of 80 years to less than one per cent.[6] These results cannot necessarily be extrapolated to all populations, but they strengthen the potential of genetic tests in risk stratification of AMD.

An increased understanding of the genetics behind the disease will clearly lead to an increased understanding or the pathogenic pathways involved in disease aetiology and can assist in estimating risks and tailoring treatment for individuals, and aid in developing new treatment strategies.

The important new information relating AMD pathology to complement dysfunction derived from genetic studies is being used by numerous commercial companies in the process of developing genetically based and complement-targeted therapeutics. These will modify complement-related AMD disease processes, acting either systemically such as eculizumab, or as intraocular preparations such as compstatin/POT-4—both of these are being trialled in geographic atrophy.[14]

The ability to stratify risk of disease, and risk and rate of progression based on genetic risk profile would be useful to practitioners. Recently the possibility that a patient's genotype might also influence the response to treatment for neovascular or wet AMD has added further interest in determining a person's genotype. Results from these and further studies will help to appropriately direct health-care resources to people likely to benefit from treatment, and allow those who would not benefit to avoid the risks, inconvenience and possible personal costs of interventions.

Screening patients at a preclinical stage for risk of a genetic disease may afford an opportunity to prevent or attenuate the disease later in life. Knowledge of an individual's genetic AMD risk should permit counselling of potential AMD patients regarding risk factor modification before they have clinical disease; and inform health-care practitioners of individuals who are at highest risk and therefore require more frequent eye examination to screen for AMD, and which patients are sufficiently low risk that the costs of repeated examination may be avoided. Routine clinical screening for AMD is not yet available and no formal screening program exists worldwide.

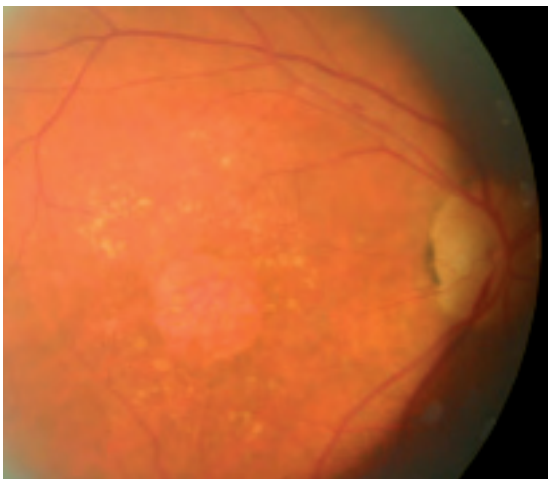

Photo: Khin Zaw Aung, CERA

As our knowledge increases about the important role that genes appear to play in many aspects of AMD and its management, it may not be long before pharmacogenetics and personalised medicine becomes a reality, leading to improvements in screening, diagnosis, prognostication, therapy and prevention.

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Miracle drug a double-edged sword

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Anti-VEGF agents have revolutionised the treatment of wet AMD, resulting in visual stabilisation or even improvement in patients who would previously have lost their vision. To obtain the impressive results observed in randomised clinical trials, monthly intravitreal Lucentis injections are required.[1,2,3] This places an enormous burden on patients and their families, and increases the risk of side-effects. Despite such intensive treatment, a minority of patients still experience visual deterioration.

Further refinement of anti-VEGF treatment is required. There are two issues critical to the future of wet AMD management.

- Frequency of treatment–can we reduce the number of injections without sacrificing visual outcomes?
- Efficacy of treatment–can we improve results by altering the dose or type of anti-VEGF agent used?

Injection frequency

Randomised controlled trials show that administering Lucentis less frequently can result in inferior visual outcomes.[4] If injections are given every three months (after the first three monthly injections), the mean visual improvement is lost within a year, although the visual results are still superior to sham treatments.

Clinical experience suggests that a subset of patients do well despite less regular treatment, and for many patients ongoing monthly injections are not a practical option. The following treatment regimens are commonly employed as alternatives to fixed monthly injections.

Treat and observe (PRN)

Method. Administer monthly injections for three months. Maintain ongoing monthly reviews thereafter, but continue reinjection only if strict criteria are met: worsening of visual, fluid on OCT, leakage on FFA and presence of a new haemorrhage.[5,6,7]

Advantages. Fewer injections are required over two years (average of 9.9 injections in the PrONTO study[6]) yet small non-randomised trials show outcomes similar to those of monthly injections.[5,6]

Disadvantages. The patient still has the burden of having to visit an ophthalmologist every month. In addition, visual or clinical deterioration must occur before treatment is given. There is the potential for macular damage each time deterioration occurs.

Treat and extend

Method. Administer monthly injections for at least three months and until the macula is dry. The injection intervals are then gradually extended with the objective of prolonging treatment for the longest time between intervals while still keeping the macula dry.[8]

Advantages. Fewer injections are required over a two-year period, and fewer visits to the ophthalmologist decrease markedly the burden placed on the patient and the health-care system. This method also aims to keep the macula dry rather than wait for deterioration.

Disadvantages. Deterioration must occur at least once to determine the treatment interval. There is risk of visual deterioration due to interval haemorrhaging if treatment intervals are too long.[9] For this reason many ophthalmologists do not extend the intervals greater than three to four months. In addition, there may be a risk of overtreating as treatment is given when the macula is dry.

Improving treatment efficacy

Predicting visual outcomes with Lucentis treatment is notoriously difficult and vision can still deteriorate despite early intensive therapy. Many new therapies are under investigation to improve the visual outcomes and at the same time potentially decrease treatment frequency. The major current trials are summarised below.

- **Increased Lucentis strength: the HARBOR trial.**

This trial compares the standard 0.5 mg Lucentis dose with a 2.0 mg dose (more concentrated but the same volume). Both doses are being administered on fixed and prn schedules, so the trial will be helpful in determining optimal injection frequency. A concern with the higher dose is whether the risk of systemic thrombotic events such as stroke and heart attack will be increased. The trial reports in 2013.

- **Alternative anti-VEGF agents: VEGF Trap-Eye**

Unlike Lucentis, which is an antibody fragment, VEGF Trap-Eye is a soluble VEGF receptor. VEGF Trap-Eye has a higher binding affinity for VEGF and also blocks another angiogenic agent, platelet derived growth factor.[10,11] Two phase 3 clinical trials comparing VEGF Trap-Eye to Lucentis (VIEW 1 and VIEW 2) will be reporting in 2011.

- **Avastin verses Lucentis**

The CATT trial compares Lucentis directly with Avastin as well as fixed dosing schedules with prn.

- **Other strategies**

Other studies will determine whether combining anti-VEGF agents with other modalities such as photodynamic therapy or intravitreal steroids can result in increased efficacy or duration of action.[11,12]

Clinical practice

While monthly Lucentis remains the gold-standard treatment for wet AMD, many ophthalmologists frequently employ alternative strategies in an attempt to individualise treatment. It is possible that schedules other than fixed monthly treatment may be compromising visual outcomes. Reassuringly, a recent study published by a group of Australian retinal practices suggests that real-world treatment employing these various treatment strategies can achieve results comparable with the randomised trials.[13]

The studies reporting over the next few years will clarify these issues further. In the future, it is hoped that novel agents will target AMD earlier in the disease process, potentially averting the neovascular stage altogether. In the foreseeable future anti-VEGF agents are likely to remain the cornerstone of wet AMD treatment so optimisation of these therapies is vital.

Case report

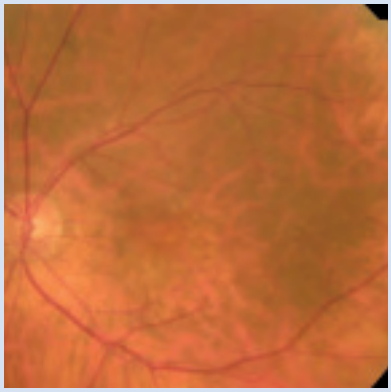

Figure 1. May 2006: fundus photograph of right eye (visual acuity count fingers at one metre); there is a small central subfoveal scar, with pigment clumping

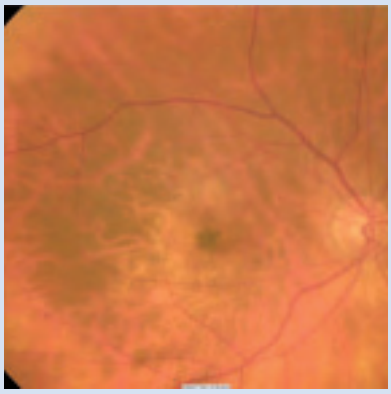

Figure 2. May 2006: fundus photograph of the left eye (visual acuity 6/18, N10) showing left subfoveal fluid without haemorrhage, and scattered drusen

In 2004, a 76-year-old female presented with a three-week history of right visual deterioration. Her general health was otherwise good. Her visual acuities were right 6/18, left 6/9, N6 and she was found to have right subfoveal fluid secondary to wet AMD with a few scattered drusen in the left eye. Fluorescein angiography confirmed an occult pattern of choroidal neovascularisation.

At the time no effective treatment was available. Six months later, her right visual acuity deteriorated subacutely to 6/30 and repeat fluorescein angiography confirmed that the lesion had become predominantly classic. She was treated with four courses of photodynamic therapy (PDT) but her right vision deteriorated to count fingers at one metre, with a small subfoveal scar.

In May 2006 she re-presented with two weeks of left eye distortion and blur, and her left visual acuity had decreased to 6/15, N10, with central subfoveal fluid but no haemorrhage. Fluorescein angiography revealed an occult pattern of choroidal neovascularisation, so she was not eligible for photodynamic therapy. She was granted Special Access Scheme approval of Lucentis and was first treated in June 2006.

Since that time, she has been having ongoing Lucentis injections every six weeks. She subsequently underwent left uncomplicated cataract surgery and lens implant, and her left visual acuity is now 6/6, N5. The plan is to continue six-weekly left intravitreal Lucentis injections indefinitely.

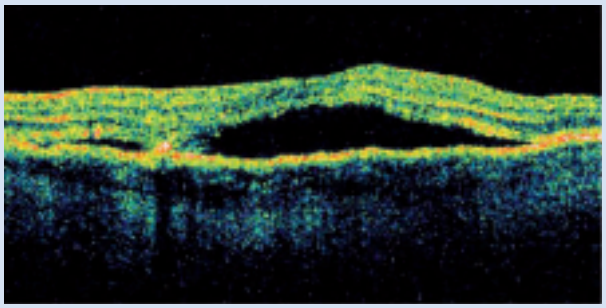

Figure 3. May 2006: time-domain OCT of the left macula, showing subfoveal fluid secondary to occult choroidal neovascularisation

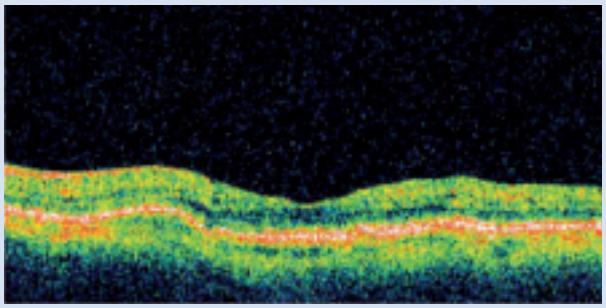

Figure 4. October 2008: Time-domain OCT of the left macula; Lucentis injections every six weeks have resulted in complete resolution of subfoveal fluid

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Lid disease more

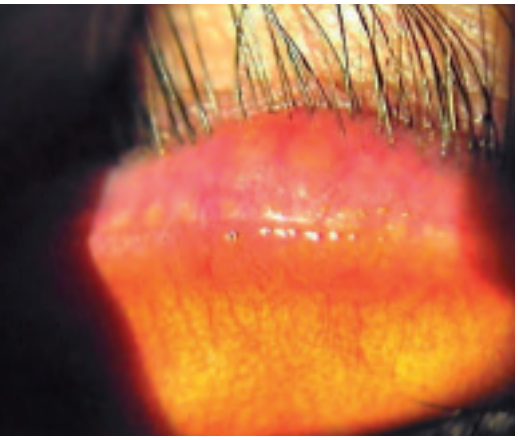

Figure 1. Right upper lid meibomian gland dysfunction; note the external hordeoleum at the base of the lashes

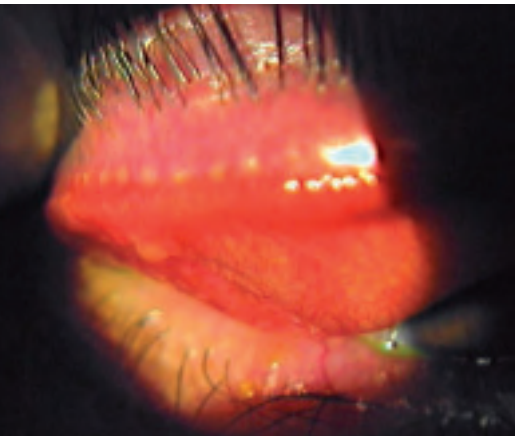

Figure 2. Marked tylosis (thickening of the lid margin) and inspissated meibomian glands with capped gland orifices

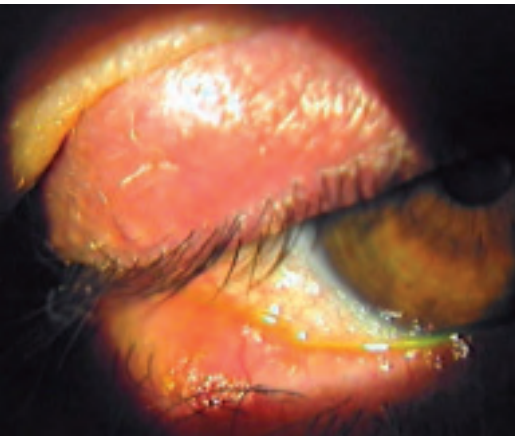

Figure 3. Right upper lid internal chalazion

Case report

Presentation

A 68-year-old male presented with a recent history of red, inflamed and sore eyelids. He was a long-term patient of our practice, with a past ocular history of bilateral cataract surgery and primary open angle glaucoma in both eyes. The patient's glaucoma had been treated with timolol 0.5% eye-drops for many years but he had been changed to Xalatan (latanoprost 0.005%) when his target pressures were no longer being met. His medical history was normal other than for well-controlled systemic hypertension.

Examination

External examination showed erythematous and inflamed upper and lower eyelid margins on both sides. Slitlamp evaluation revealed meibomian gland dysfunction with inspissation (thickening) of the meibomian secretions, capping of the gland orifices and tylosis (broadening) of the lid margins (Figures 1 and 2). There was a small hordeoleum of the R upper eyelid but no significant flakes and collarets at the base of the lashes. The conjunctiva was also inflamed but there was no staining or infiltration of the corneas. Examination of the ocular adnexa revealed a malar rash across the nose and upper cheeks on both sides.

Very mild lid disease had been noted at previous examinations but the patient had always been asymptomatic in the past.

Diagnosis

A provisional diagnosis of posterior blepharitis (meibomitis) was made.

Meibomian gland dysfunction and inflammation are attributed to biochemical changes to the lipid contents of the glands, causing the oily secretions to thicken, which clogs the glands and encourages excessive bacterial colonisation of the meibomian glands and lid margins. The ocular sequelae include lipid-deficiency dry eye, conjunctival inflammation and marginal keratitis of the peri-limbal cornea.

It was suspected that the meibomian gland dysfunction had worsened due to the addition of latanoprost to the existing glaucoma medications. Latanoprost is a prostoglandin analogue, which increases the levels of inflammatory mediators in the eye, thus exacerbating the existing lid disease and increasing the signs and symptoms of redness, heat, burning and pain.

Initial treatment

Treatment was initiated to relieve the congestion in the meibomian glands. This consisted of hot compresses with lid massage qid, and lid margin hygiene to decrease bacterial load with Steri-Lid anti-bacterial foam. A mild topical steroid eye-drop (FML 0.1%) was also added to reduce inflammation of the eyelid margins and ocular surface.

On review two weeks later, there was a worsening of the lid disease in the form of several large internal chalazia of the R upper lid (Figures 3 and 4), R lower lid (Figure 5) and L lower lid (Figure 6). There were also several large pustules on the R side of the nose and upper R cheek within the area of the malar butterfly rash.

Discussion

Given the new ocular and dermal signs, the provisional diagnosis was changed to that of oculo-cutaneous rosacea.

Rosacea is a dermatologic condition affecting the oil glands of the face (sebaceous glands) and oil glands of the eyelids (meibomian glands). The exact cause is unknown but it is suspected to be due to problems with synthesis of the lipid contents of the glands, leading to changes in lipid chemistry, such as an increase in the melting point of the oils and production of free

If topical eye-drop and lid hygiene therapy prove ineffective to treat the symptoms of lid disease, consider the possibility of rosacea

than skin deep

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fatty acids. Because the oils no longer melt at normal body temperature, the glands become congested, swollen and infected, leading to the typical signs of rosacea and meibomian gland dysfunction.

Topical eye-drop and lid hygiene therapy are often insufficient to treat the signs and symptoms of this disease during its active phase. Rosacea responds well to systemic antiobiotic therapy with the tertacycline class of antiobiotics (tetracycline, doxycycline, minocycline). Their exact mode of action is unknown but the drugs are believed to have an anti-inflammatory effect in low doses, as well as their antibiotic properties in higher dosages. It is also claimed that the drugs modify the lipid synthesis process, leading to more normal sebaceous and meibomian gland lipid secretions.

Doxycycline is typically the drug of choice in adults; it is easy to use as it is not affected by food intake and does not have to be taken on an empty stomach. It is contraindicated in young children due to the possibility of affecting bone and teeth formation, and those with a history of medical allergy to another drug in the same class. The drug takes a number of months to positively affect the course of the disease and patients need to be warned that their symptoms will not improve immediately. Typical starting dosage is 50 mg daily for four to six weeks, which can be reduced to 25 mg for long-term control of the condition.

As there were no medical contraindications to the use of doxycycline, in conjunction with his general practitioner the patient was started on low-dose oral doxycycline as well as Rozex gel for his cutaneous rosacea. Rozex contains an anti-protozoal antibiotic (metronidazole), which has a positive effect on the erythema and pustules that scar the facial regions of rosacea sufferers. The patient was warned to avoid certain triggers that exacerbate rosacea such as hot or spicy foods and alcohol, as well as avoiding sun exposure because the skin can become photosensitised when using oral tetracycline class drugs.

On review six weeks later, the facial signs had cleared considerably but the eyelid chalazia were still present. The patient was referred to an oculoplastic surgeon for surgical excision of the chalazia that were on the internal surfaces of the eyelid and causing discomfort to the patient. The patient was tolerating the oral doxycycline well, without stomach upset or diarrhoea, so he was placed on a maintenance dose of the drug.

The patient has continued to use the doxycycline continually for the past eight years, because the facial signs of rosacea return rapidly whenever he attempts to stop the medication. He attends our practice for glaucoma review every three months and to have some aberrant lashes removed as he was left with trichiasis due to ciccatricial changes to the eyelids following chalazion surgery (Figure 7).

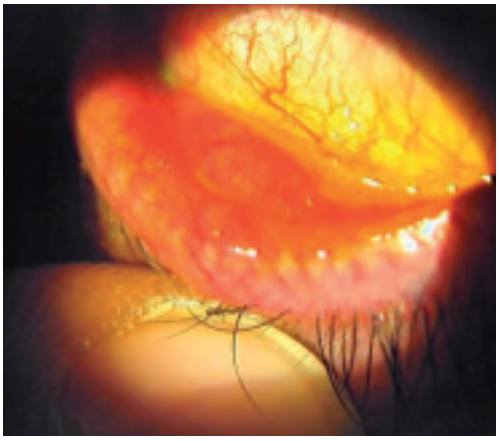

Figure 4. Right upper lid inferior edge of internal chalazion

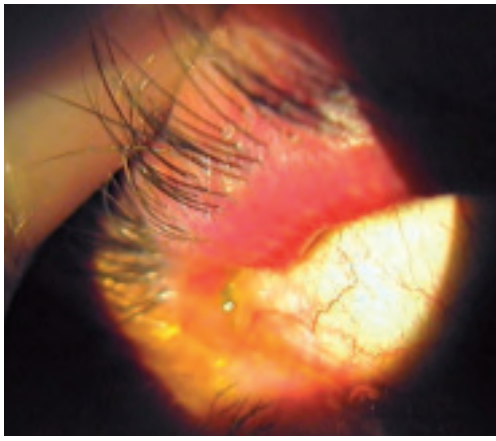

Figure 5. Right lower lid internal chalazion

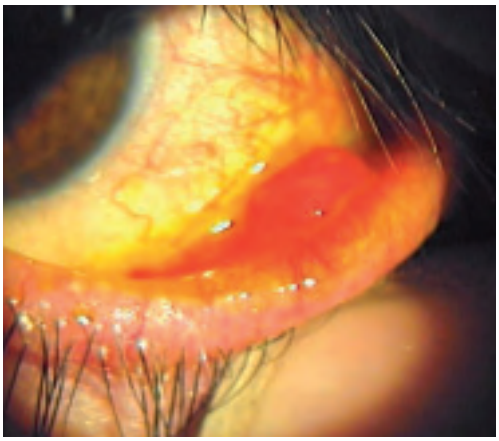

Figure 6. Left lower lid internal chalazion

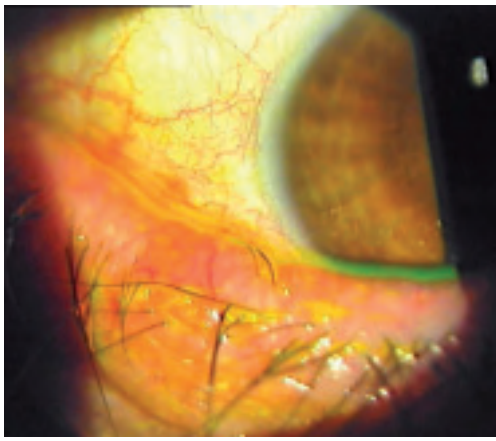

Figure 7. Trichiasis secondary to surgical excision of chalazion

Drug response different

Whether in drop or systemic form, ophthalmic medications can have side-effects in children that differ substantially from those in adults

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Serious adverse effects and differences in efficacy mean that prescribing ophthalmic medications for children can be different from prescribing for adults.

Seemingly innocuous medications in adults can be surprisingly harmful to children. For example, common over-the-counter cough and cold medications have been rescheduled to prescription-only for children under two years of age by the Therapeutic Goods Administration.[1]

This article discusses anti-glaucoma preparations, antibiotic medications, anti-inflammatory and anti-allergy agents, mydriatic and cycloplegic agents and local anaesthetic agents.

Anti-glaucoma preparations

Topical glaucoma medications fall into four broad categories.

- Prostaglandin analogues such as latanaprost, travoprost and bimatoprost
- Beta-blockers such as timolol and betaxolol
- Alpha-2-adrenoreceptor agonists such as brimonidine and apraclonidine
- Carbonic anhydrase inhibitors (CAI) such as brinzolomide, dorzolamide and acetazolomide.

There is a variation in opinion among practitioners regarding which medication to use, particularly in the first instance.

Prostaglandin analogues

The prostaglandin analogues have a good safety profile. They are used only once per day, which means they are convenient and have a reasonable compliance. Long-term effects include hypertrichiasis and iris hyperpigmentation. The issue of darkening of the irises needs to be carefully apprised with parents. It may be upsetting to them if their child's blue eyes become brown. Alternatively, if only one eye is treated, then the heterochromia may be disconcerting. These are important facts to discuss.

Beta-blockers

Timolol 0.25% is widely used. Systemic absorption can lead to side-effects relating to beta adrenergic receptor blockage including hypersomnolence, bradycardia and respiratory compromise. This can occur particularly in asthmatics so they are best avoided by patients with known cardiorespiratory problems. Using beta-blocking drugs should also be avoided in premature infants, although sometimes they can be used carefully in full-term infants with glaucoma.

A new use of beta-blocking agents in ophthalmology is for capillary haemangiomas in infants and young children.[2] Orbital and periorbital haemangiomas can cause astigmatism and subsequent amblyopia. Systemic and topical beta-blocking agents are being used more frequently to treat haemangiomas in children. Their use needs to be monitored by a paediatrician.

Alpha-2-adrenoreceptor agonists

Alpha-2-adrenoreceptor agonists, in particular brimonidine, needs to be avoided in young children. CNS depression and excessive drowsiness are not rare side-effects.[3] Most ophthalmologists avoid using it in children younger than eight to 10 years of age. When used in older children, it can cause conjunctival hyperaemia and irritation, which in some cases can lead to cessation of use or poor compliance.

Carbonic anhydrase inhibitors

Topical carbonic anhydrase inhibitors can have a synergistic effect when combined with other intraocular pressure lowering medications. They are generally well tolerated and have few ocular side-effects. Systemic absorption from topical administration does not appear to have significant side-effects.

Systemic use of carbonic anhydrase inhibitors, such as acetazolamide, can lead to significant side-effects. The most serious are metabolic acidosis, dehydration and renal stones. It is also important to note if a patient is allergic to sulphur medication because there is a weak association with acetazolamide. Children tolerate acetazolamide much better than adults. Acetazolamide is used extensively in children with benign intracranial hypertension. Children tend not to complain of paraesthesia, which adults often notice even after one dose of the medication, and are also less prone to running into the problem of hypokalaemia, which is a common issue in adults on acetazolamide.

Antibiotic drugs

Some Australian states and other countries apply topical agents to the eyes of newborns to prevent ophthalmia neonatorum. One agent used is silver nitrate. Chemical conjunctivitis is a reported side-effect. Erythromycin ointment is commonly used in the USA, whereas chloramphenicol ointment and povidone-iodine eye-drops are also used elsewhere. Recently in the USA there was a shortage of erythromycin ointment. Gentamicin ointment was used and cases of periocular dermatitis were reported.[4]

Topical chloramphenicol is used exten-

in children

sively across all age groups in Australia and many other countries. In the USA it is barely used due to the perceived risk of aplastic anaemia.[5] Chloramphenicol drops are frequently the first choice for treatment of bacterial conjunctivitis in children in Australia. It is used in children and adults extensively during the post-operative period of cataract surgery, strabismus surgery and nasolacrimal surgery.

Quinolones such as ciprofloxacin exhibit some chondrotoxicity and can damage epiphyseal growth plates.[6] Unless essential, alternatives in children are used.

Anti-inflammatory agents and anti-allergy agents

Steroids are used topically, peri-ocularly and systemically for control of inflammatory conditions such as uveitis, post-operative inflammation and uveitis.

The adverse effects of systemic steroids include growth retardation, weight gain, glucose intolerance and susceptibility to infections. Ocular side-effects of systemic use include raised intraocular pressure and posterior subcapsular cataracts. Ophthalmic surgeons use periocular steroids in children less often due to the risk of causing raised intraocular pressure. Topical use predisposes to microbial infection by way of suppressing local immunity.

Anti-allergy drugs, which include those that act as an antihistamine, mast cell stabiliser and/or inhibitor of inflammatory mediators tend not to be used in children younger than three years of age.

Mydriatic and cycloplegic agents

Mydriatic drop regimens can be very toxic in infants and children. It is instructive to consider regimens for the smallest infants. At the Royal Children's Hospital in Melbourne, the mydriatic eye-drop used for premature infants is cyclopentolate 0.25%/phenylephrine 2.5%. This eye-drop is given about one hour prior to the examination and repeated 10 minutes after the first dose. Other neonatal units have slight variations that may include tropicamide 0.33% or less.

Mydriatics in infants

Cyclopentolate is an anticholinergic drug. Reported side-effects include grand-mal seizure,[7] psychotic reactions (in children),[8] and gastro-intestinal toxicity including death from necrotising enterocolitis after six drops of 1% (in an infant).[9]

Phenylephrine is a sympathomimetic/adrenergic drug. Reported side-effects include increased blood pressure.

Tropicamide is an anticholinergic/para-sympatholytic. Reported side-effects include gastro-intestinal problems (more pronounced in children).[10]

Atropine is an anticholinergic/para-sympatholytic (anti-muscarinic) drug. Reported side-effects include increased heart rate (in any age-group but more pronounced in children),[10] gastro-intestinal,[10] atropine flush/fever (more pronounced in children) and acute confusional psychosis.

Homatropine is an anticholinergic/para-sympatholytic drug with side-effects similar to but weaker than those of atropine.

Mydriatic drops can have profound side-effects in young infants that are different from those in adults. It is important to consider the risks before dilating the pupils of young infants.

Local anaesthetic agents

Parents and carers need to be given advice when children have local anaesthetics instilled. Due to the loss of sensitivity, eye rubbing can cause extensive corneal epithelial damage without the child feeling initially any discomfort.

Topical anaesthesia partly achieves its actions through breakdown of the ocular surface epithelium, improving its penetration and efficacy. Repeated use can readily cause loss of the protective epithelium, leading to substantial pain, photophobia and corneal decompensation. In general, patients must not be given topical anaesthesia to take home as a form of analgesia.

Conclusion

Ophthalmic medications, whether in drop or systemic form, have side-effects in children that can be completely different from those in adults. It is important to be mindful of potential problems in different age groups. There is no substitute for judicious drug prescription, regular follow-up examinations and early referral where indicated.

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Abstracts

Sensitivity to DE reduced

Study reveals that Cyclosporine A, a potent immunosuppressive drug, can suppress inflammation, restore tear function and improve ocular surface integrity in dry eye.

The study has evaluated the effect of topical cyclosporine on corneal and conjunctival mechanical sensitivity in patients with established dry eye disease that was unresponsive to artificial tears. Thirty-seven dry-eye patients were compared with age-matched controls (n = 35).

Topical cyclosporine A 0.05% was used twice daily, with pre- and post-treatment (one-, three- and six-month) evaluations involving corneal and conjunctival sensitivity, subjective symptom scoring, fluorescein and lissamine green staining, Schirmer test and tear break-up time.

Mechanical sensitivity of the ocular surface was significantly reduced to tactile stimuli in chronic dry eye disease; corneal sensitivity improved significantly following three and six months of cyclosporine treatment. The authors proposed a potential mechanism of action involving a neurotrophic effect on the corneal nerves. *Cornea* 2010 Feb; 29: 2: 133-140.

Behind the laser flap

Dry eye associated with laser-assisted in *situ* keratomileusis (LASIK) was found to be more prevalent in mechanical microkeratome than femtosecond laser.

Dry eye is one of the most common post-operative complications of LASIK, affecting approximately 50 per cent of patients.

A study conducted at the Cole Eye Institute (Cleveland, Ohio, USA) compared the incidence of LASIK-associated dry eye and the need for cyclosporine-A therapy after flap creation with Intralase femtosecond laser (n = 113) versus a mechanical microkeratome (n = 70).

Examined eyes had no pre-operative dry eye signs or symptoms and were randomised to flap creation. Mean central flap thickness was significantly greater in the microkeratome group (131 ± 25 (sd) μM vs. 111 ± 14 μM, $p < 0.01$). The incidence of LASIK-induced dry eye was significantly ($p < 0.01$) higher in the microkeratome (46 per cent) than in the femtosecond (eight per cent) cohort.

Femtosecond laser flap creation resulted in reduced post-LASIK dry eye. The authors proposed that in addition to neurotrophic effects from corneal nerve cutting, other factors may be involved in the aetiology of microkeratome-induced dry eye, as there was no correlation between thick flaps (deeper ablation depth) and a higher incidence of dry eye. *J Cataract Refract Surg* 2009; 35: 10: 1756-1760.

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C. *pneumoniae* increases risk of AMD

Chlamydia pneumoniae, a prokaryotic pathogen that causes chronic inflammation, is recognised as a risk factor for cardiovascular diseases, according to study.

Choroidal neovascularization (CNV) is directly related to visual loss in age-related macular degeneration and other macular disorders.

This study investigated the association between C. *pneuominae* infection and AMD using a laser-induced CNV mouse model. Vitreous injection of the C. *pneuomiae* antigen was found to increase the extent of CNV. The ability for C. *pneumoniae* to trigger an ocular inflammatory response and promote abnormal vascular growth was found to occur via a specific pathway involving the Toll-like-2 receptor residing in the retinal pigment epithelium.

These data provide experimental evidence to imply that persistent C. *pneumoniae* infection is a risk factor for AMD.

Invest Ophthalmol Vis Sci 2010; Apr 14. (Epub ahead of print).

Transport to glaucoma

A study has found, for the first time, the presence of distal transport loss and axon pathology prior to glaucomatous retinal ganglion cell degeneration. Distal axonopathy is a feature shared by other neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease.

It was found that where retinal ganglion cells terminate in the superior colliculus, a reduction in active transport followed a retinotopic pattern resembling glaucomatous visual field loss. As in glaucoma, susceptibility to transport deficits was found to increase with age and was not specifically associated with elevated intraocular pressure.

Distal transport loss was observed to occur prior to evidence of degenerative change in proximal pathways (optic nerve head and retina), and therefore may present an early therapeutic target for glaucoma management.

Proc Natl Acad Sci USA 2010; 107: 11: 5196-5201.

Retina hotline

Researches at the department of ophthalmology, University of Bonn, Germany, evaluated a nation-wide telephone counselling service for patients with retinal disease. Calls were handled by ophthalmologists according to standardised flow charts.

Over eighteen months, 1,384 calls were documented. On average, 7.6 calls were handled per day with an average call length of 8.5 minutes. The majority of callers were females (63 per cent) who had age-related macular degeneration (ARMD). Only 17 per cent of callers were relatives. Most questions were related to therapeutic options for AMD and retinitis pigmentosa (45 per cent).

The Retina Hotline service was deemed necessary and it was concluded that staffing may be adequately performed by well-trained non-medical staff rather than ophthalmologists. *Retina* 2010; 30; 4: 635-639

Beta-blockers link to cataracts

A study has linked certain anti-hypertensive medications to the long-term incidence of both cataract and cataract surgery.

A total of 3,054 patients aged 49 years or older were examined at base-line, with 2,454 re-examined after five or 10 years. Interviewer-administered questionnaires collected information on medication usage. Crystalline lens photographs were taken at each visit and graded. Associations between anti-hypertensive medications and the 10-year incidence of cataract and cataract surgery were assessed.

The use of either or oral or topical beta-blockers had a borderline association with nuclear cataract (odds ratio, OR 1.45 and OR 2.12, respectively) and significantly predicted incident cataract surgery (OR 1.61 and OR 3.09) after adjusting for age, gender, blood pressure, intra-ocular pressure, myopia, diabetes, smoking and steroid use. Further studies are warranted to confirm and extrapolate on this finding.
Br J Ophthalmol 2009; 93: 1210-1214.

Stroke of genius

A retrospective analysis of data collected from the Taiwan National Health Insurance Research Database has identified that herpes zoster ophthalmicus (HZO) may be a useful marker for identifying patients at risk of stroke.

The study cohort comprised all patients diagnosed with HZO in 2003-2004 (n = 658), and a control cohort (n = 1974) matched for age and gender. Patients were tracked from their initial presentation for one year.

The incidence of stroke in patients affected with HZO was 8.1 per cent compared with 1.7 per cent of controls. After adjustment for patients' demographic characteristics, selected comorbidities and medications, HZO patients were found to have a 4.52-fold (95 per cent confidence interval 2.45-8.33) higher risk of stroke than the comparison cohort. There was no significant difference in the rate of stroke development between patients who had received systemic antiviral treatment and those who had not.

Neurology 2010; 74: 10: 792-793. Epub Mar 3 2010.

Post-operative adversity

Exposure to tamsulosin within 14 days of cataract surgery was found to be significantly associated with serious post-operative ophthalmic adverse events, including retinal detachment, lost lens, lens fragment or endophthalmitis.

Tamsulosin is the most commonly prescribed medication for the management of benign prostatic hyperplasia. The drug acts through systemic blockade of alpha 1 a-adrenergic receptors. As these receptors are present in the iris dilator smooth muscle, tamsulosin may also impede mydriasis during ocular surgery and lead to intraoperative floppy iris syndrome.

The study involved a large population-based analysis of post-operative adverse events experienced by patients who were prescribed tramsulosin at the time of cataract surgery. Nested case-control analysis of a population-based retrospective cohort used linked health care databases from Ontario, Canada. All men aged 66 years or older who had cataract surgery between 2002 and 2007 were included.

JAMA 2009; 301: 1991-1996.

Men more at risk

Proteinuria appears to be a risk factor for AMD among men but not among women, according to study.

Subjects were derived from a population-based cross-sectional study of people aged 75 years or older. Following adjustment for confounding factors, the presence of proteinuria was found to be positively associated with AMD among men. This effect was not observed in women, possibly due to measurement errors in detecting proteinuria in women.

AMD and renal impairment are both associated with cardiovascular risk factors and with alterations in the pro-inflammatory, complement pathways. There are limited studies on the association between AMD and chronic kidney disease.

Ophthalmic Epidemiol 2009; 16: 3: 181-186.

Undergrad therapeutics in SA

Flinders University will offer two therapeutics subjects as part of its new five-year optometry course.

The subjects will be offered in the two-year Master of Optometry program, which is preceded by a three-year Bachelor of Medical Science (Vision Science) degree.

The subject content will be finalised before first-year students—who began the course in 2010—reach their fourth year in 2013. It is yet to be determined who will be involved in the delivery of the subjects.

Professor Konrad Pesudovs, foundation chair of Optometry and Vision Sciences at Flinders University, says that therapeutics subjects are an essential component of the course. 'The evolution of the optometric profession has meant that it is no longer viable to produce graduates who have no therapeutic qualifications,' he says.

'Currently, about 30 per cent of registered optometrists in South Australia are therapeutically endorsed. Several optometrists are about to undertake the University of New South Wales postgraduate certificate in ocular therapeutics held in Adelaide, which will push this number to more than 50 per cent.

'With the introduction of our course, I think that by the end of the decade the vast majority of practitioners delivering optometry in the state will be therapeutically endorsed.'

HEALTH CARE TEAM

Dementia

Out of mind, not out of sight

Alzheimer's Australia

Visual impairment is commonly overlooked in dementia yet optometrists are well-placed to substantially improve quality of life for people with dementia.

Age brings on a range of vision problems, particularly visuo-spatial difficulties including loss of depth perception or parts of the colour spectrum. People with dementia can have added visual problems unrelated to eye disease, caused by brain damage, usually to the occipital and temporal lobes. Agnosia—an inability to recognise objects, people or shapes, even when the eyes are not defective—is one of the more common conditions identified.[1] Visual deficits increase social isolation, the risk of falls and disorientation in people with dementia.

Recent research even suggests that untreated visual deterioration may increase the risk of dementia by reducing the mental exercise that protects against some forms of the disease,[2] yet visual problems in people with dementia are often poorly understood and may go untreated.[3] Optometrists can play a key role in identifying and managing the symptoms of dementia.

What is dementia?

Dementia is not a normal part of ageing but rather describes a range of more than 100 conditions associated with progressive deterioration of the brain. Dementia affects all aspects of brain function including memory and cognitive abilities, such as planning, reasoning and decision-making, and eventually affects all aspects of daily functioning. Memory loss, often the first symptom of dementia, is more severe and progressive than in normal ageing.

In Australia there are more than 257,000 people with dementia, projected to grow to more than 1.13 million by 2050.[4] There are also 15,000 people with younger onset dementia under the age of 65 years. In New Zealand there are about 40,800 people with dementia, rising to 146,700 by 2050.[5]

Diagnosing dementia

There is no single clinical test that can be used to diagnose dementia. Depression and brain lesions can have symptoms similar to those of early dementia, so a comprehensive evaluation is required.

Early diagnosis enables people with dementia and their families to understand what is happening and to make decisions about their future and living arrangements, including financial and legal planning. Treatment for Alzheimer's disease includes the prescription medications Ebixa, Aricept and Reminyl. These appear to be more effective when commenced in the early stages of the disease process.

Alzheimer's disease

Alzheimer's disease accounts for between 50 and 70 per cent of dementia cases. Sporadic Alzheimer's disease is the most common form affecting any adults at any age but more commonly after the age of 65 years. Familial Alzheimer's disease is very rare and is linked to an inherited genetic mutation. Affected individuals will generally develop Alzheimer's disease between 30 and 50 years of age.

Alzheimer's disease generally begins with short-term memory loss and impaired ability to learn new information. This is followed by progressive deterioration of long-term memory and other functions such as language, movement, perception and executive functioning. The disease usually progresses over three to 20 years, with an average time from diagnosis to death of eight to 10 years.

Vascular dementia

Vascular dementia is the umbrella term for dementias associated with impairment of cerebrovascular circulation and is the second most commonly diagnosed form of dementia. The most common form of vascular dementia is multi-infarct dementia in which transient ischaemic attacks lead to infarction of brain tissue. These events may go unnoticed and are detected only after the clinical symptoms of dementia become apparent.

Vascular dementia tends to have a more sudden onset than Alzheimer's disease and develops differently depending on which part of the brain has been affected. Common symptoms include problems with concentration and communication (both verbal and non-verbal), memory loss, behavioural changes, delusions and hallucinations. Vascular dementia tends to progress step-wise, with a rapid progression over four to five years.

Dementia with Lewy bodies

Dementia with Lewy bodies is caused by abnormal deposits (Lewy bodies) of the synaptic protein alpha-synuclein inside the nuclei of neurons in areas of the brain that control aspects of memory and motor function.

By assisting dementia sufferers who have visual difficulties, you can significantly improve their quality of life

Dementia with Lewy bodies is characterised by three key symptoms: visual hallucinations; Parkinsonian features; and pronounced fluctuations in mental state alternating between lucid and confused, disoriented or bewildered. Other symptoms include difficulty concentrating, loss of ability to judge distances, delusions and depression.

Frontotemporal dementia

Frontotemporal dementia is a clinical syndrome associated with degeneration of the frontal and temporal lobes of the brain. It is characterised by an early breakdown in social and emotional awareness. Frontotemporal dementia can affect people at any age although it usually begins between 40 and 65 years of age.

Damage to the frontal and temporal lobes causes a variety of symptoms including lack of insight, inability to empathise, personality changes, loss of word meaning and obsessive repetition of actions. Progression from diagnosis varies from less than two to more than 10 years.

Role of optometry

Visual difficulties may be one of the earliest signs of dementia. With a good understanding of the characteristic features of early dementia symptoms, optometrists may be able to refer people on for early diagnosis and treatment.

In addition to the usual age-related degeneration, dementia may cause difficulties understanding what is seen rather than how clearly things are seen. Specific difficulties appear to emerge in relation to motion, depth, colour and contrast, as well as visual hallucinations.[6] Like all dementia symptoms, visual deficits may vary widely between individuals. Common Alzheimer-related visual deficits include various agnosias, difficulties with texture and blue-violet discrimination as well as contrast sensitivity.

Diagnosis of visual problems in dementia may be confounded by both the lack of ocular disease and the presence of cognitive deficits. Standard tests and procedures need to be adapted to the patient's needs. Teller acuity cards have been found to reliably identify visual deficits in all but the most advanced cases.[7]

Optometrists are in an excellent position to assist with vision-associated difficulties. Both surgery and spectacles may offer significant benefits for people with dementia, despite the challenges of treatment.[6] Dim lighting, common in many aged-care facilities, may exacerbate confusion and disorientation in vision-impaired dementia residents.[3] Various strategies such as enhanced lighting, appropriate visual aids, removing clutter and unneeded items from living areas, and putting in place mechanisms to help the person to distinguish between similarly coloured objects, can substantially improve quality of life for people with dementia.

With adequate support and appropriate medical care, people with dementia can live full and rewarding lives. Without good visual care, people with dementia may be unable to engage in social and mental activities that maintain their quality of life and prevent further degeneration.

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Alzheimer's Australia assists people with dementia and their families by putting them in touch with others in their situation and by providing individual support, counselling and services. For further information please contact the National Dementia Helpline on 1800 100 500 or visit the website http://www.alzheimers.org.au.

Alzheimer's disease	Normal age-related changes
Forgets entire experiences	Forgets part of an experience
Rarely remembers later	Often remembers later
Is gradually unable to follow written or spoken directions	Is usually able to follow written or spoken directions
Is gradually unable to use notes as reminders	Is usually able to use notes as reminders
Is gradually unable to care for self	Is usually able to care for self

The difference between Alzheimer's disease and normal age-related changes to memory

HEALTH CARE TEAM

Dementia

Pharmacological

Alzheimer's Australia

Good visual health is an essential component in the treatment of dementia. Deteriorating vision may be more difficult to diagnose in dementia patients, particularly where brain damage affects vision without obvious signs of ocular disease. Maintaining good vision is central to reducing the debilitating consequences of disorientation and isolation, which are common features of dementia progression. Maintaining good visual health also promotes social interactions and quality of life, and may even reduce the risk or slow the progression of dementia in some cases.

While there is currently no cure for dementia, there is a range of interventions or strategies, including drug treatments, that can be used by health professionals to relieve symptoms of dementia and to enhance quality of life of the person with dementia.[1] Different types of dementia respond differently to different drug treatments and many dementia patients, particularly the elderly, will be on complex schedules of medication for a variety of conditions. Understanding the types of drug treatments used for dementia assists all health professionals involved in dementia care to better plan and co-ordinate care strategies

Alzheimer's disease treatments

There are numerous drugs available in Australia for people with Alzheimer's disease.[2] They fall into two categories: cholinergic treatments and memantine treatments. These drugs aim to reduce the cognitive and functional decline of the person with dementia.[3]

Acetylcholinesterase inhibitors

Alzheimer's disease is characterised by low levels of the neurotransmitter acetylcholine in the brain, which is broken down by the enzyme acetylcholinesterase. Acetylcholinesterase inhibitors can increase acetylcholine levels and improve nerve transmission in some regions of the brain. While these medications may slow the cognitive and functional decline in some people, they do not affect the underlying progression of Alzheimer's disease. Acetylcholinesterase inhibitors offer some relief from symptoms of Alzheimer's for some people for a limited time and are approved for use in people with mild to moderate Alzheimer's disease.

There are three acetylcholinesterase inhibitors available in Australia: Aricept (donepezil hydrochloride), Exelon (rivastigmine) and Reminyl (galantamine). All three inhibitors work in a similar way but one may be more suitable to an individual than another, particularly in terms of side-effects experienced. There are no guaranteed predictors of how a person may respond to the medications.

People may experience adverse effects while taking acetylcholinesterase inhibitors. Some of the most common effects are gastrointestinal; particularly anorexia, nausea, vomiting and diarrhoea are associated with these medications. Heart rate may also be affected, resulting in cardiac arrhythmias. Some people may experience stomach cramps, headaches, dizziness, fatigue and insomnia.

Acetylcholinesterase inhibitors can have significant interactions with other drugs. Anticholinergic drugs such as sedating antihistamines, antispasmodics, muscle relaxants, antiparkinsonian agents and antiarrhythmics may impact on the effects of the acetylcholinesterase inhibitors.[4] Co-administration with other drugs, such as beta-blockers and calcium antagonists, may increase the risk of bradycardia and hypotension. The rate of metabolism in the liver of donepezil and galantamine may be affected by other drugs that increase or inhibit liver enzymes.

Memantine

Memantine acts differently from the acetylcholinesterase inhibitors and is the first in a new class of drugs used for people with dementia. Glutamate is another neurotransmitter associated with learning and memory, and enhances cognition at moderate levels by binding with the N-methyl-D-aspartate (NMDA) receptor.[4] Excess glutamate and excessive NMDA receptor stimulation can damage neurons. Memantine works as an NMDA antagonist by blocking the receptor and preventing excess glutamate being released without interfering with the physiological actions of glutamate. Ebixa is currently the only memantine drug available in Australia.[6]

Some studies have shown that memantine benefits Alzheimer's disease and vascular dementia but it is also used in combination with acetylcholinesterase inhibitors to assist with some dementia behaviours and improve cognition and functional performance with no increased side-effects.

Currently memantine is approved for use for people with moderate to severe Alzheimer's disease and is continued only if behaviour stabilises or improves.

While Ebixa is generally well tolerated, side-effects may include dizziness, headaches, tiredness, increased blood pressure and, on rare occasions, hallucinations and confusion. Ebixa should not be taken with other NMDA antagonists as adverse reactions may be more frequent or more pronounced. Drugs that use the same renal cationic transport system as amantadine may also interact with memantine causing increased plasma levels. These drugs include cimetidine, ranitidine and nicotine.

Vascular dementia

Currently there are no treatments that can reverse the existing damage of vascular disease. Treatment focuses on reducing the risk of further strokes such as coronary artery disease, hypertension, diabetes and arrhythmias. There is little evidence that shows that acetylcholinesterase inhibitors and memantine help treat vascular dementia but further studies need to be conducted.

Dementia with Lewy bodies

Acetylcholinesterase inhibitors, although not currently approved, are being used to

Managing patients with dementia requires a carefully co-ordinated approach in which the use of therapeutics is just one component

management

treat the cognitive symptoms of dementia with Lewy bodies and may be of some benefit to reducing psychiatric and motor symptoms. Atypical antipsychotic agents should be given in low doses as they may cause adverse side-effects similar to those of the older, typical antipsychotics including sedation, rigidity, postural instability, falls and increased confusion. Levodopa may improve motor function but may also aggravate psychiatric symptoms. People with dementia with Lewy bodies have an increased sensitivity to many drugs and all medications should be supervised by a specialist.

Frontotemporal dementia

There is no current treatment to stop or slow the progression of frontotemporal dementia. Management of the disease lies in strategies employed by carers to avoid confrontation and working around obsessions and behaviour rather than trying to change the behaviour displayed by the person.

Treating accompanying symptoms of dementia

People with dementia may display a number of behavioural and psychological symptoms of dementia. These may include depression, anxiety, sleeplessness, hallucinations, agitation and aggression. These symptoms may be triggered by other underlying environmental factors or untreated pain and should be investigated fully before resorting to medication.

Depression

Depression is common in dementia. Many people develop depression on diagnosis and in early stages of the disease when the person is most aware. Depression can also be a result of a reduced chemical transmitter function in the brain in the later stages of the disease. When depression is suspected it is important to explore all possible factors of the cause and provide a number of options such as social activities and counselling to help manage it. Antidepressants may also be an option to improve consistently low mood, irritability and mood swings.

Choosing an antidepressant will be based largely on tolerability. Antidepressants modify the neurotransmitters serotonin and noradrenaline. Selective serotonin reuptake inhibitors (SSRIs) are preferable as a first step in treating depression in dementia. These medications may cause headaches and nausea, especially when first starting treatment. Anticholinergic properties of tricyclics antidepressants may aggravate cholinergic deficit and cognitive impairment. Dry mouth, blurred vision, constipation, urinary retention and postural hypotension may also be displayed.

People with dementia may respond slower to antidepressants and should be given a therapeutic dosage for at least six to eight weeks before effectiveness is assessed.

Psychotic symptoms and aggression

People with dementia may experience hallucinations and delusions as well as agitation and aggression. If these symptoms persist antipsychotics may be prescribed, but only if there is severe distress or risk of physical harm to those living and working with the person with dementia. Newer antipsychotics such as olanzapine, risperidone and quetiapine may have fewer side-effects than older typical types. Resperidone is currently the only antipsychotic approved for the treatment of behavioural or psychological symptoms of dementia and all antipsychotics prescribed should be reviewed regularly.

Anxiety

Anxiety along with panic attacks and fearfulness may lead to demands for constant company and reassurance, which can place high demands on carers and family. Benzodiazepines may help over short periods of anxiety although their effectiveness may diminish over time once the person becomes used to their effects.[4]

Sleep disturbances

Many drugs prescribed for dementia can cause excessive sedation during the day, leading to an inability to sleep at night. Increased stimulation during the day may reduce the need for sleep-inducing medication or hypnotics at night. If excessive sedation is given at night, this may lead to incontinence as the person may not be able to wake up to use the toilet. Increased confusion and unsteadiness may also occur if the person continues to wake up during the night despite sedation.

Conclusions

People with dementia may be taking a number of medications for different symptoms. All new medications and possible side-effects need to be discussed with the doctor of the person with dementia. Pharmacological treatment should be considered as an adjunct to non-pharmacological approaches rather than a substitute. With careful co-ordination, pharmacological and non-pharmacological strategies, including optometric care, can offer substantial improvements in the quality of life for dementia patients and their carers.

Alzheimer's Australia assists people with dementia and their families by putting them in touch with others in their situation and by providing individual support, counselling, and services. For further information please contact the National Dementia Helpline on 1800 100 500 or visit the wewbsite http://www.alzheimers.org.au.

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News briefs

Heads up on IOP

Sleeping in a head-up position has been found to significantly lower intraocular pressure in glaucoma patients compared with lying flat.

Seventeen glaucoma patients with controlled IOP and new disc haemorrhage had their IOP and blood pressure assessed at two-hourly intervals from 6.00 pm to 8.00 am for two nights in a sleeping laboratory.

Sixteen of the 17 patients recorded a reduction in their IOP when sleeping with their head up at a 30-degree angle; mean IOP was 3.2 mmHg lower when patients slept in this position.

IOP dropped by 20 per cent or more in one-third of patients.

Patients slept in a supine position on the first night and in the head-up position on the second night, and were assessed four times from midnight to 6.00 am.

They were assessed in a sitting position during waking hours from 6.00 pm to 10.00 pm and again at 8.00 am.

Ophthalmology 2010; e-publication 24 Feb.

Chamber examination

Slitlamp optical coherence tomography (SL-OCT) has provided Turkish researchers with strong evidence of changes to anterior chamber parameters in patients with pigmentary glaucoma.

Patients' anterior chamber depth and volume, spur distance, central corneal thickness, and angle opening distance and trabecular iris space area (both at 500 micrometres from the scleral spur) were measured using SL-OCT.

All anterior chamber and angle parameters—except for central corneal thickness and spur distance—were significantly greater in pigmentary glaucoma patients.

'Slitlamp optical coherence tomography provided highly quantitative data on the parameters of anterior chamber and angle dimensions in pigmentary glaucoma,' researchers said.

'(It) revealed increased anterior chamber dimensions and posterior bowing of the iris consistent with the increase in angle parameters in patients with (the disease).'

Eur J Ophthalmol 2010; e-publication 13 Jan.

Screen for retinal toxicity

The probability of retinal toxicity has been found to increase five-fold after seven years of hydroxychloroquine (HCQ) therapy.

A longitudinal study assessed 3,995 rheumatoid arthritis and systemic lupus erythematosus patients who had used HCQ, including 1,538 current users.

Researchers screened patients for self-reported retinal toxicity, and then assessed those with positive reports through detailed interviews and specialist confirmation. Patients were categorised as having 'definite' or 'probable' toxicity if they suffered bull's eye maculopathy or visual field loss.

Definite or probably toxicity was found in only 0.65 per cent of patients, and the risk of toxicity was found to be low in the first seven years of HCQ therapy.

The incidence of toxicity increased to more than one per cent of patients after five to seven years of exposure.

The findings reinforce the importance for optometrists to screen patients for retinal toxicity if they are long-term HCQ users.

The majority of HCQ patients in the study were being tested regularly for toxicity, with 40.4 per cent having their eyes examined every six months and a further 50.5 per cent being examined annually.

Arthritis Care and Research 2010; e-publication 12 February.

Fat chance of reducing risk

A diet rich in olive oil and omega-3 fatty acids has been found to significantly reduce the risk of developing age-related macular degeneration.

It was revealed in a study conducted by the Centre for Eye Research Australia (CERA) that eating at least 100 millilitres of olive oil—equivalent to seven tablespoons—per week reduced a person's late AMD risk by nearly 50 per cent compared with those who eat less than one millilitre.

Those who ate foods rich in omega-3 fatty acids like fish and nuts were less likely to develop early AMD.

Researchers said that olive oil contains powerful antioxidants such as vitamin E and anti-inflammatory properties that protect the health of ocular blood vessels.

Trans-unsaturated fat intake was found to be associated with an increased risk of developing late AMD.

From 1990 to 1994, CERA researchers analysed the diets of more than 6,700 people between the ages of 58 and 69 years. Digital photographs of their maculae were examined between 2003 and 2006 for signs of early and late AMD.

Arch Ophthal 2009; 127: 5: 674-680.

AMD prevention is easily digestible

Optometrists can assist in the prevention or delay of chronic conditions such as age-related macular degeneration (AMD) by advocating to their patients a healthy diet rich in dark green vegetables, yet according to a study published in *Optometry*, many are failing to do so.

Addressing dietary intake with patients may be an important approach to reducing the risk of AMD and cataract. A higher dietary intake of foods rich in lutein and zeaxanthin such as spinach or collard greens can lower the risk of AMD, and high-doses of antioxidants can reduce the risk of progression to advanced AMD by 25 per cent, according to the study.

The study was based on a control group of optometrists in Wisconsin. The majority of those surveyed were satisfied that information being disseminated on the relationship between lutein and zeaxanthin and eye health was adequate. Their primary sources were studies published in professional journals, not-for-profit organisations dedicated to preventing eye-related disease, government organisations and pharmaceutical companies.

Although they perceived it as important to have educational and informational material on the ocular benefits of lutein and zeaxanthin to give to patients, many were unsure of where they could obtain these materials.

Optometry 2009; 80: 579-586.

Multi-pronged analysis

When diagnosing a patient for aqueous deficient dry eye, make sure you have considered all your options

Allan Ared
BOptom

Aqueous tear deficient dry eye disease is due to a failure of lacrimal tear secretion commonly caused by lacrimal acinar destruction or dysfunction.[1] This leads to a reduced aqueous tear pool, increase in tear osmolarity and subsequent tear film instability.

Aqueous deficient dry eye has two major groupings: Sjögren's syndrome dry eye and non-Sjögren's syndrome dry eye. The diagnosis of aqueous deficient dry eye disease can be made by using various clinical methods.

Symptomatic questionnaire

Questionnaires are employed to screen for the diagnosis of dry eye or in clinical practice to ascertain the effects of treatments, grade disease severity or assess a patient's response to therapy. In my practice, I have put together and routinely use a tailor-made set of questions comprising a combination of three peer reviewed questionnaires: the McMonnies,[2] the Canadian Dry Eye Epidemiology Study (CANDEES)[3] and the Ocular Surface Disease Index (OSDI)[4] randomised clinical trial.

Sufferers of aqueous deficiency will respond positively to certain questions such as 'Do you get a dry mouth, nose, throat or chest?' may help to flag an association with Sjögren's. I get patients to complete this questionnaire before the commencement of their treatment and again at the end. I find this symptomatology approach is an excellent way to gauge a patient's therapeutic response.

Basal and reflex tear secretion rates

When dealing with aqueous deficiency, the basal tear secretion rates indicate a patient's ability to produce tears. Topical anaesthetic is used to reduce reflex tearing and Schirmer strips are inserted into the lower temporal palpebral conjunctiva. The patient is then instructed to keep eyes closed for the duration of the test. Generally a score of greater than 15 mm over five minutes is considered normal. I tend to reserve the non-anaesthetic or reflex tearing Schirmer's measurement for extreme cases of the aqueous deficient dry eye disease.

Tear meniscus heights

The tear meniscus height (TMH) also plays a vital role in the presence or absence of aqueous deficiency. The goal here is to measure the TMH in a non-invasive fashion and to avoid flash light tear stimuli. The best way of doing this is to take a single photograph of the eye and use the iris as a backdrop. The patient has to look down a certain predetermined angle so that the lower lid margin tear river crosses the 4-8 o'clock iris plane. The photo is then taken and the height measured with a magnified photographic analysis.[5] Using the iris as a backdrop, the TMH will be portrayed as a shadow, making it easy to determine its exact location. This is when the concave tear river becomes convex.

Ocular surface injection

Grading ocular surface injection is paramount, especially when dealing with inflammatory eye disease. Aqueous tear deficiency and the subsequent alteration of tear film osmolarity may induce the production of ocular surface pro-inflammatory cytokines and in essence transforms the ocular surface to an 'inflamed' state. Photo documentation is my preferred way of monitoring ocular surface injection between visits.

Ocular surface staining

The NEI grid[6] is often used to standardise the way we look at corneal staining. An image of the eye is placed under the grid for effect. Each grid is summed with 0-3 score for each of the five zones—there are 15 points in total. The five zones are superior, nasal, inferior, temporal and central cornea. The greater the corneal compromise, the greater the severity of the tear film dysfunction. The one thing to note is that conjunctival staining occurs earlier than corneal staining in aqueous deficient eye disease. Lissamine green analysis is more specific in determining focal conjunctival epithelial drop-out compared with sodium fluorescein.

Tear film profiling

In the same way that a doctor performs a blood test to determine systemic disease, a tear film profile can be used to ascertain ocular surface disease. The Tear Lab is a device that I have been using for some time, which gives us an indication of tear film osmolarity. The Tear Lab platform lends itself to other modalities such as the measurement of the tear protein, whether lactoferrin levels are low indicating an aqueous deficiency, or whether IgE is elevated alluding to ocular surface allergy and a subsequent disturbance to the production of ocular surface mucins.

TFBUT and OPI

Tear film break up time (TFBUT) and ocular protection index (OPI) are more of an indicator of evaporative dry eye disease. Their diagnostic role in aqueous deficiency is limited.

Continued page 26

Multi-pronged analysis

From page 25

Management of aqueous deficient dry eye disease

Tear supplementation: lubricants

The foremost objective in caring for patients with aqueous deficient dry eye disease is to improve the patient's ocular comfort and quality of life. Our aim is to return the ocular surface and tear film to its normal homeostatic state. We can do this by increasing the tear retention time with the use of topical lubricant therapy. Although symptoms can rarely be eliminated, they can often be improved. In theory, the ideal artificial lubricant should be preservative-free, contain potassium, bicarbonate and other electrolytes, and have a polymeric system to increase its retention time.[7] The frequency of use will depend on the practitioner's judgment and is often determined after careful analysis of the ocular surface. Higher viscosity agents will be more useful in the moderate to severe forms of the disease.

- **Tear retention**: punctal occlusion, moisture chambers and contact lenses
- **Tear stimulation**: secretagogues
- **Biological tear substitutes**: autologous serum and salivary gland auto transplantation
- **Anti-inflammatory therapy**: corticosteroids and cyclosporine (Restasis)

Steroids

Nothing beats a steroid when we are required to suppress all aspects of the inflammatory cascade. As inflammation plays a significant role in many eyes that present with clinically determined aqueous tear film dysfunction, the challenge is to know which patient would benefit from anti-inflammatory therapy. Generally speaking, the greater the signs and symptoms, the greater the success of topical anti-inflammation therapy. Concurrent use of artificial tears is always recommended in all dry eye patients.

Restasis

Topical cyclosporine may slow or halt the progression of dry eye but it usually takes Restasis at least one month to render a meaningful effect. Front loading with a mild steroid quantitatively diminishes the expression of inflammation and seems to potentiate the therapeutic effect of this therapy.

Ocular and systemic associations

- **Ocular associations**: Age-related dry eye, congenital alacrima, mucous membrane pemphigoid, chemical and thermal burns, contact lens wear, neurotrophic keratitis and allergic eye disease.
- **Systemic associations**: Autoimmune connective diseases such as rheumatoid arthritis, which is the most common, or systemic lupus erythematosis, polyarteritis nodosa, Wegener's granulomatosis and exposure to certain systemic drugs.
- **Differential diagnosis**: for example evaporative dry eye and allergic eye disease.

The pre-ocular tear film is a complex hydrated mucin gel with an oily cap. It is produced by the lacrimal glands, epithelial cells on the ocular surface and meibomian secretions within the lids. Clinical syndromes of ocular irritation may result from deficiencies in one or more of these layers. The majority of patients with aqueous adequate or evaporative dry eye will suffer from meibomian gland dysfunction seen clinically as lipid tear deficiency producing a rapid tear film break up time. Aqueous tear deficiencies lead to ocular surface disease, termed keratoconjunctivitis sicca (KCS). KCS results from abnormal terminal differentiation of the ocular surface epithelia and is more often associated with a marked reduction in mucin production. Patients with severe allergies are also prone to the disruption to their mucin expression but they will often present with allergic eye signs and symptoms.

The group favoured approach taken by the Delphi Panel based treatment recommendations on disease severity. Four levels of severity were formulated as per the Table.[8] The prime directive in all dry eye therapy is to achieve an extension of the time the tear film remains intact. The Delphi Panel concluded that if patients were started on topical lubricant therapy early in their disease and educated about the importance of regular dosing, then the chances of their disease progressing to the red zone (grade 4 severity) were significantly reduced. Patients working with computers and in artificial environments were also instructed to blink more frequently and alter the humidity in their environments accordingly. The follow-up strategy is dependent on the judgement of the practitioner. I see my mild patients on a fortnightly basis and more frequently if the need arises.

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Severity	Signs and symptoms	Recommended treatment
1	Mild to moderate symptoms; no signs Mild to moderate conjunctival signs	Patient counselling, preserved tears environmental management, use of hypoallergenic products, water intake
2	Moderate to severe symptoms Tear film signs Mild corneal punctate staining Corneal staining Visual signs	Unpreserved saline, gels, ointments, cyclosporine A, secretagogues, topical steroids, nutritional support (flax seed oil)
3	Severe symptoms Marked corneal punctate staining Central corneal staining Filamentary keratitis	Tetracyclines Punctal Plugs
4	Severe symptoms Severe corneal staining, erosions Conjunctival scarring	Systemic anti-inflammatory therapy, oral cyclosporine, moisture goggles, acetylcysteine, punctal cautery, surgery

Delphi Panel consensus for dry eye management.[8] Advice given to patients and recommended follow-up schedule in mild to moderate disease with reference to the Delphi grading system.

Treatment regime

Dry eye disease and related ocular surface conditions are some of the most difficult diagnoses for practitioners to make, says leading American ophthalmologist Dr Eric Donnenfeld. In the April issue of Refractive Eyecare, he explains how he diagnoses dry eye and his preferred methods to alleviate the symptoms.

There is a wide range of symptoms associated with dry eye and many different ocular, systemic and environmental conditions that can produce those symptoms. The variety of ways in which ocular surface disease can present underscores the need for a thorough patient history, followed by a comprehensive examination. Donnenfeld says that he starts with some basic questions to see whether the patient has a history of dry eye and if any artificial tears or lubricants are already being used.

Contact lens intolerance, visual disturbances, visual fluctuation or problems performing prolonged visual tasks, such as working at a computer, may suggest that dry eye disease is present. In addition, patients who have dry eyes often have underlying medical conditions and/or medication use that needs to be noted, including history of rheumatoid disease or use of medications such as anticholinergics.

Perimenopausal hormonal changes exert a destabilising effect on ocular surface homeostasis, putting women at this stage of life at high risk for dry eye.

Because dry eye can impact visual outcomes following ocular surgery, he identifies and treats any ocular surface disease prior to surgery, usually by optimising the ocular surface with lubricants and possibly topical steroids and cyclosporine.

Whenever Donnenfeld sees a patient with signs or symptoms of dry eye—irrespective of how advanced the disease may be—he prefers to start treatment with a lubricant such as Blink Tears eye-drops, which contains a viscoadaptive agent that mimics the function of natural mucin to stabilise the tear film and provide excellent wetting of the ocular surface. He says that stabilising the tear film increases comfort and helps provide a smooth refracting surface that improves patients' quality of vision.

If the patient needs to use the tears more than the recommended four times a day or has significant corneal staining, he switches the patient to nonpreserved Blink Tears.

If the use of artificial tears alone is inadequate to manage the patient's dry eye and the condition progresses, he suggests adding topical cyclosporine 0.05% to the treatment regimen, and if signs of meibomian gland dysfunction are present, he recommends nutritional supplements with flaxseed and fish oil. Advanced cases of lid disease may require oral antibiotics such as doxycycline to alter gland function.

Dr Donnenfeld is a consultant for Abbott Medical Optics. ■

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Letter from Hong Kong

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BSc(Hons) FAAO FCOptom
MAppSc

Optometrists cannot use therapeutic medications at present in Hong Kong. The therapeutic management of patients with eye disease is undertaken by ophthalmologists, of whom there are about 260 in Hong Kong. Although ophthalmologists in private practice accept referrals from optometrists, eye departments at Hong Kong government-funded public hospitals do not, insisting that patient visit their GP first—this is despite the Health Department's decision specifically directing them to accept referrals from optometrists.

The Hong Kong Government now understands that a health system dominated by organised medicine is detrimental to its successful operation and is seeking to actively involve other health professionals. It has recognised the role of optometry in community health care, a good example of which is its plan to involve our profession in diabetic retinopathy screening programs.

The government requires tertiary courses to undertake quinquennial reviews and expects them to be deemed equivalent to their counterparts elsewhere. Therapeutic training is planned for the purposes of patient care as well as quality assurance in health care and benchmarking. This will initially be for undergraduates, with upgrading courses for optometrists anticipated later.

Optometry in Hong Kong has made great strides and there is every indication that it will continue to do so.

I have been working at the School of Optometry, The Hong Kong Polytechnic University, for nearly seven semesters. It is now the premier optometry school in Asia in terms of its teaching, research and clinical activities but it had humble beginnings.

In the 1970s, the government in Hong Kong decided to regulate optometric services. At the time, the majority of optometrists had qualified through an apprenticeship system. In 1978, formal training was established through the Section of Optometry at Hong Kong Polytechnic, which enabled optometrists to update their skills with a two-year part-time certificate in optometry.

A pivotal year for optometric education in Hong Kong occurred in 1984. A two-year part-time higher certificate was offered to those holding the prior certificate, and a three-year full-time professional diploma was established for undergraduates. The Optometrists Board of Registration came into being in 1986.

In 1987, optometry received departmental status and, together with radiography, formed the Department of Diagnostic Sciences. The four-year degree was approved in 1991. Following the transition to university status by institutes of technology that had taken place in countries such as the United Kingdom and Australia, Hong Kong Polytechnic became The Hong Kong Polytechnic University in 1994. Optometry received separate school status in 2005.

In 13 years optometric education in Hong Kong had progressed from a part-time certificate to a fully-fledged four-year degree. This extraordinary advancement is testament to the dedication and hard work of members of the profession, and successive heads of school and their academic colleagues.

How to register a group of practitioners who had diverse training and qualifications was a dilemma. Legislation for this purpose was first enacted in 1980 and went through successive revisions. The registration of optometrists in the form of a four-tiered system was promulgated in 1996.

Professional diploma and degree holders are called registered optometrists Part 1, and can practise full-scope primary care optometry including the use of diagnostic pharmaceuticals. Registered optometrists Part 2 hold the certificates noted above and can do the same as their Part 1 counterparts except for using diagnostic drugs. Registered optometrists Part 3 can only refract and cannot fit contact lenses; and some registered optometrists Part 4 can only refract but some can fit contact lenses as well.

There are about 2,000 optometrists in Hong Kong serving a population of almost eight million people, as well as the many visitors that comprise Hong Kong's thriving tourist industry. About one in three of those practitioners is registered in the Part 1 category. From time to time, the school organises courses to enable optometrists to transfer to a higher level of registration category. One such program commenced in January this year, and its successful completion will allow registered optometrists Part 4 to upgrade their status to Part 2 registration. ■

Associate Professor
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Water drinking test

For the past 80 years scientists have been devising theories on the causes of IOP fluctuations with mixed success

In 1928, Schmidt[1,2] showed that there was an increase in intraocular pressure in humans as a result of the ingestion of water. The water drinking test (WDT) was initially proposed as a diagnostic test to determine if a patient may have glaucoma. The patient was usually asked to drink one litre of water in a five-minute period and then the patient's IOP was monitored over time. The peak IOP response after the ingestion of water was thought to vary from 10 to 35 minutes but there was considerable disagreement in this regard.[3]

At the time it was felt that a 6 mmHg or greater increase in IOP suggested that the patient may have 'chronic simple glaucoma',[3] although it later became apparent that the test was unreliable due to a high false positive rate and an even higher false negative rate.[3]

How the WDT causes a rise in IOP is unknown.[4] Theories include the ingestion of water results in an influx of water into the body tissues, including the eye, because of changes in the blood-ocular osmotic gradient. Other theories are that water drinking may change episcleral venous pressure and therefore increase IOP by either choroidal engorgement causing oedema of the ciliary body or secondary rotation of the root of the iris, leading to a decrease in trabecular outflow.[4]

Drance[5] found that only 38 per cent of patients with single IOP measurements taken within office hours had their 24-hour IOP peaks detected within this timeframe. Some eye-care practitioners ask patients to return for tonometry measurements throughout the day to better establish daily IOP fluctuations and peak values, and to ascertain if pressure spikes occur that may increase the possibility of glaucomatous damage.

A study of the patients in the Advanced Glaucoma Intervention Study suggests that IOP fluctuation between visits over at least three years was an independent risk factor for glaucoma progression.[6]

In recent times, there has been renewed interest in the WDT as a means of predicting the peak diurnal (daytime) IOP.[2,7] The study by Kumar et al[7] examined 25 subjects—48 per cent of whom had primary open angle glaucoma—who at four different times throughout the daytime had their IOP measured via Goldmann tonometry. On another occasion, the same subjects were asked to drink a quantity of water proportional to their body weight in five minutes or less and their IOP was measured during the subsequent hour at 15-minute intervals.

The results suggested that the mean peak IOP measured by diurnal testing was not statistically different from that measured by the WDT, but that the IOP fluctuation measured by the two tests demonstrated a poor correlation. The conclusion to the study was that the WDT may be a reasonable tool to assess peak IOP in an office setting.[8]

In 2006, Susanna et al[8] found that eyes that had a larger increase in IOP after the WDT were more likely to have worse mean deviation values for their Humphrey visual field full-threshold 24-2 test results.

It is known that there is a 24-hour variation in IOP values and, in young normals, IOP -is highest during the night. Some studies say that this occurs in the hours prior to eye opening[10] and others suggest that this may occur on eye opening.[11] This apparent IOP elevation may be due, in part, to the supine position adopted during sleep and also to the effect of corneal oedema that occurs during eye closure, on Goldmann tonometry values.[12]

Self-tonometry has been attempted to try to obtain measurements of IOP out of office hours, but reviews of instruments such as the Proview tonometer suggest that this method is neither sufficiently accurate nor repeatable to be used in the detection and management of glaucoma.[13]

The question remains of whether the long-term fluctuation of IOP is an important measurement for the diagnosis and management of glaucoma, even with patients whose IOP appears to be stable. The same could be said of short-term fluctuations of IOP and pressure peaks as measured by the WDT. A recent major review by Sultan et al[14] suggests that more work is required to answer these questions.

As a result, the usefulness of the WDT in clinical practice and its relationship to the management of glaucoma in particular have not been established.

It is envisaged that one of the answers will come when circadian measurements of IOP can be obtained in clinical practice. Devices are already available to obtain measurements of blood pressure and blood sugar levels over a 24-hour period, with some of these devices being programmable to take measurements of increasing frequency at various times of the day. At the end of the measurement period the data is then downloaded, stored and plotted.

Contact lens and intraocular devices have been proposed to enable the circadian measurement of IOP in humans and some of these approaches are discussed in a recent article.[15] Perhaps when such devices become clinically available, the answer to the question of the importance of the in-office application of the WDT, and the application of circadian fluctuation of IOP to the diagnosis and management of glaucoma, will be answered.

Continued page 30

Drug compliance

Matt Trollope

Poor adherence among glaucoma patients to administering medication—apart from being detrimental to the patient's eyesight—presents problems because it is difficult to identify and measure.

Patients and practitioners tend to overestimate adherence,[1] and many patients will under-report or attempt to conceal their non-adherence when consulting with their practitioner. This may be because it is 'a socially undesirable behaviour which patients are reluctant to reveal'.[2]

The number of patients who fail to adhere to their glaucoma medication regimes is worrying. In an article[3] in *Optometry and Vision Science* it was stated that on average chronically ill patients take between just 30 and 70 per cent of their prescribed medication doses, and about 50 per cent of patients discontinue therapy after one month.

According to the article, these figures also relate to the use of ocular medications.

The Glaucoma Adherence and Persistence Study (GAPS) in the United States assessed the medication persistence of nearly 14,000 glaucoma patients by analysing pharmacy and medical claims data.[4] Patients were considered to be persistent with their medication if they refilled their prescription within 60, 90 or 120 days of their last dispensed quantity. This increasing length of time correlated with the size of the bottle containing the medication.

It was found that just 10 per cent of patients were continuously persistent with their glaucoma therapy over the course of one year, 54 per cent recorded gaps in time between refilling medication, and 20 per cent discontinued their therapy completely.

The study proposed several reasons for patients not adhering to their glaucoma therapy regimens. They include:

- their knowledge of glaucoma came solely from their practitioner
- they did not associate failing to take medication with loss of vision
- the medication was too expensive
- travelling caused them to forget to administer their medication
- they were not reminded by their practitioner to attend follow-up appointments
- they received eye-drop samples from their practitioner.

Other factors such as medication side-effects, an inconvenient dosing regime, multiple medications, a patient's physical limitations, and a poor relationship with their practitioner may impact on patients' adherence levels.

Despite the deflating statistics, practitioners have many options for improving their patients' approach to glaucoma therapy.

Steps like simplifying eye-drop regimes, providing patients with written instructions on how and when to take their medications, and using telephone and mail reminders, can assist in improving patient adherence.[3]

Effective communication with patients is the most crucial element for ensuring they use their medication correctly.

Practitioners should ensure that patients are knowledgeable about their condition and the potential severity of ocular ramifications if they do not persist with their medication regimes. This can be done by asking the patient questions about glaucoma; by engaging patients in discussion, you can fill any apparent gaps in their knowledge.[3]

Patients who trust their practitioners enough to discuss their condition openly are far more likely to demonstrate good adherence. Patients' trust in both their practitioner and their therapy can be achieved if practitioners promise to take care of their patient, provide them with evidence of the disease's severity through digital photos, imaging print-outs and educational resources, and use every opportunity to refresh their knowledge of the condition and discuss their medication regime.[1]

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Water drinking test

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PBS list of medicines for optometrists 19 May 2010

	Product	Max qty	Repeats
Antiglaucoma preparations			
Betaxolol eye-drops, suspension, 2.5 mg (as hydrochloride)/mL, 5 mL	Betoptic S	1	5
Betaxolol eye-drops, solution, 5 mg (as hydrochloride)/mL, 5 mL	Betoptic		
	BetoQuin	1	5
Bimatoprost eye-drops 300 mg/mL, 3 mL	Lumigan	1	5
Bimatoprost with timolol eye-drops containing 300 mg bimatoprost with timolol 5 mg (as maleate)/mL, 3 mL	Ganfort 0.3/5	1	5
Brimonidine eye-drops containing brimonidine tartrate 2 mg/mL, 5 mL	Alphagan		
	Enidin	1	5
Brimonidine with timolol eye-drops containing brimonidine tartrate 2 mg with timolol 5 mg (as maleate)/mL, 5 mL	Combigan	1	5
Brinzolamide eye-drops 10 mg/mL, 5 mL	Azopt		
	BrinzoQuin	1	5
Dorzolamide eye-drops 20 mg (as hydrochloride)/mL, 5 mL	Trusopt	1	5
Dorzolamide with timolol eye-drops containing dorzolamide 20 mg (as hydrochloride) with timolol 5 mg (as maleate)/mL, 5 mL	Cosopt	1	5
Latanoprost eye-drops 50 micrograms/mL, 2.5 mL	Xalatan	1	5
Latanoprost with timolol eye-drops 50 micrograms latanoprost with timolol 5 mg (as maleate)/mL, 2.5 mL	Xalacom	1	5
Pilocarpine eye-drops containing pilocarpine hydrochloride 10 mg/mL, 15 mL	Isopto Carpine		
	Pilopt	1	5
	PV Carpine		
Pilocarpine eye-drops containing pilocarpine hydrochloride 20 mg/mL, 15 mL	Isopto Carpine		
	Pilopt	1	5
	PV Carpine		
Pilocarpine eye-drops containing pilocarpine hydrochloride 40 mg/mL, 15 mL	Isopto Carpine		
	Pilopt	1	5
	PV Carpine		
Pilocarpine eye-drops containing pilocarpine hydrochloride 60 mg/mL, 15 mL	Pilopt	1	5
	PV Carpine		
Timolol eye-drops 2.5 mg (as maleate)/mL, 5 mL	Tenopt		
	Timoptol	1	5
Timolol eye-drops 5 mg (as maleate)/mL, 5 mL	Tenopt		
	Timoptol	1	5
Timolol eye-drops (gellan gum solution) 2.5 mg (as maleate)/mL, 2.5 mL	Timoptol XE	1	5
Timolol eye-drops (gellan gum solution) 5 mg (as maleate)/mL, 2.5 mL	Timoptol XE	1	5
Timolol eye gel 1 mg (as maleate)/g, 5 g	Nyogel	1	5
Travoprost eye-drops 40 micrograms/mL, 2.5 mL	Travatan	1	5
Travoprost with timolol eye-drops 40 micrograms travoprost with timolol 5 mg (as maleate)/mL, 2.5 mL	Duotrav	1	5

By writing a PBS prescription for an antiglaucoma agent, the prescriber is certifying that the criteria set out in the PBS guidelines are satisfied

	Product	Restriction	Max qty	Repeats
Anti-viral eye preparations		Restricted:		
Aciclovir eye ointment 30 mg per g (3%), 4.5 g	Zovirax	Herpes simplex keratitis	1	0
Antibiotics		Unrestricted		
Chloramphenicol eye-drops 5 mg/mL (0.5%), 10 mL	Chlorsig		1	2
	Chloromycetin		1	2
Chloramphenicol eye ointment 10 mg/g (1%), 4 g	Chlorsig		1	0
	Chloromycetin		1	0
Framycetin sulfate eye-drops 5 mg/mL (0.5%), 8 mL	Sofracycin		1	2
Sulfacetamide sodium eye-drops 100 mg per mL (10%), 15 mL	Bleph-10		1	2
Anti-inflammatory agents		Unrestricted		
Fluorometholone eye-drops 1mg/mL (0.1%), 5 mL	Flucon		1	0
	FML Liquifilm		1	0
Fluorometholone acetate eye-drops 1 mg/mL (0.1%), 5 mL	Flarex		1	0
Flurbiprofen sodium eye-drops 300 µg/mL (0.03%) single dose units 0.4 mL, 5	Ocufen		1	0
Hydrocortisone acetate eye ointment 10 mg/g (1%), 5 g	Hycor		1	0
Anti-allergy agents		Restricted:		
Sodium cromoglycate eye-drops 20 mg/mL (2%), 10 mL	Cromolux	Vernal keratoconjunctivitis	1	5
	Opticrom		1	5

Continued

	Product	Restriction	Max qty	Repeats
Tear supplements		Restricted:		
Carbomer eye gel 2 mg/g (0.2%), 10 g	Geltears	Severe dry eye including	1	5
	PAA	Sjögren's syndrome	1	5
	Viscotears Liquid Gel		1	5
Carmellose sodium with glycerin eye-drops 5 mg-9 mg per mL (0.5%-0.9%), 15 mL	Optive		1	3
Carmellose sodium eye-drops 10 mg/mL (1%), 15 mL	Refresh Liquigel		1	5
Carmellose sodium eye-drops 5 mg/mL (0.5%), 15 ml	Refresh Tears plus		1	5
Hypromellose eye-drops 3 mg/mL (0.3%), 15 mL	In a Wink Moist'ing		1	5
(contains sodium perborate)	Genteal		1	5
Hypromellose eye-drops 5 mg/mL (0.5%), 15 mL	Methopt		1	5
Hypromellose with carbomer 980 ocular lubricating gel 3 mg-2 mg/g (0.3-0.2%), 10 g	HPMC PAA		1	5
	Genteal gel		1	5
Hypromellose with dextran eye-drops 3 mg-1 mg/mL (0.3%-0.1%), 15 mL	Poly-Tears		1	5
	Tears Naturale		1	5
Polyethylene glycol 400 with propylene glycol drops 4 mg-3 mg/mL (0.4-0.3%); 15 mL	Systane		1	5
Polyethylene glycol 400 eye drops 2.5 mg per mL (0.25%), 15 mL	Blink Intensive Tears		1	5
Polyvinyl alcohol eye-drops 14 mg/mL (1.4%), 15 mL	PVA Tears		1	5
Polyvinyl alcohol eye-drops 30 mg/mL (3%), 15 mL	PVA Forte		1	5
Polyvinyl alcohol eye-drops 14 mg/mL (1.4%), 15 mL	Liquifilm Tears		1	5
Polyvinyl alcohol eye-drops 30 mg/mL (3%), 15 mL	Liquifilm Forte		1	5
Polyvinyl alcohol eye-drops 14 mg/mL (1.4%), 15 mL (contains sodium chorite/hydrogen peroxide as preservative)	Vistil		1	5
Polyvinyl alcohol eye-drops 30 mg/mL (3%), 15 mL (contains sodium chorite/hydrogen peroxide as preservative)	Vistil Forte		1	5
Unpreserved tear supplements		Authority required:		
Carbomer 974 ocular lubricating gel 3 mg/g (0.3%), single dose units 0.5 g, 30	Poly Gel	Severe dry eye syndrome in patients sensitive to preservatives in multi-dose eye-drops	3	5
Carbomer eye-gel 2 mg per (0.2%) , single dose units 0.6 mL, 30	Viscotears		3	5
Carmellose sodium eye-drops 5 mg/mL (0.5%), single dose units 0.4 mL, 30	Cellufresh		3	5
Carmellose sodium eye-drops 10 mg/mL (1%) , single dose unit 0.4 mL, 30	Celluvisc		3	5
Carmellose sodium eye-drops 2.5 mg/mL (0.25%), single dose units, 0.6 mL, 24	TheraTears		4	5
Carmellose sodium ocular lubricating gel 10 mg/mL (1%), single dose 0.6 mL, 28	TheraTears		3	5
Hypromellose with dextran eye-drops 3-1 mg/mL (0.3-0.1%), single 0.4 mL, 28	Bion Tears		3	5
Polyethylene glycol 400 with propylene glycol drops 4 mg-3 mg/mL (0.4-0.3%); single dose units 0.8 mL, 28	Systane		2	5
Polyethylene glycol 400 eye drops 2.5 mg per mL (0.25%), single dose units 0.4 mL, 20	Blink Intensive Tears		5	5
Soy lecithin eye spray 10 mg/mL (1%), 10 mL	Tears Again		2	5
Topical ocular lubricant ointments		Unrestricted		
Paraffin compound eye ointment 3.5 g	Polyvisc		2	5
	Duratears		2	5
Paraffin pack containing 2 tubes compound eye ointment 3.5 g	Polyvisc (2 pack)		1	5
Paraffin pack containing 2 tubes compound eye ointment 3.5 g	Ircal (2 pack)		1	5
	Lacri-Lube (2 pack)		1	5

Commercially available controlled substances that may be used or prescribed by optometrists

19 May 2010

Ocular Medicine	Vic	NT	SA	NSW & ACT	Tas	Qld	WA*	PBS Optometry	PBS Listed
Anti-infectives									
Chloramphenicol	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ciprofloxacin	✓	✓	✓	–	✓	✓	–	–	✓
Framycetin	✓	✓	✓	✓	✓	✓	–	✓	✓
Gentamicin sulfate	✓	✓	✓	–	✓	✓	–	–	✓
Ofloxacin	✓	✓	✓	–	✓	✓	–	–	✓
Sulfacetamide	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tetracycline	✓	✓	✓	✓	✓	✓	–	N/L	N/L
Tobramycin	✓	✓	✓	–	✓	✓	–	–	✓
Aciclovir	✓	✓	✓	–	✓	✓	–	✓	✓
Anti-inflammatories									
Dexamethasone	✓	✓	✓	–	✓	◆	–	–	✓
Fluorometholone	✓	✓	✓	✓	✓	✓	–	✓	✓
Fluorometholone acetate	✓	✓	✓	✓	✓	✓	–	✓	✓
Hydrocortisone	✓	✓	✓	✓	✓	✓	–	✓	✓
Prednisolone	✓	✓	✓	–	✓	◆	–	–	✓
Diclofenac	✓	✓	✓	✓	✓	✓	–	N/L	N/L
Flurbiprofen	✓	✓	✓	✓	✓	✓	–	✓	✓
Ketorolac	✓	✓	✓	✓	✓	✓	–	N/L	N/L
Decongestants, anti-allergics and astringents									
Antazoline	✓	✓	✓	✓	✓	✓	✓	N/L	N/L
Ketotifen	✓	✓	✓	✓	✓	✓	✓	N/L	N/L
Levocabastine	✓	✓	✓	✓	✓	✓	✓	N/L	N/L
Lodoxamide	✓	✓	✓	✓	✓	✓	✓	N/L	N/L
Naphazoline	✓	✓	✓	✓	✓	✓	✓	N/L	N/L
Olopatadine	✓	✓	✓	✓	✓	✓	–	N/L	N/L
Pheniramine	✓	✓	✓	✓	✓	✓	✓	N/L	N/L
Sodium cromoglycate	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tetrahydrozoline	✓	✓	✓	✓	✓	✓	✓	N/L	N/L
Anti-glaucoma preparations									
Apraclonidine	✓	✓	✓	✓	✓	◆	–	–	✓
Betaxolol	✓	✓	✓	✓	✓	◆	–	✓	✓
Bimatoprost	✓	✓	✓	✓	✓	◆	–	✓	✓
Brimonidine	✓	✓	✓	✓	✓	◆	–	✓	✓
Brinzolamide	✓	✓	✓	✓	✓	◆	–	✓	✓
Dorzolamide	✓	✓	✓	✓	✓	◆	–	✓	✓
Latanoprost	✓	✓	✓	✓	✓	◆	–	✓	✓
Pilocarpine	✓	✓	✓	✓	✓	◆	–	✓	✓
Timolol	✓	✓	✓	✓	✓	◆	–	✓	✓
Travoprost	✓	✓	✓	✓	✓	◆	–	✓	✓
Timolol+Bimatoprost	✓	✓	✓	✓	✓	◆	–	✓	✓
Timolol+Brimonidine	✓	✓	✓	✓	✓	◆	–	✓	✓
Timolol+Dorzolamide	✓	✓	✓	✓	✓	◆	–	✓	✓
Timolol+Latanoprost	✓	✓	✓	✓	✓	◆	–	✓	✓
Timolol+Travoprost	✓	✓	✓	✓	✓	◆	–	✓	✓
Mydriatics and cycloplegics									
Atropine	✓	✓	✓	✓	✓	✓	–	–	✓
Cyclopentolate	✓	✓	✓	✓	D	✓	D	N/L	N/L
Homatropine	✓	✓	✓	✓	✓	✓	–	–	✓
Pilocarpine	✓	✓	✓	–	✓	✓	–	–	✓
Phenylephrine	✓	✓	✓	✓	✓	✓	–	N/L	N/L
Tropicamide	✓	✓	✓	✓	D	✓	D	N/L	N/L
Local anaesthetics									
Amethocaine	✓	✓	✓	✓	D	✓	–	N/L	N/L
Lignocaine	✓	✓	✓	–	D	–	–	N/L	N/L
Oxybuprocaine	✓	✓	✓	✓	D	✓	D	N/L	N/L
Proxymetacaine	✓	✓	✓	✓	D	✓	D	N/L	N/L

◆ The use of these medicines by optometrists is currently being considered
* Optometrists in Western Australia do not have access to the PBS
D Diagnostic use only
N/L Substance is not listed under the PBS

THREE LINES OF VISION GAINED[5,8*]

*Based on ANCHOR and MARINA trials, at least one third of patients treated with Lucentis gained 3 lines of vision

TO HIM, IT'S THE WORLD

The vision loss caused by neovascular AMD is devastating and extremely distressing to patients.[1,2]

Lucentis is proven to help patients gain and sustain vision.[3-8] In fact, over 30% of Lucentis treated patients gained vision at two years.[5,8]

For many patients looking at going blind, Lucentis does more than restore their vision. By allowing them to maintain independence,[9] it restores their world.

Please refer to the Product Information before prescribing. Product Information is available from Novartis Pharmaceuticals Australia Pty Limited or visit www.novartis.com.au. For further information please contact Medical Information & Communication on 1800 671 203.

Indication: Treatment of neovascular (wet) age-related macular degeneration (AMD). 0.5 mg or 0.3 mg is recommended to be administered by intravitreal injection once a month. **Dosage and administration:** Recommended dose is 0.5 mg (0.05 mL) or 0.3 mg (0.03 mL) given monthly. Interval between doses should not be shorter than 1 month. Treatment might be reduced to one injection every 3 months after the first three injections but, compared to continued monthly doses, dosing every 3 months may lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months. Patients should be evaluated regularly. Must be administered by a qualified ophthalmologist using aseptic techniques. Broad-spectrum topical microbicide and anaesthetic should be administered prior to injection. Patient should self-administer antimicrobial drops four times daily for 3 days before and after each injection. Not recommended in children and adolescents. **Contraindications:** Hypersensitivity to product components, active or suspected ocular or periocular infections, active intraocular inflammation. **Precautions:** Intravitreal injections have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Proper aseptic injection techniques must be used. Monitor patients during the week following injection to permit early treatment if an infection occurs. Intraocular pressure and perfusion of the optic nerve head must be monitored and managed appropriately. Safety and efficacy of administration to both eyes concurrently have not been studied. There is a *potential* risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. *A numerically higher stroke rate was observed in patients treated with ranibizumab 0.5mg compared to ranibizumab 0.3mg or control, however, the differences were not statistically significant. Patients with known risk factors for stroke, including history of prior stroke or transient ischaemic attack, should be carefully evaluated by their physicians as to whether Lucentis treatment is appropriate and the benefit outweighs the potential risk.* As with all therapeutic proteins, there is a potential for immunogenicity with Lucentis. No formal interaction studies have been performed. Should not be used during pregnancy unless clearly needed; use of effective contraception recommended for women of childbearing potential; breastfeeding not recommended. Patients who experience temporary visual disturbances following treatment must not drive or use machines until these subside. **Side effects:** Very common: Conjunctival haemorrhage, eye pain, vitreous floaters, retinal haemorrhage, *intraocular pressure increased,* vitreous detachment, intraocular inflammation, eye irritation, cataract, foreign body sensation in eyes, lacrimation increased, visual disturbance, blepharitis, subretinal fibrosis, ocular hyperaemia, visual acuity blurred/decreased, dry eye, vitritis, eye pruritis, *nasopharyngitis,* headache, *arthralgia.* Common: Ocular discomfort, eyelid oedema, *eyelid pain,* conjunctival hyperaemia, posterior capsule opacification, punctate keratitis, corneal abrasion, anterior chamber flare, *injection site haemorrhage,* eye haemorrhage, retinal exudates, injection site reactions, conjunctivitis, *conjunctivitis allergic, eye discharge, photopsia,* photophobia, maculopathy, detachment of the retinal pigment epithelium retinal degeneration, retinal disorder, retinal detachment, retinal tear, *retinal pigment epithelium tear,* vitreous haemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, *cataract subcapsular, influenza, anaemia, anxiety, stroke, cough, nausea, allergic reactions (rash, urticaria, pruritis, erythema).* Uncommon: Keratopathy, *iris adhesions, corneal deposits,* dellen, corneal striae, *injection site pain, injection site irritation, abnormal sensation in eye, hyphema,* cataract nuclear, angle closure glaucoma, endophthalmitis, eyelid irritation, blindness, corneal oedema, hypopyon. Rare but serious adverse reactions related to intravitreal injections include endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract.

**Please note changes to Product Information in italics.*

1. Brown MM, et al. Can J Ophthalmol. 2005;40:277-287. 2. Williams RA, et al. Arch Ophthalmol. 1998;116:514-520. 3. Novack GD. Ann Rev Pharmacol Toxicol. 29008:48:61-78. 4. Dalton M. Treatment regimens for AMD focussing on anti-VEGF. EyeWorld January 2007. Available at: http://www.nei.nih.gog/health/maculardegen/armd_facts.asp. Accessed 10 Jan 2008. 5. Rosenfeld PJ, et al. N Engl J Med. 2006;355:1419-1431. 6. Brown DM, et al. N Engl J Med. 2006;355:1432-1444. 7. LUCENTIS Approved Product Information. 8. Brown DM, et al. Ophthalmol. 2009;116:57-65. 9. Chang TS, et al. Arch Ophthalmol. 2007;125:1460-469.

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NOVARTIS

LUCENTIS® RANIBIZUMAB

Improving vision. Restoring hope.[5,9]

PBS Information: Authority Required. Refer to PBS Schedule for full Authority Required Information.