



Nick Lane

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The debate about whether blue-blocking IOLs are a 'good thing' last flared up a couple of years ago. Since then, a million people have had blue-blocking IOLs implanted, and they continue to be first choice for many European surgeons. As new data enter the fray, it's time for a reassessment.

Two years ago, in the venerable pages of the *Archives of Ophthalmology*, Janet Sparrow PhD, of Columbia University (with her colleague Richard Braunstein MD), and Martin Mainster MD, PhD, of the University of Kansas, each put forward eloquent arguments for and against blue-blocking IOLs, respectively. While forceful in their arguments, each acknowledged the need for more data, to determine whether their theoretical considerations have any meaningful bearing on clinical outcomes.

Back then there were open questions on several areas of clinical relevance. Just how damaging is blue light in terms of the risk of developing AMD, especially after cataract surgery? What about changes in hue discrimination, contrast sensitivity and the quality of scotopic vision with blue-blocking IOLs? And are we interfering with the role of the blue-absorbing photopigment melanopsin in modulating circadian rhythms, mood and sleep patterns?

Recent data are starting to give some answers to these questions, so *EuroTimes* turned to Profs Mainster and Sparrow to see how their views are evolving. We also asked Jack Holladay MD, whose careful dissection of the data and forthright views cannot be ignored.

So does blue light contribute to AMD? Epidemiological data have always been equivocal on the subject, but it is notoriously difficult to ascertain how much blue light people are exposed to during a lifetime; or the times in our lives when such exposure is most damaging.

The theoretical case hasn't changed at all. Chronic low-dose photodamage is thought to be wrought mostly by the light absorption and activation of various chromophores, including mitochondrial cytochromes and lipofuscin, which includes light-sensitive by-products of retinoid cycling, such as A2E. Lipofuscin builds up over a lifetime in the cells of the retinal pigment epithelium, and absorbs in the blue, violet and UV parts of the spectrum. If activated, it can induce apoptosis, at least in vitro. It certainly looks like a smoking gun. Are appearances deceptive?

"We know that A2E is responsible for most of the autofluorescence of the human retina, and that the areas which

fluoresce most also tend to atrophy in AMD," Prof Sparrow told *EuroTimes*.

"We know that accumulation of lipofuscin is the most noticeable change in the RPE; and we know that photoreceptor loss tends to be secondary to retinal pigment epithelium damage. But formal proof of a link between lipofuscin and AMD is difficult. Advocating blue-blockers is really a matter of prudence."

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Prof Mainster and Dr Holladay both disagree with the logic here. "Blue-blocking IOLs provide less retinal photoprotection than the crystalline lens of a 50-year old. Most AMD occurs in phakic adults over 60, so youthful crystalline lenses certainly don't prevent AMD. And if a yellowed crystalline lens doesn't stop AMD, then neither will a blue-blocking IOL," Prof Mainster told *EuroTimes*.

Prof Sparrow counters: "Arguing that blue-blockers can't prevent AMD is like saying seat belts don't protect in all cases of vehicular accidents, (ie, some people sustain injury even though wearing a seat belt) so there is no point in wearing seat belts."

Whatever the merits of either argument, the real question is different – does the great flood of blue light entering an eye with a clear IOL after cataract surgery make AMD more likely than it would have been if at least some of this flood was filtered by a blue-blocker or the native lens?

There's no question that a clear IOL can be a shock to people after cataract surgery. The artist Claude Monet, no doubt more sensitive than most, was so disturbed by the transformation in his colour perception after cataract surgery that he insisted on wearing yellow-tinted spectacles. The shock of the blue was just too much. According to Prof Sparrow, much the same goes for many patients today, even if they 'settle down' after a few days or weeks.

But does this blue shock hasten the onset of AMD? There are two ways in which cataract surgery could contribute to AMD – the surgery itself, or the long-

term exposure to greater amounts of blue light. Another possibility is simply that the development of cataracts and AMD have a number of risk factors in common, making AMD more likely in people with cataracts.

Dr Holladay accepts that cataract surgery can be a risk. "The surgery itself can often cause active inflammation and leakage into the retina for periods of six weeks or so after surgery, during which

time the eye might well be vulnerable to phototoxicity. Patients should certainly wear dark glasses during this time," he told *EuroTimes*.

But what of the longer-term exposure to blue light after implantation of a clear IOL?

Again, epidemiological evidence is equivocal. Prof Sparrow notes that the largest study, a meta-analysis of the Beaver Dam and the Blue Mountain studies, with pooled data from some 6000 patients followed up for five years, implied that the risk of AMD following cataract surgery is increased two- to five-fold. These data predate the blue-blocking IOL era, and so refer to clear IOLs. A clear issue with clear lenses, then?

Not necessarily. The incidence of AMD in these studies was actually very low – only a few tens of people, out of 6000, actually went on to develop AMD, so the difference between the two groups was trivial.

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Other studies, including an analysis of AREDS data (presented by Susan Bressler MD and her colleagues at ARVO 2006) and a study published in April this year by Florian Sutter MD, and his colleagues at

the University Hospital, Zurich, imply that cataract surgery does not increase the risk of AMD. This latter Swiss study was a retrospective case-control study enrolling 499 patients, and was specifically designed to overcome the failings of the epidemiological studies.

Sutter and colleagues noted that, despite the limitations of a retrospective design, their study evaluated nearly 10 times the number of eyes with neovascular AMD than did the Blue Mountain and Beaver Dam studies combined – and had a well-matched control group.

"Data from this study do not support the hypothesis that pseudophakia is a major risk factor for the development of neovascular AMD", Sutter et al concluded. And plainly, if pseudophakia does not increase the risk of AMD, there can't be any difference between implanting a clear IOL or a blue-blocking IOL.

So what are we to conclude about AMD? There is still no direct evidence that blue-blocking IOLs lower the risk of AMD, and on the basis of recent studies, like that by Sutter et al, the theoretical case seems to be weaker now than it was a year or two ago. If there really is a relationship between cataract surgery and AMD, it is more likely related to shared risk factors, or the pro-inflammatory effects of intra-ocular surgery.

But is there a downside for those of prudent disposition? Is it better to be safe than sorry, or will you be sorry for false security?

#### **Do blue-blockers impair visual performance?**

Arguments rage about whether hue discrimination and contrast sensitivity are influenced by blue-blocking IOLs; but despite a fair amount of scrappiness in the data, it seems the two types of IOL are broadly equivalent in both regards.

Dr Holladay is quick to disagree with the contention that hue discrimination is

not affected by blue-blocking IOLs.

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even that we can measure the difference in tests.”

Prof Mainster concurs. “Most studies have shown an equivalence between blue-blocking and clear IOLs in terms of both hue discrimination and contrast sensitivity, although there are reports in the literature of colour-disparity problems requiring explantation, and blue-blocking IOLs aren't recommended for United States Air Force aircrew because of operational colour vision tasks.”

He went on: “It's not surprising that blue-blocking IOLs fail to improve contrast sensitivity: the photopic performance of pseudophakic eyes at medium and high spatial frequencies is determined primarily by wavelengths between 500 and 600 nm that are focused better on the retina than shorter or longer wavelengths. So, blue light has minimal effect on clinical contrast sensitivity.”

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**Martin Mainster MD, PhD**

But in terms of visual performance, the biggest question mark against blue-blocking IOLs is scotopic sensitivity. Because rods absorb maximally at around 500nm, in the blue-green part of the spectrum, blocking blue light cuts out a greater proportion of detectable light at night than it does during the day. The question is, how much more; and does it make a meaningful difference?

Until recently, the difference was a matter of theoretical calculation, first estimated by Prof Mainster in a joint paper with Prof Sparrow in the *BJO* in 2003. The answer is not straightforward, because a number of factors need to be taken into consideration beyond the proportion of the spectrum actually absorbed by rods and cones.

“Older adults with healthy retinas exhibit, on average, a one log unit elevation in their absolute detection threshold – which is to say a decrease in sensitivity – under dark-adapted conditions. Apart from increases in lens density, this decrease in sensitivity can be

attributed to pupillary miosis, age-related loss of rod photoreceptor cells, slower photopigment regeneration, and probably diminished neural sensitivity,” Prof Sparrow told *EuroTimes*.

Prof Mainster agrees with all of that, and indeed stresses that rod loss is greater in AMD and diabetic retinopathy; but he believes that failing to maximise the passage of blue light fails to make the most of the opportunities offered by cataract surgery.

“Optical factors decrease effective scotopic retinal illuminances for 65- and 75-year-old eyes to only 37 per cent and 26 per cent of 10-year-old eyes, respectively. On top of that, blue-blocking IOLs offer 14 to 21 per cent less scotopic sensitivity than UV-blockers. I accept that this reduction is small compared with the broad range of visual sensitivity, but it's still a loss, and one that can impact on driving, mobility and peripheral vision,” he

told *EuroTimes*.

A number of studies have examined the impact of blue-blocking IOLs on scotopic sensitivity, but Prof Mainster is sceptical of their findings.

“One recent study purported to examine scotopic vision using the Mesotest II – even from its name, obviously designed to measure mesopic vision. And when you read the paper carefully the authors did indeed measure mesopic vision, which depends on cones as well as rods, and is less affected by blue-blocking IOLs than scotopic vision. And there are other frankly misleading reports about 'scotopic' vision in the literature.”

Prof Sparrow is sufficiently concerned by these considerations to have conducted a study of scotopic sensitivity (and hue discrimination) on patients at Columbia University, published in the *JCRS* this April. Using a modified Humphrey Field Analyzer, Sparrow and colleagues found no differences in the scotopic sensitivity of nine patients with mixed

pseudophakia to 440nm, 500nm, and 650nm lights.

“Our results suggest that visual performance under scotopic conditions is not impaired after implantation of a blue-blocking IOL,” Prof Sparrow concluded.

What's more, she notes that patients rarely need to deal with true scotopic conditions these days; driving at night, for example, relies more on mesopic than scotopic vision. And visits to the bathroom in the dead of night are rarely made under truly scotopic conditions.

On the other hand, a group of nine young phakic subjects tested with yellow-tinted clip-on lenses (made from the same material as the blue-blocking IOL) did show differences in scotopic sensitivity (but not hue discrimination), especially to 44nm light, confirming theoretical predictions. This might be seen as evidence that blue-blockers can impair scotopic sensitivity in younger eyes (with fewer changes in optical structures); or merely that the younger subjects saw 'double-yellow' – once through the clip-on lenses and once through their own yellowing phakic lenses (whereas the pseudophakic patients had only one yellowish IOL).

So do blue-blockers impair visual function in a meaningful way? The more recent data suggest not, at least not in a clinically detectable way. So it looks as if we can't distinguish between blue-blocker and clear IOLs in terms of either risk of AMD or visual function; it's a one-all draw. So is the decision all down to personal preference? There is one other factor, stressed by Prof Mainster, which could be the decider – circadian rhythms.

#### **Do blue-blockers affect circadian rhythms?**

The seminal finding was that blind mice (with dysfunctional photopigments in both rods and cones) could still detect diurnal changes. The perpetrator turned out to be melanopsin, a photopigment found only in a small proportion (one to two per cent) of retinal ganglion cells, and discovered in the human eye barely a few years ago. Remarkably, the train of biochemical events kicked off by melanopsin, as well as the pigment itself, is closely related to those in invertebrate eyes – we share our circadian rhythms with shrimp. They're old and important.

Melanopsin absorbs in the blue, with a peak absorbance of around 460nm, and it controls the diurnal cycle via changes in the levels of the hormone melatonin – subject of a famous book, a few years ago, called *The Melatonin Miracle*. Melatonin may be no miracle, but it's undoubtedly important in ways that are not yet fully understood. Sleep patterns, mood,

depression – all are influenced by melatonin.

Prof Mainster draws attention to the fact that cataract surgery should aim to do more than just improve vision – it should also improve overall health.

“Insomnia and depression are well-known aging problems. Increasing blue-light-dependent unconscious circadian photoreception extends the benefits of cataract surgery beyond image-based vision to improved health and longevity,” he contends.

There is certainly good evidence that cataract surgery can help. Two studies by Asplund and Ejderik Lindblad, at the Karolinska Institute and Sundsvall Hospital, Sweden, respectively, examined sleep and sleepiness one month and nine months after cataract surgery in nearly 500 elderly men and women. Nocturnal sleep patterns improved in 12 per cent of the men and 26 per cent of the women a month after surgery, while daytime sleepiness fell in 19 per cent of men and women. And both sleep and sleepiness improved further after nine months.

These studies were carried out in 2002 and 2004, using clear IOLs. The implication is that the more blue light the better, as far as circadian rhythms are concerned. But of course this too is an unproved conjecture: it may also be that the shock of the blue is too much for some people and that allowing in somewhat more blue light, without opening the flood gates with a clear IOL, is the best answer. These are open questions, which have not yet been explored at all.

Prof Mainster argues that, “After 3.5 billion years of evolution, life on earth is well adapted to its blue sky.”

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**Martin Mainster MD, PhD**

That is certainly true, but ageing and degeneration are not adaptive processes, and how well an old body can cope with the shock of the blue is another matter. Yet all else being equal, if there is a null hypothesis now, it ought to be that blue light is good for the health. Advocates of blue-blocker IOLs should now prove otherwise.