

Blue Light Filtering IOLs and Ocular Health

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Key Messages:

- Our current lifestyle exposes us to an abundance of blue light in our daily lives in the form of laptops, cell phones and tablets
- Short wavelength/high energy blue light with an excitation peak around 440 nm, has a negative effect on retinal health as it leads to creation of free radical oxygen species which have a damaging effect on retinal cells, including the retinal pigmented epithelium (RPE) cells and photoreceptors
- Experimental evidence suggests that blue light induces retinal toxicity and damage
- Clinical studies support that there are no clinically meaningful differences between short term BCVA and functional vision between blue-light filtering (BLF) and non-BLF IOLs and that BLF IOLs do not interfere with circadian rhythms and mood
- Clinical evidence shows that BLF IOLs reduced photostress recovery time and glare disability
- Clinical studies have not definitively demonstrated a protective benefit of blue-light filtering lenses on macular health

Light and ocular health

Worldwide, cataract and age-related macular degeneration (AMD) are among the leading causes of blindness.¹ Light is essential for vision, but also has the ability to cause ocular damage. Although all light can cause ocular damage with high enough magnitudes, particular attention has been paid to UVA (315 nm to 400nm), UVB (280 nm to 315 nm) and high energy visible light (HEVL), which includes high-frequency blue/violet light between wavelengths of 400-500 nm in the visible spectrum.

UV light and ocular diseases

The damage from UVC (100-280 nm) in sunlight is usually negligible due to its absorption by the ozone in the upper atmosphere.² The cornea, iris and crystalline lens absorb almost all UVA and UVB radiation and thus, UV light has been linked to eyelid malignancies, pterygium, corneal damage and cataract formation.^{3,4} The UV light that does pass through the cornea, iris and lens is further absorbed by the melanin in the retinal pigmented epithelium (RPE). With age, ocular melanin is photobleached and the retina's innate protection against UV-induced damage is decreased.⁵ However, the light transmission in the lens of an older adult shifts to longer wavelength, starts at 400 nm and peak at 575 nm compared to the lens of a young child, which transmit light from 300 nm and peak at 380 nm. Yam and Kwok (2014) reviewed the literature on UV exposure and ocular disease, and found insufficient evidence to link UV exposure to the diseases in the back of the eye (AMD and uveal melanoma).

It is now widely accepted that UV radiation is a risk factor for cataract⁴ and several population based studies have shown a link between cataract formation and ambient UV light exposure.⁶ However, most studies found mixed associations for AMD and ambient UV light exposure, and the most recent population based study found an increased risk for low- and high-exposures.⁶ Other studies assessing UV radiation and AMD have similarly found mixed associations: the Maryland Watermen Study found no association⁷; the Beaver Dam Eye Study found no association of AMD with ambient UVB exposure⁸⁻¹⁰; the Blue Mountains Eye study found late-AMD association with high and low sun sensitivity index, and sun skin sensitivity¹¹ and an Australian study found AMD association with lower time of ocular sunlight exposure.¹²

Overall, the UV light damage to the retina and choroid remains low due to the light screen effect from cornea, iris and natural crystalline lens. Studies on early intraocular lens that allowed all UV and visible light to pass showed they could cause significant retinopathy by overexposure to UV light.¹³ The use of UV blocking IOL has been widely accepted in cataract surgery since the mid-1980s.¹⁴

Blue light, retinal toxicity, and AMD

Although previous studies found mixed association between AMD and UV exposure, other studies have found evidence that blue light exposure and AMD may be linked.^{7,15} Unlike most UV light, blue light is not absorbed by the cornea, and most can pass through the lens and reach the retina (Figure 1). An age-related decreasing of blue light transmission through lens is reported and proved by in vitro and in vivo measurement.¹⁶ As blue light hits the retina, blue light accelerates the cellular damage¹⁷ that has been hypothesized to contribute to the pathophysiology of AMD. Blue light induces acute phototoxicity, and it is established that the damage is photochemical in nature and damage peaks around 440nm.^{18,19}

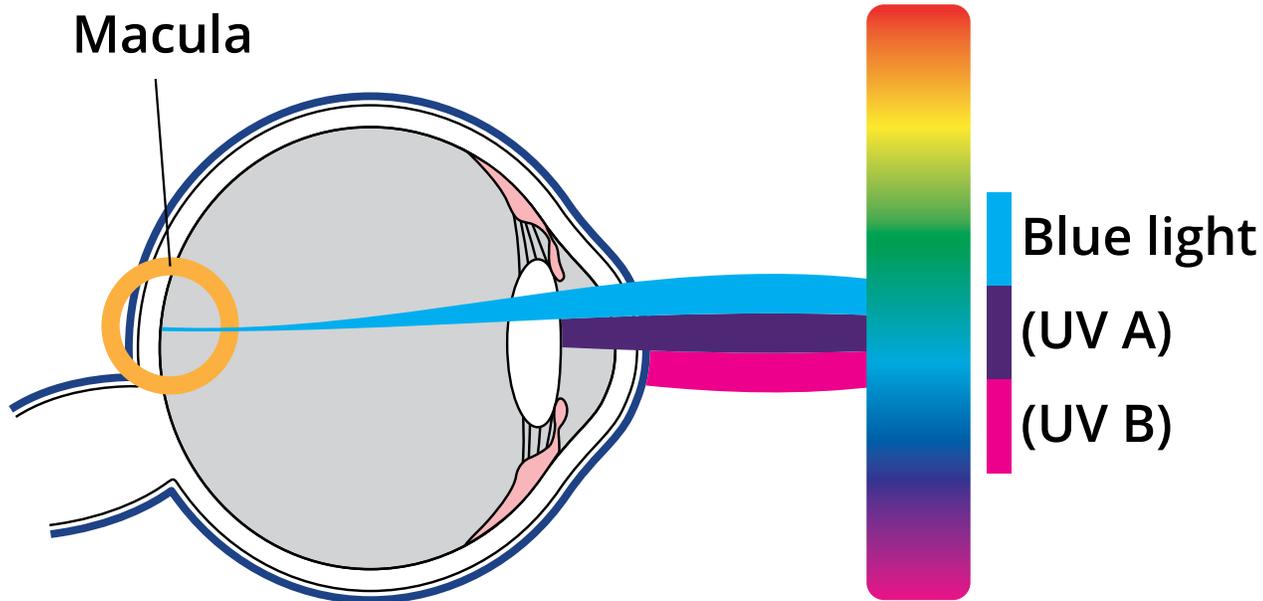


Figure 1: Light transmission through the eye

Blue light is hypothesized to induce retinal damage in several ways and may interact with several pigments in the retina, as well as with cellular structures. The main sites of retinal toxicity are the retinal pigmented epithelium cells and the photoreceptor cells (Figure 2).

Mitochondrial reactive oxygen species production

Reactive oxygen species (ROS) can form from mitochondrial cytochromes after blue light exposure in RPE cells.²⁰ This eventually leads to cell death through the mitochondria's electron transport chain.²⁰

Pigments and blue light

It has also been shown that pigments, including rhodopsin, lipofuscin and melanin, can mediate light induced damage in the retina.²¹⁻²⁶ Recent studies have sought to establish the molecular underpinnings of how blue light may mediate damage through these various pigments. After light hits opsin in photoreceptors, chromophore 11-cis retinal (11CR) is transformed into all-trans retinal (ATR) and RPE cells convert ATR back.^{27,28} Studies have found that dysfunction in the 11CR regeneration process can result in retinal ATR accumulation in the retina and ATR-mediated retinotoxicity that may eventually lead to AMD.²⁹ ATR can photooxidize in photoreceptor cells, generating ROS that mobilize calcium to induce cytotoxicity and apoptosis.^{29,30} A recent study also found that blue light-excited ATR and 11CR perturb phosphatidylinositol 4,5 bisphosphate (PIP2) signaling, leading to photoreceptor cell death.³¹

In the RPE, photodegraded ATR is also linked to cytotoxicity.³² Furthermore, ATR accumulation leads to formation of lipofuscins, and RPE cell lipofuscin accumulation is one of the first clinical markers for macular degeneration in AMD.^{33,34} Lipofuscins are fluorescent pigment molecules composed of lipid residues from lysosomal degradation, and lipofuscins have been demonstrated to produce ROS.³⁵ In

the presence of short wavelength (400–430 nm) blue light, accumulated lipofuscins can also act as a photooxidizing agent that leads to cellular damage.³⁶⁻³⁸ Additionally, lipofuscins contain a fluorophore called A2E that has been shown to be toxic through several mechanisms (impaired RPE cell phagocytosis, detachment of cytochrome c from mitochondria and induction of RPE cell apoptosis).³⁹⁻⁴³

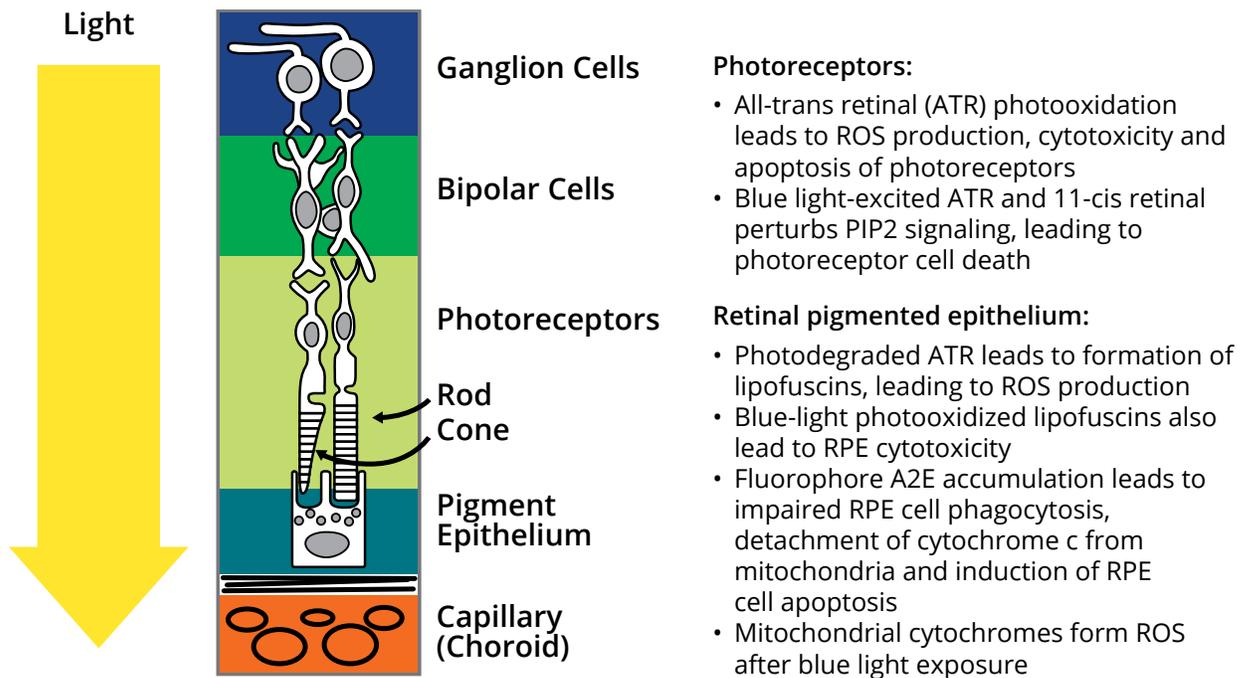


Figure 2: Summary of blue light-induce retinal damage

Blue-light filtering intraocular lenses

In-vitro experimental evidence for blue-light filtering intraocular lenses

As stated previously, as the eye ages, the lens accumulates yellow pigment which attenuates blue light penetration to the retina.⁴⁴⁻⁴⁵ Unfortunately, the accumulation of pigment and other proteins in the lens also leads to a loss of lens opacity and cataract formation. Following surgical removal of a cataract lens, intraocular lenses (IOLs) are implanted to replace the natural lens. Most modern IOLs block UV light and these lenses have been widely adopted. More recently, IOLs containing a yellow chromophore that filters blue light have been developed to protect from the potentially harmful effects of HELV and blue light. Given all the evidence showing that blue light damages photoreceptors and RPE cells, blue light filtering IOLs were designed to mimic the adult crystalline lens. For example, Alcon AcrySof® BLF IOLs contain a proprietary yellow chromophore that approximates the light transmission of a natural lens (Figure 3).⁴⁶ As shown in Figure 3, not all blue light is blocked. AcrySof® blue-light filtering IOLs reduce transmittance of blue light wavelengths from 62% at 400 nm to 23% at 475nm.

Experimental in-vitro studies have shown that blue-light filtering IOLs can protect from blue light induced retinal pigmented epithelial cell death^{47,48} and reduce vascular endothelial growth factor production, an important vascular angiogenesis growth factor in AMD and uveal melanoma pathogenesis.⁴⁹ BLF IOLs also inhibited proliferation of melanoma cell lines in-vitro.⁵⁰

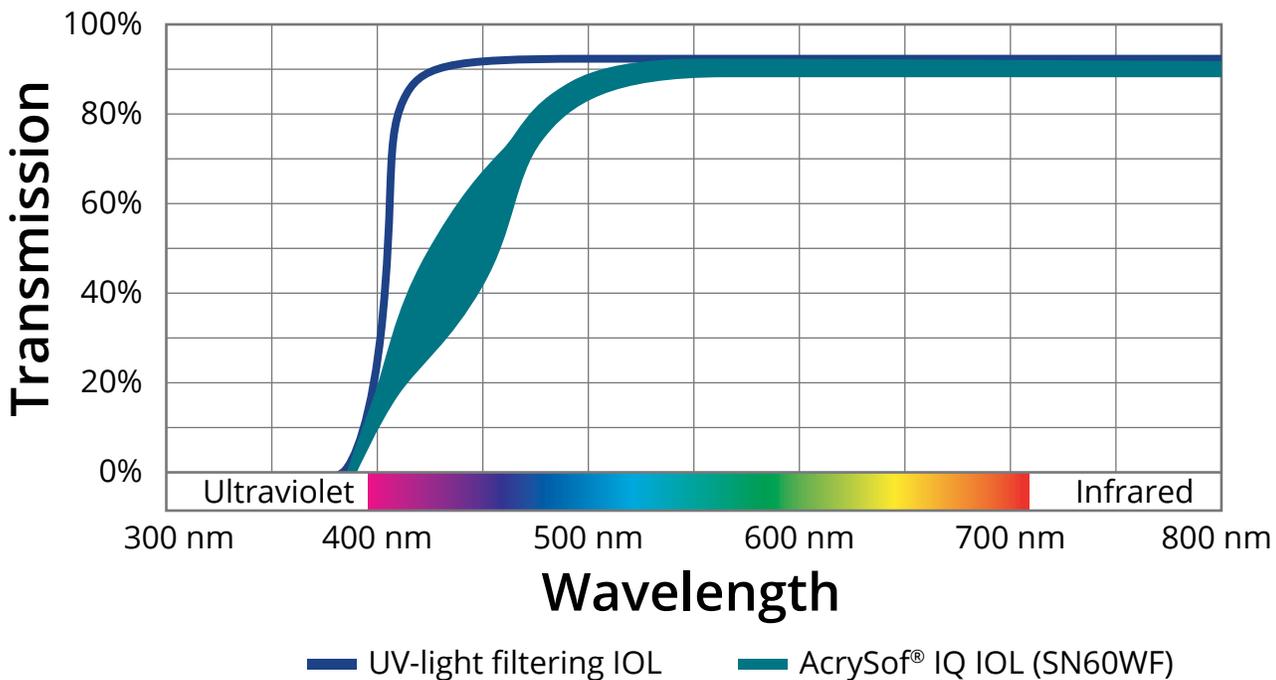


Figure 3: Light Transmission Across the Spectrum⁴⁶

Criticisms of blue-light filtering IOLs

Blue-light filtering IOLs have been debated since their inception in 1990s. Initial criticisms of chromophore-containing lenses included their potential ability to disrupt circadian rhythms. The photopigment found in retinal cells that controls circadian rhythms (the photopigment melanopsin in intrinsically photosensitive retinal ganglions cells, or iPRGS) reaches peak light absorption at blue light wavelengths around 480 nm. Additional concerns included the disruption of some visual functions, including contrast sensitivity, color vision, scotopic vision and visual acuity. Furthermore, critics have pointed out that there is not enough clinical evidence to suggest that filtering blue light may help prevent macular degeneration.

Clinical evidence on blue-light filtering IOLs: circadian rhythms

Sleep, mood and circadian rhythms in patients with blue-light filtering IOLs remain normal, according to multiple clinical studies.^{16,51-55} A recent randomized controlled study showed that intrinsic activation of iPRGCs by blue light was not significantly different between patients randomized to blue-light filtering or non-blue-light filtering IOLs.¹⁶ Furthermore, the authors found that there was no significant differences between blue light filtering or non-blue-light filtering IOLs in other parameters that may be affected by disrupted circadian rhythms, including salivary melatonin concentration, objective and subjective sleep quality, and circadian rhythm assessment by actigraphy.¹⁶ Another recent randomized controlled study found no significant differences in patients implanted with blue light filtering or non-blue light filtering IOLs in terms of sleep time, sleep latency, total sleep duration, quality of sleep and Beck Depression Inventory (BDI) scores.⁵³ Overall, the data support that there are no meaningful differences in outcomes related to circadian rhythms in patients implanted with blue light filtering or neutral IOLs following cataract surgery.

Clinical evidence on blue-light filtering IOLs: functional visual outcomes

Several studies on yellow chromophore-containing/blue-light filtering IOLs have now shown that visual acuity, contrast sensitivity and other visual functions are not disrupted in patients with blue-light filtering IOLs. A recent meta-analysis compared blue-light filtering IOLs with non-blue-light filtering IOLs to assess visual outcomes with respect to providing a benefit to macular health and function.⁵⁶ This study included 51 randomized controlled trials (RCT) from 17 countries, and included outcomes of over 5,000 eyes implanted with IOLs. To date, this is the most comprehensive analysis of all available RCT data, although the authors employed stringent exclusion criteria for examining grouped outcomes. The main outcomes considered in this study were:

1. the change in distance best-corrected visual acuity (BCVA), as a continuous outcome, between baseline and 12 months of follow-up (primary outcome)
2. postoperative contrast sensitivity
3. postoperative color discrimination
4. macular pigment optical density (MPOD)
5. postoperative proportion of eyes with a pathological finding at the macula (including, but not limited to the development or progression of AMD, or both),

Overall, this meta-analysis supports that there was no clinically meaningful difference in short-term BCVA between blue-light filtering IOLs and non-blue light filtering IOLs.⁵⁶ Due to different study design and measurement methods, no relevant combinable data was available for color discrimination and MPOD analysis. However, the paper acknowledged that most individual studies that considered effects on color perception reported no significant differences between IOL interventions. This result is consistent with a previous review paper and meta-analysis.^{14,57} Furthermore, there was no clinically meaningful difference between IOL interventions in contrast sensitivity.^{56,57} The study also found that there were no differences in safety, as assessed by pre- and post-operative complications between the two interventions.⁵⁶

Original experimental studies suggested that blue light filtering IOLs induce a moderate reduction of the scotopic sensitivity, the same magnitude as that of a 53-year-old human lens.^{58,58} However, further analysis disputed this result, because of the use of inappropriate controls.⁶⁰ Further clinical studies did not find significant differences between UV blocking and BLF IOLs in terms of scotopic sensitivity.^{61,62}

Clinical evidence on blue-light filtering IOLs: Visual performance under glare conditions

Hammond found that patients with the BLF lenses had shorter photostress recovery times and significantly reduced glare disability compared with patients who received clear IOLs.^{63,64} Furthermore, pseudophakic patients implanted with clear IOLs and addition of blue-light-filtering glasses had a shorter photostress recovery and reduced glare disability compared with those wearing clear, non-blue light filtering glasses (a patient masked, randomized clinical study).⁶⁵ Gray also reported blue-light filtering IOLs reduced glare disability on driving performance.⁶⁶ All these studies support that blue-light-filtering help quickly to regain sight and have better functional vision under intense light conditions. Furthermore, several papers have suggested that blue-light filtering IOLs may improve chromatic contrast relative to non-BLF IOLs^{67,68} and that blue light is a risk factor for uveal melanoma and filtering blue light may provide protection against this disease.⁶⁹ However, more clinical research is needed on these topics.

Clinical evidence on blue-light filtering IOLs: macular health

Two recent meta-analysis studies concluded that based upon the current, best-available clinical data, the evidence surrounding whether blue-light filtering IOLs provide greater macular protection than non-blue-light filtering is inconclusive.^{56,57} Indeed, it is very difficult to show that blue-light filtering IOLs slow down or prevent AMD disease progression. The pathogenesis of AMD is currently well accepted as multifactorial, including a mixed interaction of genetic, metabolic and environmental factors, including blue light exposure. The disease is a slow, progressive process. Thus, further rigorous clinical research with a core set of outcome measures as suggested by Downie⁵⁶ is necessary to determine if blue-light filtering IOLs confer protection against macular degeneration.

Conclusions

There is much experimental evidence showing that blue light poses a hazard to macular health induces retinal toxicity and damage. Clinical evidence shows that there is no interference with visual performance or circadian rhythms with blue-light filtering IOLs. Clinical evidence also shows that BLF IOLs reduced photostress recovery time and reduced glare disability. However, current clinical studies have not definitively demonstrated a protective benefit of blue-light filtering lenses on macular health. More well-designed studies are necessary.

AcrySof® IQ Restor® Family of Intraocular Lenses

Important Product Information

CAUTION: Federal (USA) law restricts this device to the sale by or on the order of a physician.

INDICATIONS: The AcrySof® IQ ReSTOR® Posterior Chamber Intraocular Lens (IOL) is intended for primary implantation for the visual correction of aphakia secondary to removal of a cataractous lens in adult patients with and without presbyopia, who desire near, intermediate and distance vision with increased spectacle independence. The lens is intended to be placed in the capsular bag.

WARNINGS/PRECAUTIONS: Careful preoperative evaluation and sound clinical judgment should be used by the surgeon to decide the risk/benefit ratio before implanting a lens in a patient with any of the conditions described in the Directions for Use labeling. Physicians should target emmetropia, and ensure that IOL centration is achieved. Care should be taken to remove viscoelastic from the eye at the close of surgery.

Some patients may experience visual disturbances and/or discomfort due to multifocality, especially under dim light conditions. As with other multifocal IOLs, visual symptoms may be significant enough that the patient will request explant of the multifocal IOL. Spectacle independence rates vary with all multifocal IOLs; as such, some patients may need glasses when reading small print or looking at small objects.

Clinical studies with the AcrySof® ReSTOR® lens indicated that posterior capsule opacification (PCO), when present, developed earlier into clinically significant PCO. Prior to surgery, physicians should provide prospective patients with a copy of the Patient Information Brochure available from Alcon for this product informing them of possible risks and benefits associated with the AcrySof® IQ ReSTOR® IOLs.

Studies have shown that color vision discrimination is not adversely affected in individuals with the AcrySof® Natural IOL and normal color vision. The effect on vision of the AcrySof® Natural IOL in subjects with hereditary color vision defects and acquired color vision defects secondary to ocular disease (e.g., glaucoma, diabetic retinopathy, chronic uveitis, and other retinal or optic nerve diseases) has not been studied. Do not resterilize; do not store over 45° C; use only sterile irrigating solutions such as BSS® or BSS PLUS® Sterile Intraocular Irrigating Solutions.

ATTENTION: Reference the Directions for Use labeling for a complete listing of indications, warnings and precautions.

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