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REVIEW ARTICLE

Recent studies provide an updated clinical perspective on blue light-filtering IOLs

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Abstract
Background Recent reviews of blue light-filtering intraocular lenses (IOLs) have stated their potential risks for scotopic vision and circadian photoentrainment. Some authors have challenged the rationale for retinal photoprotection that these IOLs might provide. Our objective is to address these issues by providing an updated clinical perspective based on the results of the most recent studies.
Methods This article evaluates the currently available published papers assessing the potential risks and benefits of blue light-filtering IOLs. It summarizes the results of seven clinical and two computational studies on photoreception, and several studies related to retinal photoprotection, all of which were not available in the previous reviews. These results provide a clinical risk/benefit analysis for an updated review for these IOLs.
Results Most clinical studies comparing IOLs with and without the blue light-filtering feature have found no difference in clinical performance for; visual acuity, contrast sensitivity, color vision, or glare. For blue light-filtering IOLs, three comparative clinical studies have shown improved contrast sensitivity and glare reduction; but one study, while it showed satisfactory overall color perception, demonstrated some compromise in mesopic comparative blue color discrimination. Comparative results of two recent clinical studies have also shown improved performance for simulated driving under glare conditions and reduced glare disability, better heterochromatic contrast threshold, and faster recovery from photostress for blue light-filtering IOLs. Two computational and five clinical studies found no difference in performance between IOLs with or without blue light-filtration for scotopic vision performance and photo entrainment of the circadian rhythm. The rationale for protection of the pseudophakic retina against phototoxicity is discussed with supporting results of the most recent computational, in-vitro, animal, clinical, and epidemiological investigations.
Conclusions This analysis provides an updated clinical perspective which suggests the selection of blue light-filtering IOLs for patients of any age, but especially for pediatric and presbyopic lens exchange patients with a longer pseudophakic life. Without clinically substantiated potential risks, these patients should experience the benefit of overall better quality of vision, reduced glare disability at least in some conditions, and better protection against retinal phototoxicity and its associated potential risk for AMD.

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Introduction

The most common cause of vision loss in elderly patients is the development of cataract, and intraocular lens (IOL) implantation at the time of cataract surgery is the most effective treatment for vision restoration. In addition to the large number of elderly cataract patients, there is an increasing global population of pediatric cataract and presbyopic lens exchange patients who will have an even longer life expectancy after IOL implantation. Because of this longevity, the eyes of these patients will be more likely to be vulnerable to retinal phototoxic effects which may cumulatively influence the development of age-related macular degeneration (AMD). The natural human lens filters and thereby protects the potential retinal damage from high-energy photons of ultraviolet radiation (UVR) and short wavelength light. Since the early 1980s, UVR-filtering IOLs have been widely used. They are colorless and filter UVR to various degrees. They may not completely block UVR, and hence we will refer to them in this article as UVR-filtering IOLs. PMMA (poly methyl methacrylate) yellow tinted IOLs which filter both ultraviolet radiation (UVR) and blue light have been under investigation since the mid 1980s, and have been available into the global market with an advanced technology foldable version which approximates normal light transmission by the natural crystalline lens (light normalizing) introduced in 2003 [1]. These lenses, with each brand (and each power within the brand) having slightly different transmission characteristics, are also referred to in the literature as blue-blocking IOLs, yellow-tinted IOLs, ultraviolet-cut noncyanopsia IOLs, or light-normalizing IOLs. But for this article they are generically referred to as blue light-filtering IOLs, with the proviso that they completely block UVR as well. The rationale for their use has been to better approximate the transmission of electromagnetic radiation via the natural crystalline lens, by reducing the relatively excessive transmission of short wavelength energy which colorless UVR-filtering IOLs allow. It has been assumed that this normalization would improve overall vision performance and reduce phototoxicity, which might provide retinal protection against the risks of development or progression of AMD. These IOLs have been judged safe and effective by the rigorous testing process of the US FDA, and obtained approval by that body in 2003. An exhaustively complete 2005 review paper by two of the current authors (Davison and Patel) in International Ophthalmology Clinics provided a detailed history, rationale for potential retinal photoprotection, correction of cyanopsia, and a possible improvement in contrast sensitivity by these IOLs [1]. It also reviewed epidemiological literature available in 2005, and concluded that long-term clinical study would be required to provide the ultimate support to the hypothesis that blue light-filtering IOLs might provide retinal photoprotection against the development or progression of AMD.

For several reasons, a contrary school of thought began to develop in opposition to the use of blue light-filtering IOLs [2–8]. Those authors have expressed concerns about the potential of reduced photoreception due to blue light-filtering, and have challenged the rationale for the potential of retinal phototoxicity reduction and its possible benefit in modifying the development or progression of AMD. Initially, there was an understandable concern over color vision effects for blue light-filtering IOLs, which still continues for mesopic color vision. But, as clinical investigations allayed most of these color vision related concerns, new discussions emerged regarding potential effects on scotopic vision performance and concerning possible sleep disturbances related to photoentrainment of the circadian rhythm [2–8]. The concern for these potential risks has been generated on the basis of theoretical considerations and computations. This review critically examines these potential risks with all currently available clinical and alternate computational studies.

Over the last 5 years, new comparative computational and clinical investigations including some by the current authors on blue light-filtering IOLs addressed these potential risks. A 2009 review paper by Cuthbertson et al. [9] cited some of the available results of investigations addressing the potential benefits and side effects of these lenses. However, this paper [9] did not contain relevant computational and clinical studies for scotopic vision and circadian rhythm-sleep disturbance risks [10–13]. In 2010, the debate continued in two new "viewpoint" papers by Mainster & Turner [14] and Henderson & Grimes [15]. In the viewpoint paper against the use of blue light-filtering IOLs by Mainster and Turner [14], there were absences of reference to two relevant clinical investigations on scotopic vision [11, 16, 17] and three studies related to circadian photoentrainment and sleep disturbance [10, 18]. The authors put forth their computations as evidence for concern for potential risks for scotopic vision and circadian photoentrainment. These computations also form their basis for doubt of the rationale of retinal protection which might be provided by blue light-filtering IOLs. Interestingly, and in an apparent contradiction to himself, the first author of the anti-blue light-filtering viewpoint [14] has previously published an actual preference for violet-blocking IOLs [2, 3], and is the principal inventor in a patent filed in 2005 and issued in 2007 for violet-

blocking IOL technology [19]. This patent states that "high transmission levels of blue and violet light (wavelengths from about 390 nm to about 500 nm) has been linked to retinal damage, macular degeneration, retinitis pigmentosa and night blindness. In addition, blue and violet light tends to be scattered in the atmosphere, especially in haze, fog, rain and snow, which in part can cause glare and diminished visual acuity". A similar list of newer citations was also not included by Henderson and Grimes in their pro-blue light-filtering IOL viewpoint paper, but based on the ones that were cited; these authors concluded that the potential negative effects of scotopic vision and sleep disturbance for blue light-filtering IOLs appear to be minimal, and may not be clinically relevant [15]. In this review, we will provide those additional, references for scotopic vision [16, 17] and for circadian rhythm-sleep disturbance [10, 13, 18] which were not discussed or cited in this pro-blue light-filtering view point paper [15].

Since the publication of the pro and anti blue light-filtering reviews, some new relevant computational and clinical studies have been performed by the current authors and others, and are included in this updated review.

Ultimately, as part of the informed consent process, patients must make decisions regarding various advanced technology features of the prosthetic lens which will be used to rehabilitate their vision after cataract surgery. The choice between UVR with blue light-filtering and UVR-only filtering IOLs represents one of those decisions. The objective of this article is to provide an updated review and clinical perspective to practicing surgeons so that they can inform and guide their patients regarding their choice of an IOL. This updated review addresses potential risks and benefits for blue light-filtering IOLs by providing relevant results and discussion of all studies up to February 2011.

Material and methods

In order for this to be an updated review, we carried out an exhaustive literature search using resources of Pubmed and American Society of Cataract and Refractive Surgery for each of the issues of photoreception and the various types of studies for photoprotection for the blue light-filtering IOLs. We then created, and present here, a summary of all currently available (to February 2011) results of all relevant investigations on photopic vision, mesopic vision, scotopic vision, and sleep disturbance related to photoentrainment of circadian rhythm. New investigations which test for glare and photopic vision performance and sleep disturbance are also presented, since they were not addressed in the recent review papers. Available results of in-vitro, animal, clinical and epidemiological studies are also summarized. We also refer to and discuss a new systematic review for cataract surgery and progression of AMD, and the EUREYE epidemiological study for AMD and blue light exposure. These summaries and discussions provide an overall risk/benefit analysis to create an updated clinical perspective for selection of IOLs with or without blue light-filtering technology.

Results

Concerns about the performance of blue light-filtering IOLs [2–8, 14] can be divided into three categories: 1. quality of vision: photopic and mesopic photoreception, which includes measurements of visual acuity, contrast sensitivity, glare, and color vision under those conditions, and scotopic photoreception; 2. photoentrainment of the circadian rhythm and its consequences on sleep; and 3. the potential for retinal protection from high-energy short-wavelength light and its implication in the process of AMD. Various existing and new investigations for comparative evaluations of IOLs and their results relevant to such concerns and questioning are given below, with special emphasis on those which were not discussed in the recent review and viewpoint papers [9, 14, 15].

Photoreception in pseudophakic eyes with the blue light-filtering IOLs

Photopic and mesopic vision: visual acuity, contrast sensitivity, and glare

At least 15 prior comparative clinical investigations in pseudophakic eyes exist [17, 20–33]. Included in this list is one for United States Food and Drug Administration approval, in which one of us (Davison) participated, for comparing blue light-filtering IOLs versus UVR-filtering IOLs [27]. None of these investigations showed any negative effect on visual acuity or contrast sensitivity for blue light-filtering IOLs in normal eyes for photopic and mesopic vision. Three comparative clinical investigations for blue-light filtering IOLs have reported improved contrast sensitivity [34–36]. Rodrıguez-Galietero et al. reported that blue light-filtering IOLs provide better contrast sensitivity in diabetic eyes, without inducing any defect in color vision [35]. Niwa et al. reported improved contrast sensitivity in photopic and mesopic conditions for middle spatial frequencies of 6 and 12 c/deg for blue light-filtering IOLs in healthy normal eyes [34]. In addition, they reported that blue light-filtering IOLs reduced the effect of central glare during contrast sensitivity testing. It should be noted that this clinical investigation used a 3 mm artificial pupil, thereby controlling retinal illumination and ocular

aberrations. Yuan et al. also reported statistically significant higher contrast sensitivity in healthy normal eyes implanted with blue light-filtering IOLs [36].

External yellow filter investigations

In addition to clinical investigations for yellow-tinted IOLs, there are several investigations in phakic human subjects which have also reported improvement in contrast sensitivity with external yellow filters [37–43]. The degree of the improvements depended on the transmission characteristics of the filters and wavelengths of the targets and backgrounds. Several explanations have been proposed for these improvements. They include a reduction of short-wavelength light scattering, reduction in chromatic aberration, and an increase in contrast between long-wavelength targets against short-wavelength backgrounds. A detailed investigation [38] with yellow goggles also reported an increase in perceived brightness, and faster reaction time for detection of midrange spatial frequency gratings of low contrast. These results were discussed by the investigators in view of known retinal circuitry based achromatic/chromatic theory of color vision. According to this theory, the achromatic system detects brightness by addition from middle- and long-wavelength cones, and the chromatic system detects color by subtraction of the output of one type of cone from the activity of another type of cone, resulting in the red–green and the yellow–blue opponency [38]. Care in interpreting these results needs to be taken though, since external filters modify the natural transmission of light in phakic eyes. The filters act like sunglasses, and add to the normal reduced transmission of shorter wavelengths by the crystalline lenses. This creates an additive cumulative filtering effect which would be greater than if such filters were tested in pseudophakic eyes implanted with UVR-only filtering IOLs.

Glare studies

The following two new comparative clinical investigations found improved driving against glare for the blue light-filtering IOLs and reduced glare, faster photostress recovery, and improved heterochromatic contrast threshold for the blue light-filtering IOLs [44, 45].

New clinical investigation #1 of 2011 for glare

Gray et al. reported a comparative cross-sectional clinical investigation using a driving simulator to assess the effect of glare in normal healthy elderly pseudophakic eyes on driving performance against low-sun conditions [44]. All patients had good visual acuity and a valid driver's license. The simulator required the patient to make left-turn maneuvers at an intersection which required judgment of safety against possible collision with oncoming vehicles in the opposite lane. The safety margin was defined as the time to collision minus the time taken to turn at the intersection with oncoming traffic. The same measures were also made in the presence of a glare source simulating low-sun conditions as in day-time driving. In subjects implanted with blue light-filtering IOLs, the reduction in left-turn safety margin produced by glare (mean ± SD=0.445±0.237 seconds) was significantly less ($p<0.001$) than the reduction in left-turn safety margin produced by glare for subjects implanted with only the UVR-filtering IOL (mean ± SD=0.775±0.242 seconds). Furthermore, when compared between no-glare and glare conditions, subjects implanted with blue light-filtering IOLs showed significantly lower glare susceptibility, experienced a significantly lower number of collisions with the oncoming car, had a significantly lower impact on intersection approach speed, and made a significantly lower percentage of turns in front of approaching vehicles than subjects implanted with UVR-filtering IOLs. The authors concluded that the real-world benefit of blue light-filtering IOLs is presumably mediated by a stronger signal to detect approaching objects (motion-in-depth signal) in the presence of glare, as a result of an increase in the contrast of the retinal image of the oncoming vehicle [44].

New clinical investigation #2 of 2010 for glare

Hammond et al. reported a comparative clinical investigation in normal healthy elderly (average age 76±9 years) pseudophakic eyes with a blue light-filtering IOL in one eye and a UVR-filtering IOL in the contralateral eye [45]. They employed a two-channel Maxwellian view optical bench set-up which eliminated the effects of variably sized natural pupil diameters as they conducted three clinical experiments. In the first, they found a significant reduction in glare disability using a bright white light annulus while detecting a central 645 nm dominant (light orange) target grating of 8 c/deg. A 1.97±0.44 log $\mu W/cm^2$ intensity was required of the glare-producing annulus to produce a disappearance of the target in the group of eyes with blue light-filtering IOL, versus 1.88±0.43 log $\mu W/cm^2$ for the group of eyes with UVR-filtering IOL ($P=0.04$). The authors emphasized that similar situations are likely to occur in the real world when a driver is looking into oncoming headlights. By filtering some of the abnormally high amount of transmitted short-wavelength light that is transmitted in the UVR eyes, the visibility of a target within an individual's line of sight would be improved, as was demonstrated by the simulation in this study. The glare source used in the study was generated by a Xenon bulb which has relatively greater energy contributed from longer wavelength than shorter, but was basically white light containing energy across the 400–700 nm region. The extent to which an intraocular filter absorbs the short-

wavelength scattering source should determine the degree to which that filter will reduce glare disability with respect to identification of longer wavelength targets. Consistent with this presumed mechanism, a past study that presented stimuli with relatively little short-wavelength background energy to subjects with blue light-filtering IOLs reported minimal effects on glare disability [17]. Under natural conditions, i.e., outdoors in sunlight, the effect of a blue light-filter on glare disability could be even more substantial, since the natural background could contain even more short-wave energy. In the second experiment, they found an average 5-second faster recovery to visualize the same central target after photostress created by a 24° field exposure for 5 seconds of 5.0 log Trolands intensity from the same Xenon bulb source [45]. Such a faster recovery while driving at 60 miles per hour equates to 440 feet distance travelled, and thus may provide safer driving against bright oncoming headlight or bright sun at low angle. The contralateral design of the study eliminated many other factors which might have influenced the kinetics of regeneration of bleached photopigment and the results thus depended only on the filtering differences between the two IOL types. In the third experiment, they found significantly better heterochromatic contrast threshold for detection of the same mid–long wavelength halogen light illuminated target grating against a progressively brighter 430 nm blue background for eyes with blue light-filtering IOLs. Better detection of the target against the background, which was selected to simulate blue sky atmospheric haze, suggests better detection of targets in real-world outdoor conditions [45].

Color vision in photopic and mesopic conditions

Human color vision results from complex neurophysiologic renormalization processes which address change in transmittance of ocular media, variations of luminance and spectral composition [46–49]. This results in color constancy with varying illumination conditions, and in a relatively stable suprathreshold color perception with minimal effect of aging. A recent study by Hoffmann et al. compared multifocal electroretinograms with or without blue light-filtering in the same pseudophakic eyes which had colorless IOL. They found a minor short term effect of blue light-filtering; thus suggesting an insignificant difference in activity at the input stage of the visual system [50]. Supporting this physiology of color vision, there are at least 17 clinical studies which found no significant difference in color vision between eyes with blue light-filtering IOLs and eyes with UVR-filtering IOLs in photopic and mesopic conditions [16, 17, 20–28, 30, 31, 33, 35, 51, 52]. Additionally a questionnaire-based study assessing quality of life also did not find any difference between the two types of IOLs [53]. This was also true for eyes with preexisting color vision defects [54]. A clinical investigation with a separate evaluation of box 3 of the FM 100-hue test showed a difference between the two IOL types for the first 6 months postoperatively under photopic condition and even for up to about 1 year in mesopic condition, but all measured total error scores were within the normal range of overall color perception [55]. Some of the recent clinical investigations for comparative color vision reported color vision testing results as equivalent under photopic conditions, but with more mistakes for blue light-filtering IOLs under mesopic conditions for blue to blue–green bands of color discrimination at 1 and 8 weeks to 3 months postoperatively [29, 32, 56]. But none of them reported any significant difference in overall color discrimination or discomfort in mesopic conditions when subjective perception evaluation was carried out by a questionnaire to the patients [27, 32, 33, 56]. Also, any concern for mistakes primarily only during mesopic condition for hue discrimination testing for blue to blue–green bands of color needs to be balanced against any lack of effect on overall subjective color discrimination and the potential benefit that blue light-filtering might provide against potential damage of shortwave-sensitive aging retina at neural level by cumulative exposure to high-energy photons [57–59], which UVR-filtering IOLs will allow for many years.

Patients such as artists, clothing and apparel designers, etc., who have a finer sense of color perception, have reported post-operative cyanopsia and difficulty in color matching for UVR-filtering IOLs and their reduction by blue light-filtering [1, 60–62]. However, according to one study, post-surgical cyanopsia with UVR-filtering IOLs tended to disappear 3 months after surgery suggesting some level of adaptation over time [24]. Another recent study reported that three patients out of 24 found differences in perception between the eye implanted with a blue light-filtering IOL compared to the fellow eye implanted with a UVR-filtering IOL [63]. All three patients had jobs (paperhanger, architect, and florist) dealing with fine discrimination of colors. Thus, mixed implantation in such patients should probably be avoided. But for the majority of patients without such a highly developed sense of color perception, the overall conclusion from all available studies is that there is no significant difference in color perception between eyes implanted with blue light-filtering and eyes implanted with UVR-filtering IOLs in either photopic or mesopic conditions.

Short wavelength automated perimetry (SWAP)

Results of a 24 degree field full-threshold short-wavelength automated perimetry (SWAP), also known as blue on yellow test, was reported to be without any statistically

significant difference between a blue light-filtering IOL in one eye and UVR-only filtering IOL in fellow eye in 27 elderly patients [64]. Another recent study compared the results between standard perimetry and SWAP in similar patients, and found some difference in results for SWAP between the clear and blue light-filtering IOLs [65]. A detailed correspondence on this paper discussed the limitations of the study, and suggested a need for caution in conducting SWAP in elderly patients and identifying clinical significance through interpretation of its results [65–67]. Another paper using a blue-on-yellow test restricted to 10-degree macula field test in a similar type of patients reported only foveal threshold differences [63]. The foveal threshold results were mostly overlapping, but with a statistically significant difference between the two IOLs, attributable to abnormally high transmission of 440 nm blue-light through the UVR-filtering IOL. Results for both IOLs were similar to those found in a normal age-matched phakic population [63].

Scotopic vision

Scotopic vision is realized in environments of extremely low luminance after dark adaptation, and is totally mediated by rods. Blue light-filtering IOLs filter more of the overlapping wavelengths of scotopic spectral sensitivity curve compared to UVR-filtering IOLs. Thus, there is a theoretical potential for a decrease in scotopic vision in eyes implanted with blue light-filtering IOLs. The possible advantages of UVR-filtering IOLs for better scotopic vision performance have been discussed and intensely investigated both by computational investigations and in clinical studies as follows.

Computational investigations for scotopic vision

The first computational paper addressing blue light-filtering IOLs and scotopic vision was written by authors in the school not favoring those IOLs [5]. This paper had two sources of significant error. The first error was related to the transmission curve used to characterize the blue light-filtering IOL, and the second was related to the application of a phakic rather than aphakic scotopic spectral sensitivity curve. These errors were discussed and placed in a more clinically appropriate context after different computations were carried out by Schwiegerling, one of the authors of this article [68]. The more appropriate computational result demonstrated a net increase of 52% in scotopic spectral sensitivity relative to a young phakic individual, instead of the earlier reported 25.5% decrease in scotopic spectral sensitivity compared to a patient with a UVR-filtering IOL [5, 68]. Comparative computations showed a larger increase in scotopic spectral sensitivity for UVR-filtering IOLs, the differences between the two types of lenses being proportional to the areas under their respective transmission curves. However, according to the later computations, both types of lenses cause dramatic increases in the amount of light available to the pseudophake when compared to phakic young subjects [68]. Thus any concern for the adequacy of scotopic vision with blue light-filtering IOL should be allayed with this more appropriate computation, which was further discussed in two letters and their replies [4, 69–71]. Werner presented an additional significant perspective on the expected consequences of the difference between the two IOLs after discussing the principal of univariance for the wavelength-independent effect of photons for scotopic vision [72]. He concluded that under broadband illumination the expected reduction in scotopic sensitivity of ~0.07 log unit for blue light-filtering IOL is visually insignificant relative to the ~4.0 log unit range of scotopic sensitivity, and it translates to a contrast sensitivity reduction of only ~0.01 log unit [72]. He expressed the view that this difference is too small to reliably detect for broadband stimuli [72].

The three investigations summarized below were undertaken to discover any clinically significant difference between the two types of IOLs for scotopic vision performance [11, 16, 17]. These papers have not been collectively discussed in the recent review or viewpoint papers [9, 14, 15] and none of them were reported in the anti-blue light-filtering viewpoint paper [14].

Clinical investigation #1 of 2007 for scotopic vision

Muftuoglu, one of the authors of this article, reported an investigation which studied the right eyes of 38 patients implanted with blue light-filtering IOLs and right eyes of 38 age-matched control patients implanted with UVR-filtering IOLs [17]. Scotopic contrast sensitivity was measured in all eyes in similar fashion using a Mesotest II apparatus. No clinically statistically significant difference in scotopic contrast sensitivity was found between the blue light-filtering and UVR-filtering IOLs with and without glare. The difference in the spectra of stimuli and glare source between the Mesotest II apparatus and the Maxwellian two-channel apparatus used in the new clinical investigation #2 of 2010 for glare as given above, may explain the difference in effect of glare between the two studies [17, 45].

Clinical investigation #2 of 2007 for scotopic vision

Greenstein et al. reported a clinical investigation in nine patients, each having a blue light-filtering IOL in one eye and a UVR-filtering IOL in the fellow eye [16]. They measured dark-adapted scotopic spectral sensitivities at

440 nm, 500 nm and 650 nm for each eye using a Humphrey Field Analyzer, and did not find any significant difference in sensitivities between the two groups of eyes. They also reported no difference in hue discrimination performance between the groups as measured by the Farnsworth–Munsell (FM) 100-hue test [16].

Clinical investigation#3 of 2008 for scotopic vision

Kiser et al. reported a comparative clinical investigation in 22 bilateral pseudophakes having UVR-filtering IOLs [11]. All patients, average age 81 years, had early AMD with visual acuity >6/24. A full-field flash test was done to measure scotopic threshold in dilated dark-adapted eyes of these patients with and without a filter, with transmission characteristics of a widely used blue light-filtering IOL. No significant difference in scotopic threshold was found in these tests. Scotopic sensitivity of these patients was measured by determining their timed performance during block manipulation and walk-through of two different mobility courses in the scotopic illumination, with and without a NoIR Medical's wrap-around 751 H filter. This filter closely mimics the spectral characteristics of the same blue light-filtering IOL, but exaggerates its attenuation (1.76 db vs 0.47 db). The results of neither of these tests, which had been designed to simulate situations that patients might encounter in real life, produced a clinically significant difference in performance. It should be noted that the second test was done with a filter that exaggerated the filtering characteristics as compared to blue light-filtering IOLs, and hence the color discrimination test done by these patients did not represent that for the blue light-filtering IOL [11].

Photoentrainment of the circadian rhythm and sleep disturbances

The following computational and supporting clinical investigation for objective assessment of sleep disturbance related to circadian rhythm were unavailable in the 2009 review paper by Cuthbertson et al., and incompletely available and discussed in the two 2010 viewpoint papers [9, 14, 15].

Computational investigation of 2009

Patel, one of the authors of this article, reported new computations after study and review of eight available action spectra for photoentrainment of the circadian rhythm [13]. Earlier investigations for UVR-filtering IOLs by Charman, and those published subsequently for both types of IOLs by the authors opposing the blue light-filtering IOL, used an action spectra for photoentrainment with a peak of 460 nm [3, 7, 14, 73]. This peak was based on two action spectra published in 2001 with serious errors of construction, as discussed in detail in this latest computational investigation [13]. Subsequent to the discovery of intrinsically photosensitive retinal ganglion cells (ipRGC) in 2002, many investigations, including a new melatonin suppression study in humans, found action spectra for photoentrainment with much higher peaks—from 480 to 500 nm [13, 18]. Using these more updated action spectra, the new computational study concluded that both blue light-filtering IOLs and UVR-filtering IOLs can be expected to provide adequately effective photoentrainment of the circadian rhythm, including melatonin suppression, under average household illumination [13]. The following two clinical investigations have validated the expectations of this computational study.

Two clinical investigations for sleep disturbance related to circadian rhythm

Landers et al. reported a comparative retrospective sleep study in patients with bilateral implantation of either UVR-filtering or blue light-filtering IOLs [12]. The results of the Pittsburg Sleep Quality Index (PSQI) questionnaire, with almost 20 years of demonstrated validity and reliability, showed no significant difference on any effect of sleep quality between the two groups of patients, who had a mean age of 80±8 years [12].

In another prospective sleep study, Cunha, one of the authors of this article, employed the same PSQI questionnaire method plus an additional objective 7-day actigraphic monitoring method and the Epworth Sleepiness scale in two groups of elderly patients, with bilateral implantation of either UVR-filtering or blue light-filtering IOLS [10]. The evaluations demonstrated no detectable clinical differences in sleep quality between the two groups of patients. It should be pointed out that this study is a very small study with only 16 bilateral pseudophakic patients divided into two groups of eight each with UVR-filtering and blue light-filtering IOLs [10]. Such quantitative studies, even though difficult, need be accomplished with a greater number of patients.

The rationale for photoprotection of the pseudophakic retina by blue light-filtering IOLs

The natural human crystalline lens filters and thereby protects the retina against potential damage from high-energy photons of UVR and short-wavelength visible light. Reviews of phototoxicity by UVR and visible light and the relationship between cumulative photon energy and wavelength are available elsewhere [1, 9, 74]. Following removal of the cataractous lens, the protection of the retina

in a pseudophakic eye depends upon the filtering provided by the cornea and the implanted IOL. Initially, IOLs did not filter significant UVR or any visible light. UVR-filtering IOLs were created in the early 1980s, after erythropsia and CME developed postoperatively in some pseudophakic patients. The potentially harmful effects of UV radiation were also demonstrated in animal studies. No clinical studies were done to validate the rationale of UVR filtering, primarily because the UVR filtering could not negatively affect vision, since visible wavelengths remained unaffected by such filtering. The photon energy of the lower wavelengths of visible light is also relatively high, and has also been found to generate retinal damage in animal studies with acute, intermittent, and chronic exposures, including the so-called "blue-light hazard" [1, 9, 74–76]. Additionally there is a considerable age-related accumulation of lipofuscin in the retinal pigment epithelium (RPE) of elderly eyes. This accumulation and associated photochemical processes results in free radical generation and oxidative stress which can create cell damage [9]. This age-related lipofuscin accumulation-mediated retinal phototoxicity for shorter-wavelength light exposures, along with potential depletion of anti-oxidants, plays a potential role for AMD, as critically reviewed by Young in the late 1980s [77, 78]. Subsequently, considerable new research has been published on the processes resulting in age-related macular degeneration and pathobiology of RPE lipofuscin [74, 79–83]. Several investigators [78, 84, 85] in the 1980s had logically suggested additional filtering by IOLs for lower-wavelength light. Thus, the rationale of blue light-filtering IOLs is to provide protection against retinal phototoxicity and to minimize the risk factor of excessive transmission of short-wavelength high-energy light for developing or accelerating AMD after cataract surgery. By selecting transmission and thus filtering characteristics that would mimic that of the young adult human lens, photoreception function was not expected to be negatively affected, and indeed the results given earlier in this article confirm that this expectation has been met.

The following investigations support the scientific rationale of retinal protection in pseudophakic eyes provided by blue light-filtering IOLs.

Computational investigations for age-dependent lipofuscin mediated retinal phototoxicity

Margrain et al. computed age-dependent relative phototoxicity action spectra and the increase in relative phototoxicity related to RPE lipofuscin accumulation for phakic eyes of various ages [86]. They arrived at these action spectra by combining the effect of the available data for human lipofuscin accumulation with age, the laboratory data of photoreactivity of lipofuscin in isolated human RPE cells from human donors, and the age-related reduction in transmission characteristics of the human crystalline lens. Their computations reveal an almost 9-fold increase in relative retinal phototoxicity from the first to ninth decades of life in phakic eyes. Subsequently, age-dependent aphakic action spectra were created for an additional computational study for pseudophakic eyes participated in by Patel, one of the current authors [87]. This study computed lipofuscin accumulation-mediated relative retinal phototoxicity and protection offered by various IOLs. It demonstrated that lipofuscin accumulation-mediated retinal phototoxicity increases significantly with age, and is significantly higher with UVR-filtering IOLs than for blue light-filtering IOLs in elderly pseudophakic eyes [87].

In-vitro and animal investigations showing retinal protection by blue light-filtering IOLs

While there are many in-vitro investigations on the damaging effect of blue light on RPE cells as mediated by the lipofuscin fluorophore A2E, there are five independent in-vitro investigations which have reported protection offered by blue light-filtering IOLs to human RPE cells [88–92]. They found reduction in light exposure induced death for RPE cells with accumulated aging lipofuscin fluorophore A2E. They also found more inhibition of light-induced VEGF production in cells protected by blue light-filtering IOLs. These in-vitro investigations thus support the scientific rationale for blue light-filtering IOLs.

One comparative electrophysiological investigation in pigmented rabbits reported less damage to their retinas protected by blue light-filtering yellow IOL material, and subsequently discussed its advantage for retinal protection [93, 94].

Clinical and epidemiological investigations suggesting the protective effect of filtering blue light

In a pioneering clinical investigation ranging up to 14 years for various types of filtering by IOLs, Miyake reported reduced blood–retinal barrier disruption and autofluorescence of the posterior polar retina in eyes with blue light-filtering IOLs compared to those with UVR filtering after 5 years [95].

As reviewed earlier [1, 78], progression of AMD after cataract surgery was reported as early as 1918 by van der Hoeve in Graefe's Archives of Ophthalmology [96]. A recent systematic review and analysis of literature concluded that "The scientific level of evidence of these articles was not high and results were inconsistent; nevertheless, a promoting influence of cataract surgery on the progression of early age-related macular degeneration can be assumed" [97]. The Age-Related Eye Disease Study (AREDS)

concluded that people older than 55 years with risk of AMD should consider taking a supplement of antioxidants plus zinc such as used in the study [98]. This investigation confirmed the role of oxidative processes in AMD. An ongoing epidemiological multi-country European Eye (EUREYE) study recently reported an association between cumulative environmental blue light exposure and neovascular AMD in patients with low antioxidants in the blood [99].

There is a new intriguing finding of an increase in the density of yellow macular pigment in eyes with blue light-filtering IOLs [100]. Long-term investigations are needed to better understand this unanticipated finding and its implications for reduction of risk of AMD development and/or its progression by blue light-filtering IOLs.

Need for definitive proof that blue light-filtration provides protection against AMD

The above summarized totality of studies as well as the variety of study methods provides adequate scientific rationale to support the clinical use of blue light-filtering IOLs, even without definitive proof of protection against AMD, in the same reasonable way as UVR filtering was accepted on scientific rationale without definitive clinical trial. Extensive clinical trials, including the monitoring of antioxidant blood levels as suggested by the EUREYE study, are needed to prove beyond any reasonable doubt that blue light-filtering IOLs protect against AMD by delaying or minimizing its progress [99]. It is quite understandable that these studies have not yet been carried out, since they would be unrealistically long-term, complex, and expensive [82, 99].

Discussion and conclusion

In practice, patients must make choices between the advanced technological attributes of the IOLs they will select to have implanted in their eyes. These important choices will be based in part on their surgeon's understanding and recommendations of these available attributes. One significant choice patients may make will be to select IOLs which attempt to mimic the spectral transmission and filtration of UVR and visible light of natural lenses, and which are thus functionally "light-normalizing". Or they may elect to have IOLs implanted which filter only UVR, but transmit, and thus fail to filter, greater than normal amounts of high-energy short-wavelength electromagnetic radiation to their retinas [1].

The filtering effects of the natural human crystalline lens and macular luteal pigments are intrinsic in the definition of normal adult human photopic, mesopic, and scotopic vision. Those pigments also provide protection of retina against potentially harmful amounts of short-wavelength violet and blue light. Recently discovered photosensitive ganglion cells, along with rods and cones, help create normal photoentrainment of the circadian rhythm, which is accomplished with blue light-filtering IOLs just as it is by the natural human crystalline lens. Thus, blue light-filtering IOLs which mimic the various functions of natural lenses are intended to restore cataract patients to as close as can be approximated normal adult human vision and circadian rhythm, while providing protection of retina against short-wavelength light. This clear reasoning in favor of the use of blue light-filtering IOLs has been questioned by some authors, based on their comparative theoretical computations between the two types of IOLs [3, 5, 7, 14]. They have stated potential risks of reduced scotopic vision and photoentrainment of circadian rhythm, resulting into potential sleep disturbance. However, these concerns should be allayed by subsequent computations which better contribute to understanding and appreciation of their clinical significance as summarized above [13, 68]. More important, none of the new independent clinical studies found these risks to be clinically significant. We have reasonably demonstrated that there is no risk for scotopic vision performance based on the presented results of one computational and three clinical investigations. We have also reasonably shown that there are no risks for circadian photoentrainment and sleep disturbance based on the presented results of one computational and two clinical investigations. Additionally, these new investigations have not identified any clinically significant incremental benefit for IOLs which filter only UVR. Finally, patients function almost entirely under photopic (daylight, office, and normal home illumination) or mesopic conditions (night driving which does not involve subtle hue discrimination in the blue–green band of colors) and hardly ever function in a scotopic (moonless night) environment. Thus, pseudophakic patients with UVR-filtering IOLs could suffer the potential damaging effects of excessive short-wavelength light transmission almost all of the time, without a meaningful chance to receive some potential benefits that have been clinically undetectable.

Additionally, two new investigations comparing glare effects between the two IOLs indicate benefits of blue light-filtering IOLs for reducing glare, improving heterochromatic contrast sensitivity, reducing photostress and reducing glare while driving [44, 45].

Clinical trials for blue light-filtering IOLs which might demonstrate delays in onset or reductions in progression and severity of AMD after cataract surgery have yet to be carried out. However, available results of in vitro, animal, computational, clinical, and epidemiological investigations generally support the scientific rationale that retinal photoprotection might be an important potential benefit derived

from the use of blue light-filtering IOLs. The EUREYE study [99] has shown that patients with a low blood level of antioxidants are especially vulnerable to blue-light exposure. This finding also corroborates findings of the AREDS study [98] which recommended supplements of antioxidants and zinc for patients with high-risk AMD. Both of these studies validate the scientific hypothesis that high-energy blue light and its associated oxidative processes are potential risk factors for AMD, especially in elderly pseudophakic eyes [9, 74, 77–83].

In summary, blue light-filtering IOLs have no clinically substantiated risks and have potential to create the benefits of better vision and reduced glare, and may have a protective effect against retinal phototoxicity and the development and progression of AMD. This risk/benefit analysis provides a clinical perspective which suggests the selection of blue light-filtering IOLs for use in pseudophakic patients. This choice is especially prudent in modern times, when an increasing number of IOL implantation surgeries are being done for pediatric cataract patients and for clear lens exchange in younger presbyopic patients, both of them with expected significantly longer duration of life after such surgeries. The size of the elderly cataract population and their longevity are both expected to increase globally because of continued economic development [1, 101]. Current treatment modalities for advanced AMD are very expensive and limited in their effectiveness. Thus, implantation of blue light-filtering IOLs which mimic the natural human lens should be considered as a safe and relatively inexpensive preventive measure to reduce the potential risk for retinal phototoxicity and its associated potential risk for AMD in pseudophakic eyes.

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