THE PHYSIOLOGY OF SCOTOPIC VISION, CONTRAST VISION, COLOR VISION, AND CIRCADIAN RHYTHMICITY

Can These Parameters be Influenced by Blue-Light-Filter Lenses?

ALBERT J. AUGUSTIN, MD

Purpose: Evaluation of the potential effects of blue-light-filter lenses on sensory and physiologic factors.

Methods: Scientific knowledge on circadian rhythm and scotopic vision will be summarized and potential effects of blue-light-filtering lenses on these parameters will be assessed on a theoretical basis. Clinically relevant studies will also be discussed.

Results: As far as circadian rhythm is concerned, it should be noted that at 480 nm, i.e., at maximum visual excitation of the light intensity to be measured, blue-light-filtering lenses show roughly the same transmission characteristics as the human crystalline lens. Interference with the circadian rhythm due to blue-light-filtering lenses, therefore, is not to be expected. Regarding scotopic vision, no clinically significant impairment is to be expected from blue-light-filter lenses because maximum excitation in scotopic light reception occurs at 507 nm whereas the light transmission of blue-light-filter lenses is 85%—this is higher than that of a child's crystalline lens. Numerous clinical studies corroborate these findings and demonstrate that color vision and contrast vision are not compromised by blue-light-filter intraocular lenses.

Conclusion: Based on current findings, we do not anticipate blue-light-filter lenses to have a clinically significant effect on physiologic parameters such as scotopic vision, color, and contrast vision or the circadian rhythm.

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The finding that not only UV light but also blue light (400–500 nm) may cause phototoxic damage to the retina[1–5] led to the development of intraocular lenses that, in addition to blocking UV light, also attenuate light from wavelengths between 400 nm and 500 nm. Although such blue-light-filter lenses from various suppliers have been routinely used in the clinic for around 5 years, their implantation is accompanied by critical debate as to the potential impact of blue-light-filtering lenses on circadian rhythm, scotopic vision, and color vision.[6] An introductory summary on current scientific knowledge on circadian rhythm and scotopic vision will be provided to permit a well-founded assessment of the actual effects that blue-light-filter lenses may be expected to exert on different sensory and physiologic factors. The subsequent discussion will concentrate on findings from

From the Augenklinik, Klinikum Karlsruhe, Karlsruhe, Germany.

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Reprint requests: Albert J. Augustin, MD, Augenklinik, Klinikum Karlsruhe, Moltkestrasse 90, 76133 Karlsruhe, Germany; e-mail: 106020.560@compuserve.com

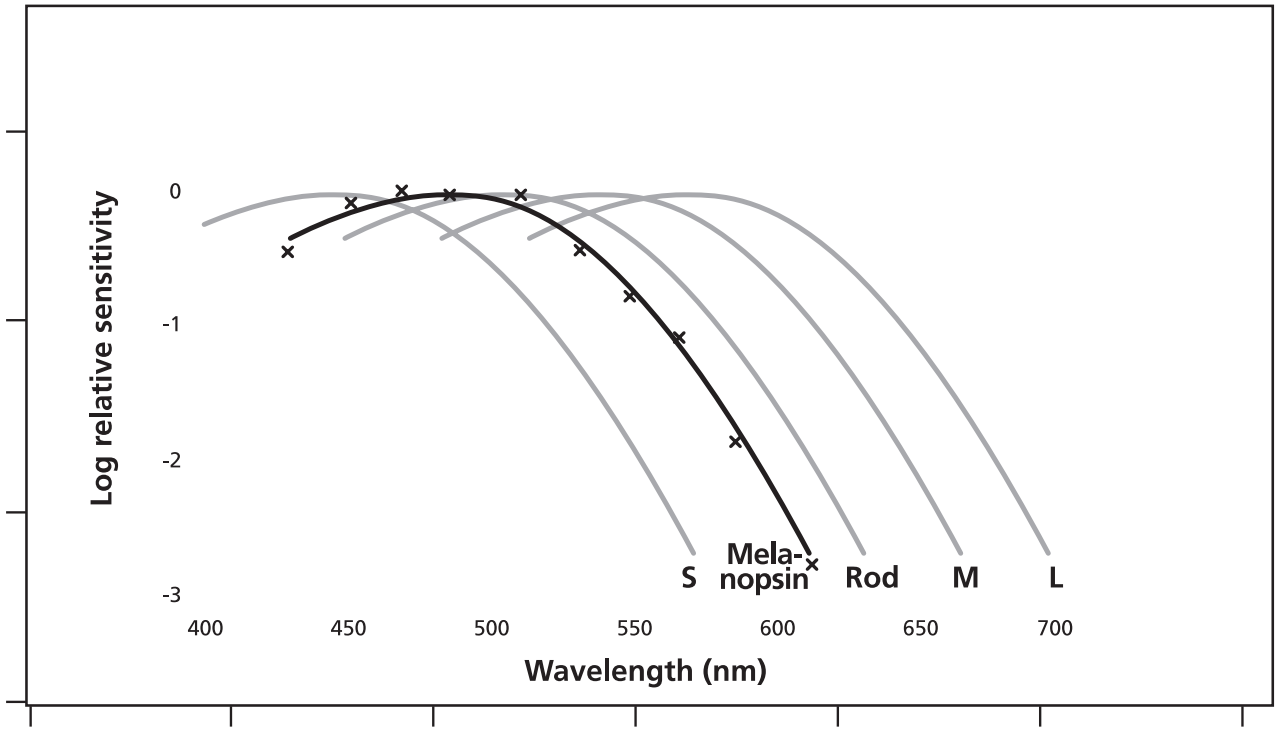

Fig. 1. Sensitivity to light of different wavelengths. The sensitivity curves of the three cone types, S = S-cones, M = M-cones, L = L-cones, and of rods are represented in gray. The sensitivity curve for melanopsin is represented in black. All curves correspond to A_1 nomograms. Melanopsin shows maximum excitation at around 480 nm. Modified from Nature 2005;433:749–754.

relevant scientific studies on color and contrast sensitivity function.

Circadian Rhythmicity and the Internal Clock

Many organisms, among them man, are geared to a circadian rhythm.[7] Rhythmic fluctuations are regulated by a multitude of endogenous oscillators (internal clocks) in the central nervous system.

In principle, man follows an endogenous, genetically determined baseline rhythm of approximately 25 hours that persists without any outside cues.[8] This baseline rhythm is adapted to the environment with the help of synchronizers, such as social signals and the diurnal light/dark cycle.[9]

In man, the central pacemaker regulating the circadian rhythm is located in the suprachiasmatic nucleus (SCN), a core zone of the hypothalamus.[10,11] The SCN receives information about light intensity from a specialized subpopulation of retinal ganglion cells: the intrinsic photosensitive retinal ganglion cells (ipRGCs). These are located in the inner retinal layers and make up less than 0.2% to 0.8% of all retinal ganglion cells.[12,13] Their axons project directly in the SCN, forming the retinohypothalamic tract.[14–17] IpRGCs are capable of measuring light intensity by expressing melanopsin-a photopigment that was discovered only recently.[18–24]

The excitation spectrum of melanopsin is consistent with that of a typical A1 photoreceptor, with a Gaussian curve and an excitation maximum of approximately 480 nm (Figure 1). Melanopsin mainly responds to light impulses in the photopic range over approximately 4 log units to 5 log units[14,22] (Figure 2). The light sensitivity of melanopsin is slightly less than that of cones and distinctly less than that of rods which have a stimulus threshold of approximately 10^7 photons $s^{-1} \cdot cm^{-2}$ (Figure 2).[12]

Melanopsin measures light intensity and transmits that information via the retinohypothalamic tract to the SCN—the master clock of circadian rhythm. From the SCN, efferent axons reach several different brain areas and ultimately control the release of melatonin from the pineal gland, which in turn acts as the "dark signal" for the body. The intensity of day light—as measured by melanopsin and via the SCN—thus causes the suppression of melatonin release.[25,26] In short, the dark signal is suppressed during daylight hours and the body adjusts to being "active/awake." However, the nonvisual system of measuring (melanopsin in ipRGCs) and transmitting light intensity is not just a simple "path," but a highly complex system,

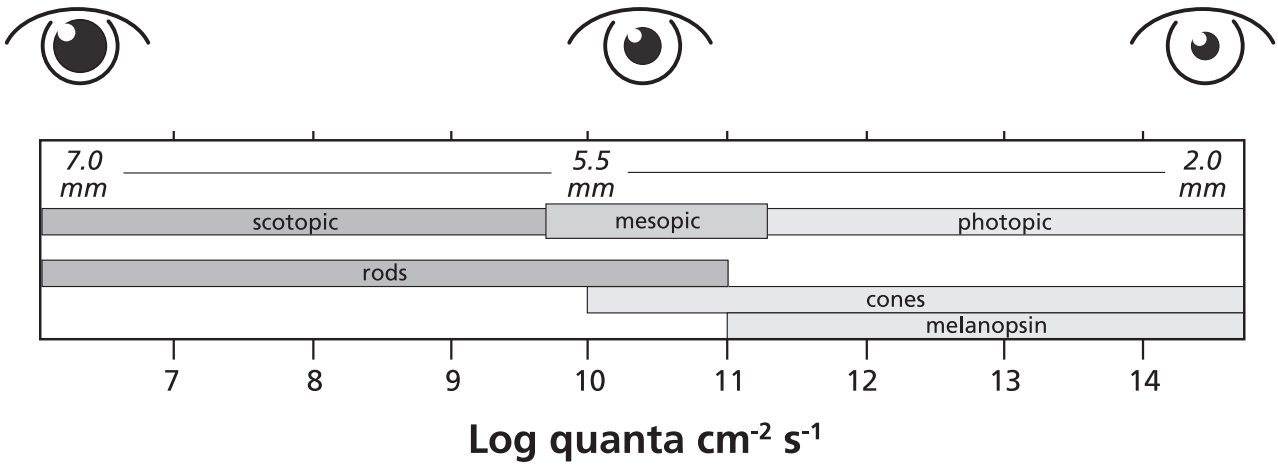

Fig. 2. Sensitivity ranges of rods, cones, and melanopsin in different lighting conditions (intensities given in photon $cm^{-2} \cdot s^{-1}$) and pupillary diameters (7.0–2.0 mm). Melanopsin mainly responds to light stimuli in the photopic range with illuminance values from approximately 10^{11} to 10^{14} photons $s^{-1} \cdot cm^{-2} \cdot I$, exhibiting a slightly lower light sensitivity than cones and a markedly lower sensitivity than rods. Modified from Nature 2005;433:749–754.

whose regulatory mechanisms are far from being sufficiently understood.[27] Its complexity becomes even more intricate in its interactions with the visual photoreceptor system (cones/rods). Although the two systems function independently in principle,[28–31] cones and rods may still interfere with and modulate the phototransduction cascade of the ipRGCs, providing at least partial compensation for any melanopsin deficiency.[32–36] Moreover, the melanopsin system can adapt its sensitivity to long-term changes in the intensity of environmental light[37,38] and appears to regulate the visual photoreceptor system in the retina.[39]

Light is perceived via two very complex, separate systems which influence each other.

Potential Effects of Blue-Light-Filter Lenses on Circadian Rhythmicity

Regulation of the day/night rhythm is an extremely complex process which is controlled by several factors. Because light merely influences the "fine tuning" of the circadian rhythm to approximately 24 hours per day, blue-light-filter lenses should not have any considerable impact on this important physiologic parameter. Nevertheless, epidemiologic and clinical research still needs to establish the effect—if any—on the regulation of the circadian rhythm of implanting blue-light-filter lenses.

Apprehensions that this new generation of lenses may have a negative impact on the circadian rhythm have been expressed regularly. A recent publication reported the following finding: "Blue-blocking intraocular lenses provide 27% to 38% less melatonin suppression than a UV-only blocking intraocular lens."[40,41] This statement requires one principal restriction: most of the intraocular lenses currently available from various suppliers are actually not blue-blocking lenses, but blue-light-filter lenses. To evaluate the potential effects of this IOL generation on sensory-physiologic factors, it is absolutely essential to differentiate between 1) blockers in terms of a full cutoff filter and 2) filtering lenses. Within the range of between 400 nm and 500 nm, blue-light-filter lenses do, in fact, transmit some blue light, from approximately 10% at 400 nm to approximately 80% at 500 nm.[42] This means they filter the short-wave, high-energy part of blue light rather than the low-energy part of blue light with longer wavelengths. The light in this precise range (480–510 nm) is more relevant to the preservation of sensory and physiologic functions such as scotopic vision or circadian regulatory mechanisms than short-wave light.

Moreover, the statement that a "blue-blocking IOL" provided "27% to 38% less melatonin suppression than a UV-only blocking lens" is misleading. This statement is founded on two studies from 2001[43,44] which demonstrate that it is mainly light with a wavelength of 460 nm that leads to the suppression of melatonin secretion in the pineal gland. However, the percentages given merely indicate how much blue light is filtered by a blue-filtering lens at 460 nm in comparison to a UV-blocking lens. Equating this percentage with "melatonin suppression," implies that there is a 1:1 relationship between the light intensity measured in the retina and the amount of melatonin released from the pineal gland. This would mean that a reduction of light transmission of 1% was reflected in a 1% reduction of melatonin suppression. Such a conclusion might at best be permissible in respect of

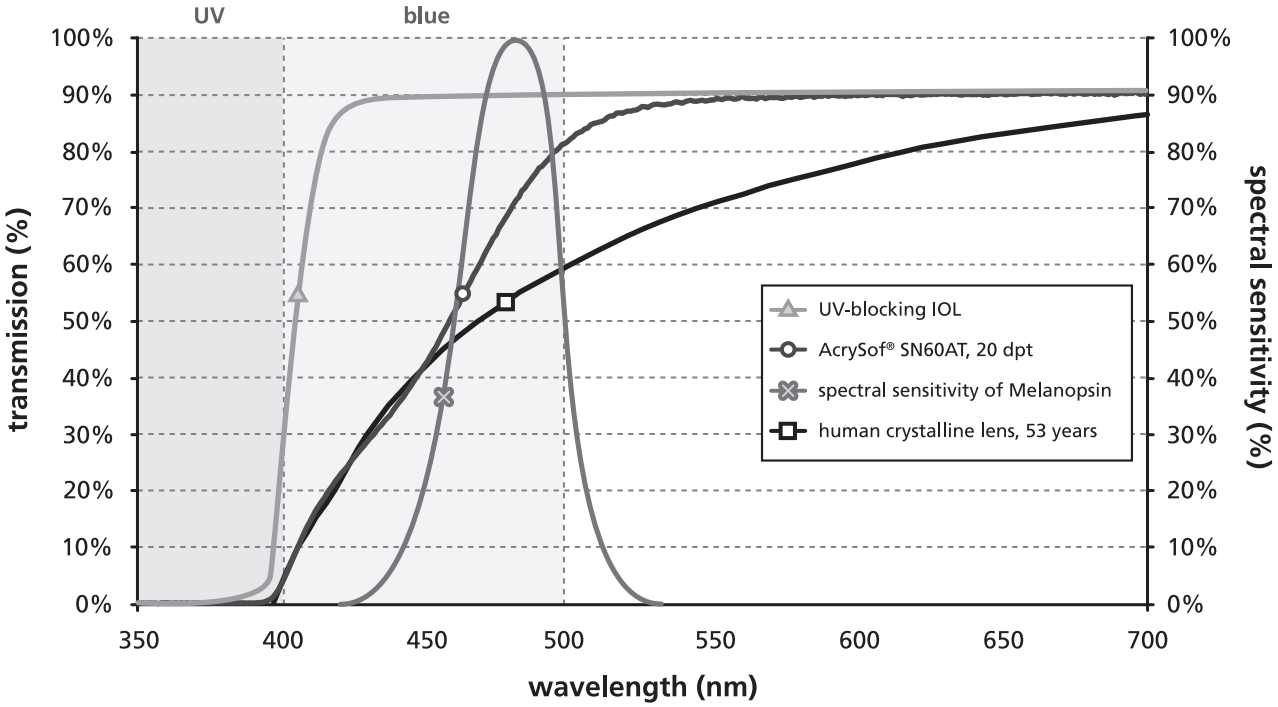

Fig. 3. Transmission behavior of a 20 dpt UV-absorbing lens (gray line), the 20 dpt blue-light-filter lens AcrySof® Natural (data according to Dr. Laube, personal communication) and of the crystalline lens of an adult (53 years) as against the spectral sensitivity of melanopsin. Modified from Science 2005;307:600–604.

some amphibian and avian species. In these animals, the pineal gland itself is photosensitive and plays a central role in circadian regulation,[45] which makes a 1:1 effect of the light signal on circadian rhythm conceivable. The human pineal gland, however, is screened from direct light by the skull cap, and can only be reached via complex deviations (retina–retinohypothalamic tract–SCN). This makes it hardly surprising that a 1:1 correlation has not been demonstrated. Quite the contrary, in fact, in a study investigating melatonin suppression, completely unchanged melatonin concentrations were found in elderly patients.[46] Clinical studies investigating the dependence of melatonin suppression on light intensity in humans were also unable to prove a 1:1 relationship.[47–49]

As mentioned above, the mechanism controlling melatonin release and circadian rhythm in humans is highly complex. Even if light intensity was reduced significantly by blue-light-filter lenses, this would not lead to a reduction of melatonin suppression at a 1:1 ratio, but would be balanced out to a certain extent by downstream modulation, feedback effects, and adaptation processes.

Instead of assessing the effects of blue-light-filter lenses on circadian rhythm based on melatonin suppression, it would seem more appropriate to begin by establishing whether blue-light-filter lenses have a significant modifying effect on the input signal, i.e., the measuring of light intensity by melanopsin in the ipRGCs. If a blue-light-filter lens does not even have a significant effect on the input signal, an impact on circadian rhythmicity is not to be expected. As described above, light sensitivity is generally measured via a dedicated photosensitive system, i.e., by melanopsin in the ipRGCs.[18] Because the maximum excitation of melanopsin occurs at high illuminance from exposure to light with a wavelength of 480 nm, light of this wavelength has a markedly stronger influence on the circadian rhythm than light of other wavelengths. Most blue-light-filter lenses transmit 70% to 80% of 480 nm light, approximately the same as a child's crystalline lens. An AcrySof® Natural (Alcon Laboratories Inc., Ft. Worth, TX) of 20 dpt, for instance, transmits approximately 80% of 480 nm light (Alcon Data on file) (Figure 3). This is slightly more, even, than is transmitted by the crystalline lens of a 4-year-old child (76%). With 55% at 480 nm, the transmission of the crystalline lens in a 53-year-old person clearly falls behind that of blue-light-filter lenses.[50] Melanopsin photoreception through the crystalline lens of young people is clearly fully sufficient to maintain an intact, stable circadian rhythm and mental alertness. At least, no study to date has shown that implanting UV-absorbing or edge-filter lenses added any benefits in terms of more "stable" or "improved" circadian rhythmicity, and no such evidence

is expected to be found.[51] At 480 nm, at the peak of the process of measuring light intensity, blue-light-filter lenses show much higher transmission than the crystalline lens of a 53-year-old and the input signal for melatonin suppression corresponds to that of a young person. Interference with the circadian rhythm due to blue-light-filtering lenses thus needs not be assumed—especially when considering that light is just a synchronizer for the fine tuning of the circadian rhythm and that the light-dependent regulation is a highly complex mechanism involving many factors and adaptive processes.

In a randomized comparative multicenter study, postoperative data on quality of life and general health after bilateral implantation of either a blue-light-filter lens or a conventional UV-absorbing lens were obtained from 257 patients. No statistically significant differences could be established between the two patient groups as regards mental health and improved quality of life.[52] These clinical findings are consistent with theoretical concepts and demonstrate that patients implanted with blue-light-filter lenses do not appear to have a disturbed sleep/wake rhythm.

Scotopic Vision

Scotopic vision, seeing in the dark (luminance of approximately 3×10^{-6} cd/m^2 to approximately 0.003–0.03 cd/m^2), is mediated by rods, whereas photopic vision (luminance beyond 3–30 cd/m^2) is mediated by three types of cone. Whereas spectral sensitivity in photopic vision is highest at approximately 550 nm, maximum sensitivity in scotopic vision shifts to approximately 507 nm.[53] For a variety of causes, scotopic vision declines steadily during adulthood and deteriorates more noticeably and faster than photopic vision.[54,55] Although preretinal factors such as a miotic pupil and an age-related increase in the optic density of the crystalline lens contribute to the decline in scotopic vision, they should not be considered to be its main cause.[56,57] Part of the reduction in age-related scotopic sensitivity (approximately 0.5 log units) is probably attributable to neural causes,[55] which, however, are not yet fully understood.[38,58,59] Rod degeneration is not the sole reason for the deterioration of scotopic vision in old age.[60] Another potential cause for the deterioration of scotopic vision lies in excitation transduction being compromised by the aging process.[60,61] An impaired magnocellular path is currently being discussed as the possible cause of reduced scotopic contrast sensitivity.[61,62]

Potential Impact of Blue-Light-Filter Lenses on Scotopic Vision

Theoretical concepts based on the Purkinje shift consider the impairment of scotopic and mesopic vision by blue-light-filter lenses.[6] As mentioned above, rod sensitivity peaks at 507 nm, so that light around this wavelength is of particular importance for scotopic vision. Braunstein and Sparrow[63] point out that the blue-light-filter of the AcrySof® Natural, for instance, transmits approximately 85% of light in this range, which is comparable to a child's crystalline lens. With 90% at approximately 500 nm, UV-absorbing lenses only insignificantly transmit more UV light. In adults, the transmission of the crystalline lens at this wavelength is considerably lower at around 60%.[50]

The mere comparison of these transmission characteristics shows that there is not even a theoretical probability that blue-light-filters impair scotopic vision to a clinically relevant extent. This observation is corroborated by detailed calculations on the effect of blue-light-filters on scotopic vision. A previous calculation, which had established a reduction of scotopic sensitivity with blue-light-filter lenses by 25% compared with UV-absorbing lenses,[64] included two methodical inaccuracies.[65] To be accurate, the calculation should be based on the scotopic sensitivity curve of an aphakic person. There are two more recent calculations which have corrected these methodological flaws; their results show that the blue-light-filter of a 20 dpt AcrySof® Natural reduces scotopic sensitivity under broadband illumination by only approximately 14.6% compared with a UV-absorbing lens.[65,66] According to Werner, to assess clinical significance, the reduction of scotopic sensitivity must be as low as 0.07 log units. Considering the span of approximately 4 log units for scotopic sensitivity, this is negligible. The author assumes that in natural lighting conditions, patients will not perceive the difference between a blue-light-filter lens and a UV-absorbing lens in terms of scotopic vision. Again, it is not apparent why UV-absorbing lenses were used as the reference value. An improvement of scotopic vision through the implantation of a UV-absorbing lens/cutoff filter over a blue-light-filtering lens has yet to be demonstrated.

The results of clinical studies confirm these theoretical considerations and calculations. In an interindividual comparative study of 76 patients, Muftuoglu et al[67] found no significant difference in contrast sensitivity, either under photopic or under scotopic conditions, between the two patient groups—one being implanted with blue-light-filter lenses and the other with conventional UV-absorbing lenses. There was, however, a decrease in contrast sensitivity in both

patient groups with increasing age. These findings show that with increasing age there is a general decrease in scotopic contrast sensitivity whereas glare sensitivity increases, no matter whether a blue-light-filter lens or a UV-absorbing lens is implanted. It follows that the blue-light-filter lens does not compromise scotopic vision; neither does a UV-absorbing lens provide any benefits in this respect. Against this background, the recommendation[6] that the elderly, in particular, should be provided "with all the blue light they can get to ensure best possible scotopic vision after cataract surgery" appears to be unsubstantiated. Considering that a deterioration of scotopic vision with age is not necessarily because of a reduction in rods but may be caused by the impairment of the downstream magnocellular path,[55,61] an enhancement of blue-light transmission of intraocular lenses cannot be expected to improve scotopic vision with age. There have not been any clinical studies which demonstrate that conventional UV-absorbing lenses are able to compensate for the age-related deterioration of scotopic vision.[67]

The results of the comparative study into the quality of life after cataract surgery, described above, also show that blue-light-filter lenses do not compromise vision in dim light: postoperative driving in daylight, at night, and in poor light conditions was better than before surgery both in patients with blue-light-filter lenses and in patients with UV-absorbing lenses; these results were statistically significant. The same is true for negotiating stairs, steps, and curbstones. No statistically significant difference could be established between the two patient groups.[52]

A multicenter study including 1,727 patients whose quality of life and vision were evaluated using the validated visual function index (VF14) showed that patients provided with a blue-light-filtering intraocular lens attain very high VF14 scores and thus good functional vision, i.e., they can "see well" in a wide range of conditions.[68]

It can therefore be said that there are neither convincing theoretical concepts nor reliable estimates to suggest that any clinically significant impairment of scotopic vision due to blue-light-filter lenses is to be expected under natural lighting conditions.

Potential Impact of Blue-light-Filter Lenses on Color and Contrast Vision

Photopic cone vision is distinguished from scotopic vision by higher resolution and better color vision. It is mediated by three types of cones, the S (short), M (middle), and L (long) wavelength cones; these differ in occurrence and in their sensitivity to the light of different ranges of spectral wavelength (Figure 1).[69,70] Blue-light-filter lenses absorb a certain portion of light between 400 nm and 500 nm, a fact which has triggered discussions on potential color vision disturbances but also on improved contrast sensitivity due to reduced chromatic aberrations after the implantation of blue-light-filter lenses.[71–74]

Numerous investigations, some of them randomized, have shown that neither an impairment of color vision nor of contrast vision can be attributed to blue-light-filter intraocular lenses.[75–85] Also, a comparison with peer patients with clear crystalline lenses revealed no significant changes in the color perception of patients implanted with AcrySof® Natural.[79] At the same time, blue-light-filters appear to restore almost natural contrast vision. Bhattacharjee et al[80] found that contrast vision of patients with blue-light-filter lenses was closer to that of patients with crystalline lenses, whereas the performance of patients with UV-absorbing intraocular lenses was slightly inferior (Figure 4). In an admittedly small patient number (n = 19), Leibovitch et al[86] found no difference in the contrast sensitivity (Pelli-Robson) even under mesopic conditions (3 lux) between patients with blue-light-filter lenses and those with conventional UV-absorbing lenses. In diabetic patients, a blue-light-filter lens may even significantly improve both contrast sensitivity and color discrimination in the blue–yellow axis.[87] A recently published randomized study was also unable to corroborate the deterioration of the preexisting color vision defects that often is presumed to be associated with the implantation of blue-light-filter lenses.[88]

Conclusions

The perception of light relies on two systems (visual/nonvisual) which use different photopigments with defined excitation peaks. Mutually interacting circuits, adaptive processes, and projections to different brain areas make for enormous complexity. In view of this highly complex neuronal processing of light signal inputs, the present assessment of the effects of blue-light-filter lenses on various sensory and physiologic parameters started by focusing on their impact on specific input signals. As far as the circadian rhythm is concerned, it should be noted that, at the point of maximum action for the measuring of light intensity—480 nm—blue-light-filter lenses have very similar transmission characteristics to a child's crystalline lens. Hence, no interferences with the circadian rhythm are to be expected from blue-light-filter lenses. Comparative clinical studies into quality of life and mental health confirm this assessment. No clinically significant interference with scotopic vision is to

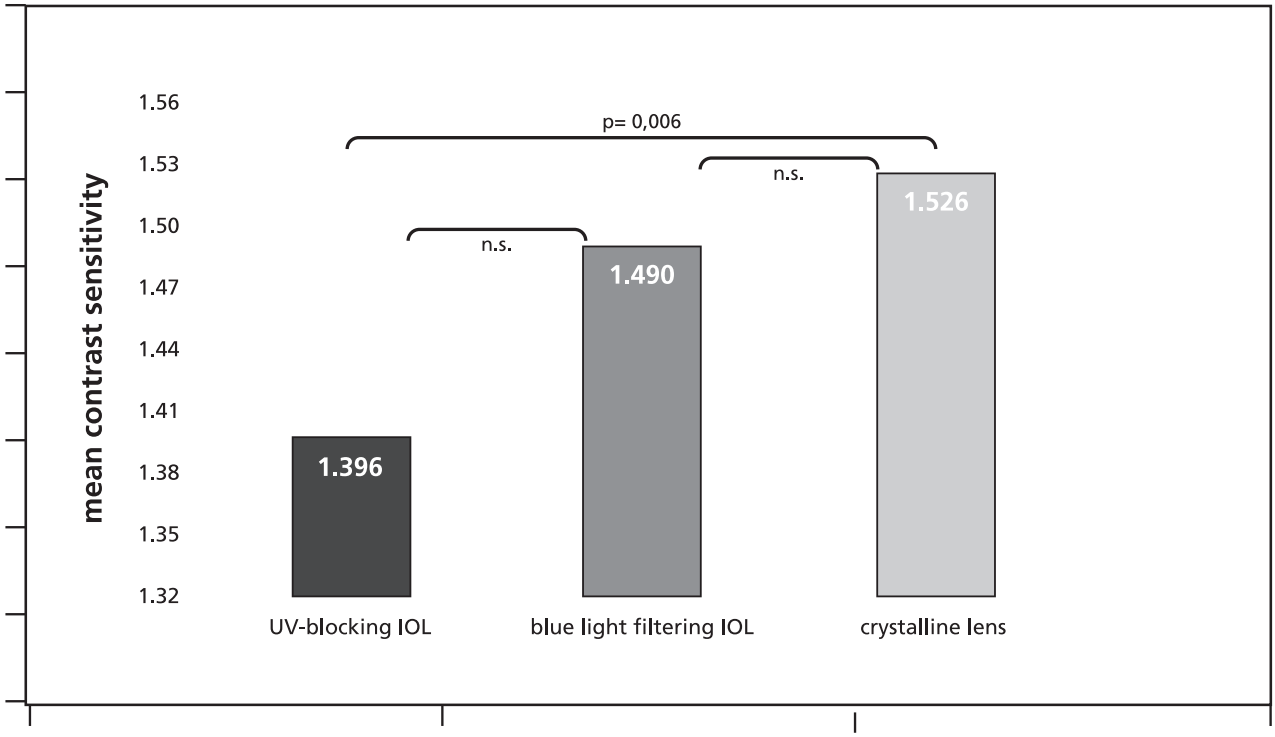

Fig. 4. Comparison of contrast vision (Pelli-Robson) in peer-aged patients with conventional UV-absorbing lenses, blue-light-filter lenses or clear crystalline lenses. Although contrast vision does not differ significantly in patients with a blue-light-filter lens vs. those with a clear crystalline lens, there is a significant difference between patients with a UV-absorbing lens and those with a clear, crystalline lens. Modified from J Cat Refract Surg 2006;32:451–455.

be expected under natural lighting conditions after the implantation of blue-light-filter lenses because, at the peak of scotopic light reception, 507 nm, the light transmission of a blue-light-filter lens is 85%, even slightly higher than that of a child's crystalline lens. Again, this finding is confirmed by clinical studies. The implantation of a UV-absorbing or cutoff filter intraocular lens has no positive effect on the physiologic parameters described that would be consistent with an improvement of scotopic vision, for instance, or a more "stable" circadian rhythmicity. Clinical studies comparing UV-blocking lenses and blue-light-filter lenses confirm this assessment. There is currently no evidence of blue-light-filter lenses having a clinically significant impact on physiologic parameters such as scotopic vision, color vision, or contrast vision because blue-light-filtering lenses lacks documentation. What is more, evidence of blue-light-filter lenses protecting against high-energy blue light has already been obtained in laboratory and animal experiments.[89–91] It goes without saying that this data will have to be confirmed by a prospective epidemiologic study. Such a study should also aim to address issues such as "indications for blue-light-filter lenses" in "potential risk populations."

Key words: blue-light-filtering intraocular lens, UV-absorbing intraocular lens, circadian rhythm, scotopic vision, color vision, contrast sensitivity, functional vision, melanopsin, melatonin.

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