Relative effectiveness of a blue light–filtering intraocular lens for photoentrainment of the circadian rhythm

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PURPOSE: To compare the relative effectiveness of photoentrainment of the circadian rhythm by a blue light–filtering tinted intraocular lens (IOL) (AcrySof Natural SN60), an untinted UV-only filtering IOL (AcrySof SA60), and human lenses in 4 age groups.

SETTING: Scientific consultant and Department of Biological Structure and National Primate Research Center, University of Washington, Seattle, Washington, USA.

METHODS: Three of 8 action spectra for circadian photoentrainment published from 2001 to 2007 were used to compute the relative effectiveness of the cumulative photon flux absorption from 400 to 600 nm reaching the retina from 4 light sources through the cornea, pupil, and 6 lenses.

RESULTS: The effectiveness of the tinted IOL was 35% to 54% and 69% to 114% greater with the action spectra of 2002 to 2007, with a peak around 484 nm and 492 nm, respectively, compared with the 2001 action spectra, with a peak around 460 nm. The difference in effectiveness between the 2 IOLs ranged from 32% to 12%. With newer action spectra, differences in effectiveness between the tinted IOL and the lenses of a young standard observer and a 30- to 39-year-old were age dependent (+7% to −10% and +6% to −13%, respectively).

CONCLUSIONS: The tinted IOL was significantly more effective for photoentrainment of the circadian rhythm with newer action spectra. The computational results suggest that the effectiveness of the tinted IOL in 60- to 85-year-old patients would be within +6% to −13% of that in 30 to 39 year olds. Both tinted and untinted IOLs are expected to be effective for melatonin suppression under average household illumination.

J Cataract Refract Surg 2009; 35:529–539 © 2009 ASCRS and ESCRS

In healthy subjects, the sleep/wake cycle, body temperature, and secretion of various hormones such as insulin, cortisol, and melatonin have a circadian rhythm of roughly 24 hours. These circadian rhythms are synchronized by the endogenous master circadian rhythm created by a pacemaker located in the suprachiasmatic nucleus of the hypothalamic region of the brain.[1,2] This master circadian rhythm, referred to in this paper as the circadian rhythm, is free running and is synchronized by external cues called Zeitgebers (from the German for "time givers"). Any compromise in this synchronization may have a significant effect on various health aspects of patients including sleep patterns, mood, seasonal affective disorder, and other more serious diseases that are still under investigation.[3,4] Jet lag and shift worker's sleep disorder are the most commonly experienced consequences.[5]

Although light through the eye was long known as the key external cue for this synchronization, also known as photoentrainment, significant progress has been made in the past few years in delineating the underlying complex physiology.[6–22] This progress

Submitted: September 10, 2008.
Final revision submitted: October 26, 2008.
Accepted: November 15, 2008.

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Anil S. Patel, PhD, is a retiree of and a consultant to Alcon Research Ltd., Fort Worth, Texas, USA. Neither author has a financial or proprietary interest in any material or method mentioned.

Rick Potvin, MASc, OD, Alcon Laboratories Inc., Fort Worth, created some figures and performed some computations.

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0886-3350/09/$—see front matter
doi:10.1016/j.jcrs.2008.11.040

resulted from a breakthrough discovery of the intrinsically photosensitive retinal ganglion cells (ipRGC) with melanopsin photopigment with peak sensitivity at approximately 480 nm in 2002.[16–20] These newly discovered cells are able to maintain the circadian rhythm, even in profoundly blind patients without functional rods or cones.[21] It is now established that ipRGC, along with classical photoreceptors rods and cones, provide an important nonimage-forming function that some[22] call the nonimage-forming third eye, which is separate from the normal well-known image-forming function of the eye.[6,21] This function includes photoentrainment of the circadian rhythm as well as certain aspects of the pupillary reflex.

The available light level for photoentrainment of the circadian rhythm increases after cataract surgery. Charman[23] was the first to quantify this effect in 2003 with a mathematical computational study. His computational results led him to conclude that an intraocular lens (IOL) that filters ultraviolet (UV) light only can restore the light available for melatonin suppression in elderly cataract patients to almost youthful levels after cataract surgery. Van Gelder,[24] in a 2004 letter, expressed concern over the potential for compromising the photoentrainment in patients with blue light–filtering IOLs. Subsequently, Mainster amplified and quantified this potential concern in a 2008 presentation (M.A. Mainster, "Blue Light: To Block or Not to Block. Cataract Surgery Should Improve Vision and Health, and Blue Light Is Essential for Both," Cataract & Refract Surg Today Europe, 2007, pages 64–68. Available at: http://www.crstodayeurope.com/Pages/whichArticle.php?id=109. Accessed November 22, 2008; M.A. Mainster, P.L. Turner, "Intraocular Lens Chromophores, Light Sources, Circadian Photoreception, and Good Health," presented at the ASCRS Symposium on Cataract, IOL and Refractive Surgery, Chicago, Illinois, USA, April 2008).[25]

Charman,[23] as well as Mainster, quantified the photoentrainment effect using action spectra for the photoentrainment of the circadian rhythm as published in 2001 (M.A. Mainster, P.L. Turner, "Intraocular Lens Chromophores, Light Sources, Circadian Photoreception, and Good Health," presented at the ASCRS Symposium on Cataract, IOL and Refractive Surgery, Chicago, Illinois, USA, April 2008).[26,27] Both action spectra of 2001 had estimated sensitivity peaks around 460 nm. Since the ipRGC discovery in 2002, considerable research in this area to better understand the underlying physiology has produced 6 additional action spectra,[11,12,14,19–21] with peaks ranging from 480 to 492 nm for photoentrainment of the circadian rhythm.

This paper presents all 8 action spectra and selects 3 of them that are distinct for computations of the relative effectiveness of the photoentrainment of the circadian rhythm. The objective is to quantitatively compare the relative effectiveness of the blue light–filtering AcrySof Natural IOL (SN60, Alcon Laboratories Inc.), referred to here as the tinted IOL; the UV-only filtering AcrySof IOL (SA60, Alcon Laboratories Inc.), referred to here as the untinted IOL; and human lenses in 4 age groups with 4 light sources with the 3 action spectra.

MATERIALS AND METHODS

For quantification of the relative effectiveness of the photoentrainment of the circadian rhythm, using the same notation as Charman,[23] a slightly different equation is given as follows. The derivation of this equation is given subsequent to the explanation of notations and clarification of this difference.

$$R = \int_{400}^{600} E(\lambda) \times \lambda/hc \times Tc(\lambda) \times A \times T_L(\lambda) \times S(\lambda) \times d\lambda$$

where R is the relative effectiveness of the photoentrainment of the circadian rhythm, λ is wavelength (nm), $E(\lambda)$ is the spectral power distribution of the light source in radiometric unit of W/cm^2, h is Planck's constant 6.626×10^{-34} $W.s^2$, (s = second), c is the speed of light in a vacuum as 3.00×10^{17} nm/s, $Tc(\lambda)$ is the transmission characteristic of the cornea, A is the pupil area (cm^2), $T_L(\lambda)$ is the transmission characteristic of the lens, $S(\lambda)$ is the relative sensitivity for effectiveness of the photoentrainment of the circadian rhythm as represented by action spectrum for it, and $d\lambda$ is the small interval of wavelength, an independent variable for the integration between 400 nm and 600 nm. This equation, as with that of Charman,[23] ignores the contribution of the Stiles-Crawford effect.

Note that this equation differs from that given by Charman[23] by an additional term, λ/hc, because the standard notation and values for irradiance by light sources $E(\lambda)$ in this equation is given in the units of W/cm^2, as per the standard practice. Because $S(\lambda)$ of the equation is derived with photon flux units, representing effective absorbed photons in the retinal photoreceptors, $E(\lambda)$ must be converted from its radiometric irradiance units of W/cm^2 into required photon flux units of photons/cm^2/s by the additional multiplying factor of λ/hc. This multiplication factor is simply derived by the fact that at a given wavelength λ, the energy per photon is hc/λ. Charman[23] did not specify in his paper whether he converted irradiance of light into photon flux in his calculations or meant $E(\lambda)$ in the units of photons/cm^2/s. Because it will affect the results of computations, it is clarified here.

For the derivation of the equation, the total number of photons reaching the retina for a given small interval $d\lambda$ at a given wavelength λ in nanometers was determined by the $[E(\lambda) \times \lambda/hc]$ photons of light transmitted through cornea with its transmittance $T_C(\lambda)$ and then through the pupil of area A, which is a constant value independent of λ, and through the lens with its transmittance $T_L(\lambda)$, thus requiring multiplication of all these terms. These photons are absorbed by the photopigments in the retina responsible for the effectiveness of the photoentrainment of the circadian rhythm as determined by the relative sensitivity $S(\lambda)$, which is usually published and referred to as the action spectrum. This additional term was further multiplied for computing the relative effectiveness of the photoentrainment of the circadian rhythm for the small interval $d\lambda$ at the wavelength λ. The integration from 400 to 600 nm provided the cumulative final result, which represents the value of the relative

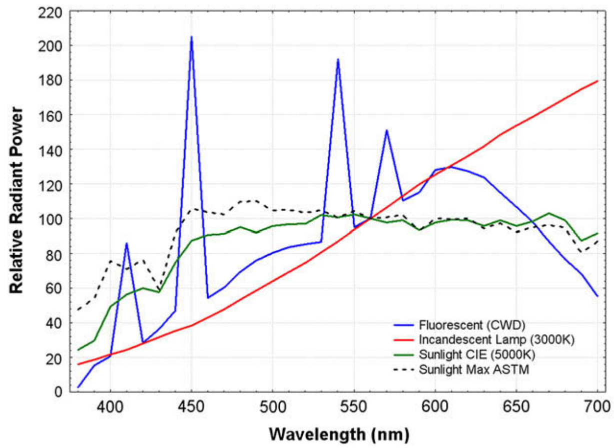

Figure 1. Relative radiant spectral power distributions of the 4 light sources with normalized value of 100 at 560 nm.

effectiveness of the photoentrainment of the circadian rhythm. The range of the integration was selected based on availability of all 3 selected action spectra where they are most effective.

To perform computations for the above equation, the following selections were made:

1. For E(λ), 4 light sources with very different relative spectral power distributions (Figure 1) were selected. To critically evaluate the blue-light filtering by the tinted IOL, the Cool White Deluxe fluorescent lamp and the Sunlight Max ASTM, as representative of other such artificial-lighting sources, were selected because they have relatively higher power distribution in the blue region. Selection of the Sunlight 5000K and incandescent lamp completed the list of common environmental illumination sources. All sources except the Sunlight Max ASTM represent the majority of indoor household lighting environment. The Sunlight Max ASTM represents similar artificial light sources with relatively high power distribution in the blue region for some household environments and many night-shift workers' light environments. The ASTM G-173-3 standard[28] provided the digitized data needed at 10 nm intervals for maximum solar irradiance on earth. The GE Electric Lighting products web page (http://www.gelighting.com/na/business_lighting/education_resources/learn_about_light/distribution_curves.htm. Accessed November 20, 2008) provided the spectra for the selected fluorescent and incandescent sources to represent artificial indoor lighting. These 2 spectra were also digitized at 10 nm intervals. The lowest relative daylight solar spectrum for 5000K color temperature was selected from a table of digitized values at 10 nm intervals with value of 1 at 560 nm in accordance with CIE method.[29] For the objective of computations for relative effectiveness, the spectral radiant power distribution for each source in W/cm^2 was similarly normalized as 100 at 560 nm. Because exact irradiance for all selected sources depends on many factors, such normalization facilitates relative quantitative interpretation of the effect of spectral distribution of different sources. The mercury lines of the spectrum for the fluorescent lamp appear wider in Figure 1, consistent with Charman,[23] as a result of spectral resolution of the available data.
2. For T_C (λ), values were calculated at each 10 nm between 400 nm and 600 nm using an equation[30] that models the direct transmittance of the cornea by wavelength.
3. Pupil area A was based on available relative pupil area versus age data from Charman's Figure 2[23] for all light-adapted and dark-adapted mesopic and photopic conditions relevant to the photoentrainment of the circadian rhythm. The midrange values after needed digitization to represent 65 ± 5, 70 ± 5, and 80 ± 5 year age groups were used in the computations given in Tables 1 to 3.
4. For T_L(λ), the transmission curves are shown in Figure 2 for 2 IOLs and 4 human lenses. The transmission curves for AcrySof SN60 Natural IOL of 20.0 diopters (D) and AcrySof SA60 single-piece IOL of 20.0 D in water are as reported in an earlier publication.[31] After extensive review of all available human lens transmission curves, the digitized available data were used for the young adult (age 17 to 30 years) standard observer[29,32,33] and for 2- to 9-year, 30- to 39-year, and 70- to 79-year human lenses.[34] These selected data for different age groups were from the latest measurements with the largest sample size available from the research sponsored by the U.S. Food and Drug Administration.[34]
5. For S(λ), the selections of the 3 distinct action spectra with their linear values included in Figure 2 were made after critical examination for the quantitative differences between all available action spectra for photoentrainment of the circadian rhythm in the English language published literature from 2001 to 2007. This paper gives the name of the first author only for describing the action spectrum published by multiple authors.

Earlier quantitative analysis[23] for impact of light filtering by an IOL on photoentrainment of the circadian rhythm used action spectra of Thapan[26] and Brainard,[27] both of which were published in 2001 before the discovery of ipRGC. Both spectra were based on studies of light-induced melatonin suppression in humans. The Brainard action spectrum was converted from linear *y*-axis to logarithmic *y*-axis and is shown in Figure 3 as is the practice by all other investigators of action spectrum. Because the Brainard and

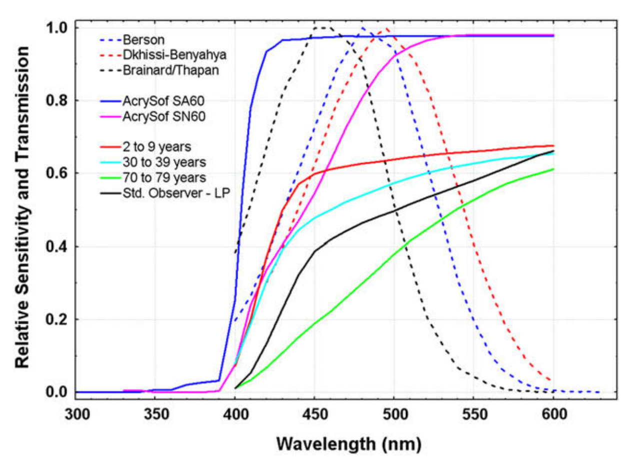

Figure 2. Relative sensitivity curves of the 3 action spectra: Berson,[19] Dkhissi-Benyahya,[14] and Brainard/Thapan, representing the average of Brainard[27] and Thapan.[26] Also shown are the transmission curves of the 2 IOLs (AcrySof SA60 = untinted IOL; AcrySof SN60 = tinted IOL) and the 4 human lenses (2 to 9 year old; 30 to 39 year old; 70 to 79 year old; standard observer) (LP = large pupil).

Table 1. Summary of comparative relative effectiveness of circadian photoentrainment of all lenses, light sources, and action spectra with normalized value of 100 for the standard observer for Sun 5000K as the light source for the Berson action spectrum.

				Human Lenses		
Parameter	Tinted IOL*	Untinted IOL*	Std Obs†	2–9 yo	30–39 yo	70–79 yo
Relative pupil area	0.57	0.57	0.90	0.86	0.80	0.50
Light source/action spectrum‡						
Sun 5000K						
Brainard[27]/Thapan[26]	76.98	109.99	73.90	102.22	80.36	26.56
Berson[19]	106.43	134.46	100.00	128.32	104.58	39.56
Dkhissi-Benyahya[14]	135.38	161.03	126.65	156.14	129.64	53.39
Fluorescent lamp						
Brainard[27]/Thapan[26]	69.78	101.92	68.48	93.85	74.19	24.27
Berson[19]	98.61	125.54	93.88	120.00	97.78	37.28
Dkhissi-Benyahya[14]	132.28	156.77	124.99	152.54	127.09	53.46
Incandescent 3000K						
Brainard[27]/Thapan[26]	45.89	62.43	43.48	124.99	152.54	16.25
Berson[19]	70.57	85.10	65.70	82.17	67.80	27.09
Dkhissi-Benyahya[14]	98.17	111.74	91.59	109.68	92.30	40.25
Sunlight Max ASTM						
Brainard[27]/Thapan[26]	87.49	126.33	84.09	115.77	91.77	30.01
Berson[19]	118.21	150.91	111.23	143.54	116.70	43.61
Dkhissi-Benyahya[14]	147.54	177.39	138.14	171.41	141.91	57.67

IOL = intraocular lens; Std Obs = standard observer; yo = years old
*Mean age 65 years ± 5 (SD)
†Age range 17 to 30 years
‡First author of the publication providing the spectrum (average for Brainard/Thapan)

Thapan spectra of 2001 are almost identical (Figure 3), digitization of the average of the 2 curves was performed and the resultant values converted back from a logarithmic to a linear scale as S(λ). This is the Brainard/Thapan action spectrum, which was used by Mainster[25] for expressing his opinion on the potential compromise in circadian photoreception by blue light–filtering IOLs (M.A. Mainster, P.L. Turner, "Intraocular Lens Chromophores, Light Sources, Circadian Photoreception, and Good Health," presented at the ASCRS Symposium on Cataract, IOL and Refractive Surgery, Chicago, Illinois, USA, April 2008). Therefore, it was selected for comparative computations with 2 more recent action spectra for circadian photoreception. An additional 6 action spectra from 6 different investigations[11,12,14,19–21] between 2002 and 2007 are shown in Figure 4. They are superimposed to show nearly identical results, except the Dkhissi-Benyahya[14] action spectrum is slightly shifted to the right with higher wavelength for its peak. Of the 5 overlapping curves, Berson[19] (λmax = 484 nm) and Dacey[12] (λmax = 482 nm) action spectra are the only 2 based on electrophysiological responses as direct measure of circadian photoreception from isolated ipRGC with melanopsin photopigment without input from rods and cones; thus, their selection over the other 3 based on indirect measure. Of these 2, because the Berson action spectrum is available for the widest range of wavelengths, it was digitized and selected as the second action spectrum for the computation to represent 5 of the 6 curves in Figure 4. The Dkhissi-Benyahya[14] action spectrum was the third selected action spectrum because it models the combined response of ipRGC and middle wavelength (MW) cones. Although studies in the primate[12] have shown cone input to ipRGC, direct evidence in the human retina has not been reported. The digitization of the selected action spectra at each 10 nm was performed by importing scanned images of these action spectra into Microsoft Photo Editor software where the *x*, *y* cursor provided accurate coordinates for digitizing of the curves using the axes as the scaling references.

The computations for the selected light sources, lenses, and action spectra were performed by creating tables with the relevant input data using Microsoft Excel and then transferring these data to Microsoft Access, where the computations for each permutation were performed and the results for each lens–light source–action spectrum combination were summed. The final results were transferred back into a Microsoft Excel worksheet and further normalized to provide comparative results.

RESULTS

Table 1 shows the complete comparative results of the relative effectiveness of the photoentrainment in eyes with various lenses. The computed results are given as normalized so that the relative effectiveness for the young adult 17- to 30-year-old human lens of the standard observer with the Sun 5000K spectrum and the Berson action spectrum was 100. This table of complete relative results can be used to create comparative results of relative effectiveness with any other preferred normalization in a table or a chart form. Figure 5 shows a chart of the comparative relative effectiveness

Table 2. Summary of comparative relative effectiveness of circadian photoentrainment of all lenses with separate normalized value of 100 for each light source for the tinted IOL for the Brainard/Thapan action spectrum to show relative increases for the other 2 action spectra for each light source.

				Human Lenses		
Parameter	Tinted IOL*	Untinted IOL*	Std Obs†	2–9 yo	30–39 yo	70–79 yo
Relative pupil area	0.57	0.57	0.90	0.86	0.80	0.50
Light source/action spectrum‡						
Sun 5000K						
Brainard[27]/Thapan[26]	100.00	142.88	96.00	131.49	104.39	34.51
Berson[19]	138.26	174.67	129.90	166.69	135.85	51.40
Dkhissi-Benyahya[14]	175.86	209.19	164.53	202.83	168.41	69.35
Fluorescent lamp						
Brainard[27]/Thapan[26]	100.00	146.06	98.14	134.50	106.31	34.79
Berson[19]	141.31	179.91	179.12	171.97	140.13	53.43
Dkhissi-Benyahya[14]	189.57	224.66	94.76	218.60	182.13	76.61
Incandescent 3000K						
Brainard[27]/Thapan[26]	100.00	136.04	143.17	126.80	101.68	35.41
Berson[19]	153.79	185.45	131.39	179.07	147.75	59.04
Dkhissi-Benyahya[14]	213.93	243.49	199.58	239.00	201.13	87.70
Sunlight Max ASTM						
Brainard[27]/Thapan[26]	100.00	144.39	96.11	132.32	104.90	34.31
Berson[19]	135.12	172.49	127.13	164.07	133.39	49.84
Dkhissi-Benyahya[14]	168.64	202.75	157.89	295.92	162.20	65.91

IOL = intraocular lens; Std Obs = standard observer; yo = years old
*Mean age 65 years ± 5 (SD)
†Age range 17 to 30 years
‡First author of the publication providing the spectrum (average for Brainard/Thapan)

between the various lenses with all 3 action spectra for the Sunlight 5000K light with normalization value of 100 for relative effectiveness for the standard observer lens with the Berson action spectrum.

Table 2 shows the increase in the effectiveness for all lenses for the Berson and the Dkhissi-Benyahya action spectra with normalized value of 100 for the Brainard/Thapan action spectrum for each light source separately. The light source dependent increases in effectiveness for the tinted IOL were 35.12% to 53.79% and 68.64% to 113.93% with the action spectra of 2002 to 2007, with peaks around 484 and 492 nm, respectively. Figure 6 shows considerably higher relative effectiveness for each of the 4 light sources for the tinted IOL with the Berson and the Dkhissi-Benyahya action spectra when compared with the earlier Brainard/Thapan action spectrum.

The first column of data in Table 3 shows that the difference in the effectiveness between the tinted and untinted IOL diminished from as high as −32% with Brainard/Thapan action spectrum with a 460 nm peak to as low as −12% with Dkhissi-Benyahya action spectrum with a 492 nm peak. The next 6 columns of data in Table 3 show the difference in effectiveness for tinted IOL in 65 ± 5-year-old, 70 ± 5-year-old, and 80 ± 5-year-old patients compared with human lenses of the 17- to 30-year-old standard observer and 30 to 39 year old. With newer action spectra, the tinted IOL provided age-dependent differences in effectiveness of +7% to −10% and +6% to −13% compared with the lenses of the young standard observer and the 30 to 39 year old, respectively.

DISCUSSION

All of the comparative effectiveness results are the lowest when calculated with the Brainard/Thapan action spectrum, with its peak around 460 nm. The effectiveness increases with the Berson action spectrum, with its peak at 484 nm, and further increases for the Dkhissi-Benyahya action spectrum, with its peak at 492 nm, for all lenses and light sources. The corneal transmission and the spectral power distribution contribute less to the variability over the range of wavelengths for the integration. The primary reason for the increase in the relative effectiveness is that the higher peaks of the later-derived action spectra are in the region of higher transmission for the lenses (Figure 2). The secondary modulating effect of the difference in the spectral power distributions of the light

Table 3. Summary of comparative relative effectiveness of circadian photoentrainment between the tinted IOL and the untinted IOL, lens of the standard observer, and lens of a 30 to 39 year old.

	Difference in RE of Tinted IOL Compared with lenses Below (RE = 100 for Lenses Below)						
Parameter	Untinted IOL	17–30 yo Standard Observer			30–39 yo Human Lens		
Age (y) for patient with tinted IOL*	Any	65	70	80	65	70	80
Relative pupil area	Any	0.57	0.53	0.49	0.57	0.53	0.49
Light source/action spectrum†							
Sun 5000K							
Brainard[27]/Thapan[26]	−31	+4	−3	−10	−4	−11	−18
Berson[19]	−21	+6	−1	−9	+2	−5	−13
Dkhissi-Benyahya[14]	−16	+7	−1	−8	+4	−3	−10
Fluorescent lamp							
Brainard[27]/Thapan[26]	−32	+2	−5	−12	−6	−13	−19
Berson[19]	−21	+5	−2	−10	+1	−6	−13
Dkhissi-Benyahya[14]	−16	+6	−2	−9	+4	−3	−11
Incandescent 3000K							
Brainard[27]/Thapan[26]	−26	+6	−2	−9	−2	−9	−15
Berson[19]	−17	+7	0	−8	+4	−3	−11
Dkhissi-Benyahya[14]	−12	+7	0	−8	+6	−1	−9
Sunlight Max ASTM							
Brainard[27]/Thapan[26]	−31	+4	−3	−11	−5	−11	−18
Berson[19]	−22	+6	−1	−9	+1	−6	−13
Dkhissi-Benyahya[14]	−17	+7	−1	−8	+4	−3	−11

IOL = Intraocular lens; RE = relative effectiveness; yo = years old
*Each age represents the midrange value ± 5 years; thus, 65 = 60 to 70, 70 = 65 to 75m, and 80 = 75 to 85
†First author of the publication providing the spectrum (average for Brainard/Thapan)

sources is best illustrated for the relative effectiveness results of the tinted IOL in Table 2 and Figure 6. The increase in the relative effectiveness with increase in the peak of the action spectrum from around 460 nm to 484 nm to 492 nm was the greatest for the incandescent lamp and the least for the Sun Max ASTM source. These results corresponded to their relatively low- and high-power spectral distributions in the blue regions, as shown in Figure 1, where the tinted IOL filtered more light, as shown in Figure 2.

There was an age-dependent pupil size reduction effect as shown in Table 3 on the relative effectiveness of the tinted IOL. For the IOL in a 65 ± 5-year-old patient, with newer action spectra, it was +1% to +7 % higher than for the lenses of the standard observer and the 30- to 39-year-old for all light sources. But for 70 ± 5-year-old patients, these differences decreased to almost 0 to −6. For 80-year-old patients, the differences ranged from −8% to −13 % for the newer action spectra. Thus, with newer action spectra, based on the calculations here, 60- to 85-year-old patients with the tinted IOL are expected to have the photoentrainment of their circadian rhythm restored to relatively healthy values within +7% to −13% range of values for normal individuals 17 to 30 years of age and 30 to 39 years of age. The first data column in Table 3 compares the effectiveness of the 2 IOLs and is independent of age because the pupil size is identical for both IOLs at any age. The tinted IOL had lower effectiveness than

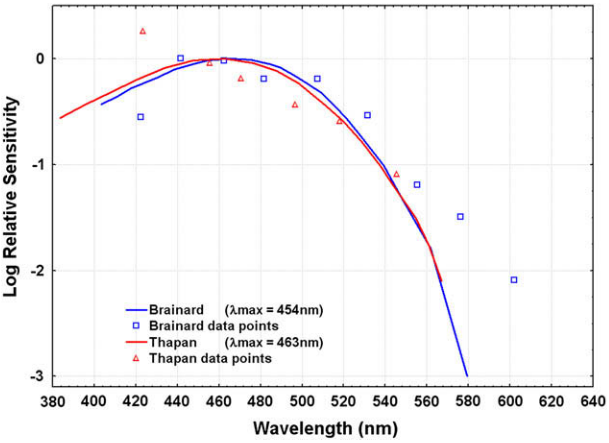

Figure 3. Log relative sensitivity versus wavelength for the Brainard[27] and the Thapan[26] action spectra for light-induced human melatonin suppression as representing the photoentrainment of the circadian rhythm. These were published before the discovery of ipRGC.

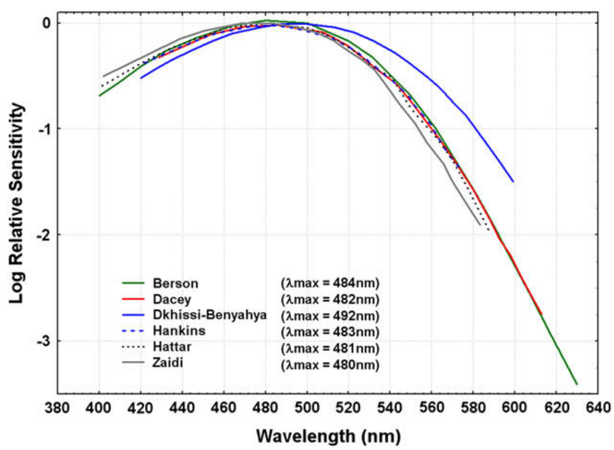

Figure 4. Log relative sensitivity versus wavelength for Berson,[19] Dacey,[12] Dkhissi-Benyahya,[14] Hankins,[20] Hattar,[11] and Zaidi[21] action spectra representing the different endpoints for the photoentrainment of the circadian rhythm in rat, primate, mice, human, mice, and human respectively. All of these were published after discovery of ipRGC.

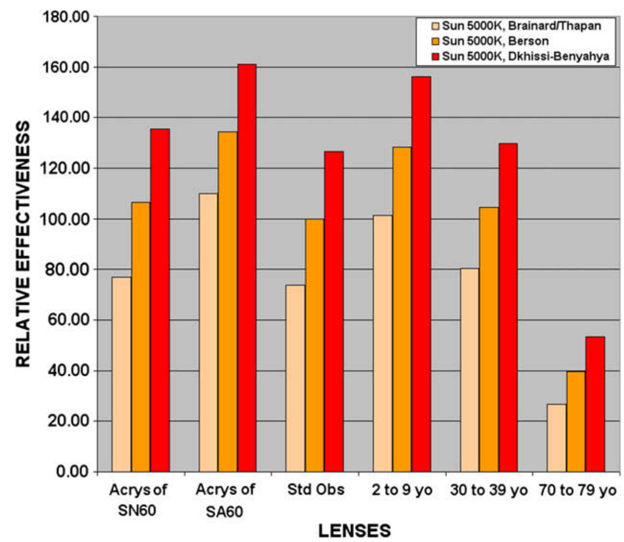

Figure 5. Relative effectiveness of the photoentrainment of the circadian rhythm for all 6 lenses for Sun 5000K light source with value for standard observer for the Berson action spectrum normalized as 100 (AcrySof SA60 = untinted IOL; AcrySof SN60 = tinted IOL; Std Obs = standard observer; yo = year old).

the untinted IOL because the tinted IOL had the lower transmission in the blue region. This difference significantly decreased for each light source as the action spectrum peak increased. As an example for the Sun 5000 K light source, as the action spectrum peak increased from around 460 nm to 484 nm to 492 nm, the difference between the effectiveness of the 2 IOLs decreased from −31% to −21% to −16%. The −12% difference was lowest with the incandescent light, which has minimal blue power.

Close examination of the relative effectiveness of the tinted IOL in Table 2 and Figure 5 shows improvement as the peak of the selected 3 action spectra increases. Starting from the Brainard/Thapan action spectrum with lowest peak, the effectiveness was significantly improved with Berson action spectrum, with the Dkhissi-Benyahya action spectrum, it almost reached the value of the untinted IOL for the Berson action spectrum. Thus, the overlap relationship between the transmission curve of the IOL and the action spectrum, which is represented by wavelength for its peak, was the most deterministic for the consequent comparative relative effectiveness. The recent research, which increased the estimates of the peak wavelength for sensitivity in regard to photoentrainment, has reduced the comparative difference between the 2 IOLs.

To discern the validity of the result with any 1 of the 3 action spectra, the background of the 3 selected action spectra and their differing peaks requires a brief examination. The significant discovery of the ipRGC with melanopsin photopigment occurred in 2002.[16–20] In 2001, Thapan et al.[26] and Brainard et al.,[27] before the identification of this responsible photopigment, were constructing the action spectrum following a generally accepted method. The methodology published in subsequent years[35,36] requires many rigorous steps to achieve the correct action spectrum, and these later papers describe the potential problems.

In Figure 3, the Thapan et al.[26] curve seems to have 3 of 6 data points far from the derived curve. The 424 nm data point shows the highest sensitivity, with no reduction for lower wavelengths, as suggested by the fitted action spectrum, which has a peak and lower sensitivities on both sides of the peak. Also, a correction for lens absorption would shift the wavelength for the fitted peak curve to a longer wavelength by reducing the effective intensity and thus increasing the

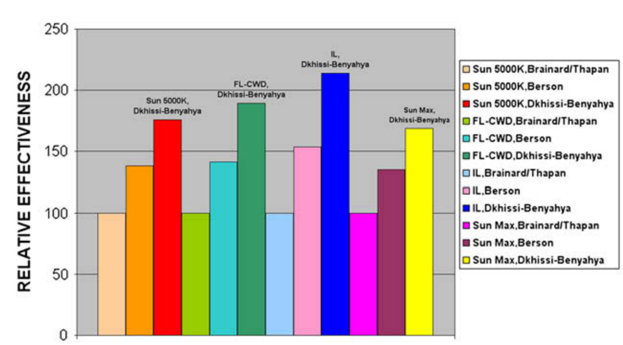

Figure 6. Relative effectiveness of the photoentrainment of the circadian rhythm in eyes with tinted IOL for 4 light sources with value for Brainard/Thapan action spectrum normalized as 100 (FL-CWD = fluorescent lamp; IL = incandescent light; Sun Max = Sunlight Max ASTM).

sensitivity, as reported in another recent publication.[21] Such a shift to a higher peak wavelength after correcting for the lens absorption is recognized[33] for all spectral sensitivity curves of all 3 types of cones. Thapan et al.[26] note this but fail to explain the shown correction and consequent shift to a lower peak wavelength. For this reason, the Thapan action spectrum, with its peak at 454 nm peak, is not in agreement with many other studies of light-induced melatonin suppression in humans (Cooper HM, et al. IOVS 2004; 45:E-Abstract 4345. Available at: http://abstracts.iovs.org/cgi/content/abstract/45/5/4345. Accessed November 22, 2008).[37–39]

The Brainard et al.[27] action spectrum was constructed with a linear instead of logarithmic *y*-axis (sensitivity) and thus is potentially error prone. The rigorous steps for constructing a valid action spectrum specifically detail[35,36] the magnitude of error of curve fitting of a photopigment template with relative sensitivity (*y*-axis) when expressing it in linear instead of logarithmic value. This curve fitting by the mathematical method[35,36] of nonlinear regression requires an iterative process with the 50% response point of a series of the sigmoidal irradiance response curves (IRCs). From the 8 sigmoidal IRCs for 440, 460, 480, 505, 530, 555, 575, and 600 nm wavelengths given separately in the Brainard et al. paper,[27] only 4 IRCs were selected and superimposed with both axes coincident to create a new figure shown as Figure 7. It shows that the IRCs for 460, 480, and 505 nm are almost identical; this brings into question the 460 nm peak arrived at by Brainard et al., possibly the result of the error-prone method of curve fitting, including linear rather than logarithmic construction of the action spectrum. The Figure 7 curve suggests an almost flat action spectrum from 460 to 505 nm; several other studies[37–39] support higher peak wavelengths up to 514 nm for the action spectrum for melatonin suppression in humans. A 2004 abstract reported optimal sensitivity to wavelengths between 460 nm and 500 nm for human melatonin suppression, which also supports Figure 7 (Cooper HM, et al. IOVS 2004; 45:E-Abstract 4345. Available at: http://abstracts.iovs.org/cgi/content/abstract/45/5/4345. Accessed November 22, 2008).

The selected Berson et al.[19] action spectrum from 2002, with its peak at 484 nm, was constructed directly for isolated rat ipRGC by electrophysiological measurements as the endpoint and thus directly represents the newly discovered physiology[6–21] of circadian photoreception with its melanopsin pigment. The peak around 480 nm is in agreement with the other 4 action spectra in Figure 4. Three of these 4 action spectra are also for only ipRGC because input from cones and rods was absent in the investigations by Dacey et al.[12] for primate ipRGC in 2005, Hattar et al.[11] for mice ipRGC in 2003, and Zaidi et al.[21] for ipRGC of a profoundly blind human with autosomal-dominant cone–rod dystrophy in 2007. Hankins et al.,[20] in 2002, also provided the action spectrum from an investigation of light dose–induced effect on the b-wave latency in humans and considered their action spectrum for the nonclassical photoreceptor implying ipRGC.

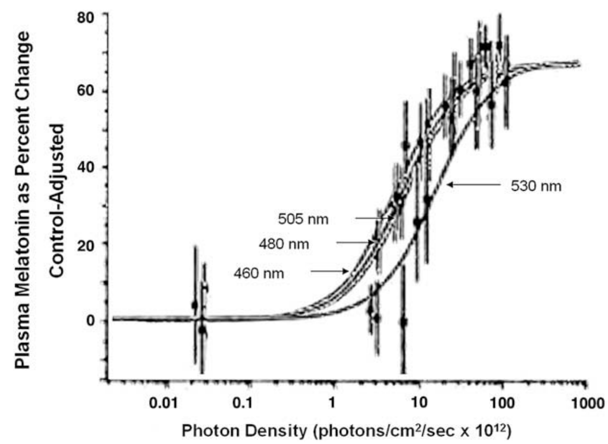

Figure 7. Superimposed irradiance response curves for 460, 480, 505, and 530 nm for control-adjusted plasma melatonin percentage change as photon density increases; based on the published 8 IRCs for the construction of the Brainard action spectrum for the light-induced melatonin suppression in the humans.

The selected Dkhissi-Benyahya et al.[14] 2007 action spectrum, with a still higher peak at 492 nm for mice, represents the additional contributory input of the MW cone. It was based on measurements of light-induced phase shifting in mice, which specifically lacked MW cones, and subsequent modeling of the relative contribution from opsin of these cones and melanopsin of ipRGC. Although the MW cone input to ipRGC has also been found in the macaque primate retina[12] and such input from classical photoreceptors was earlier suggested by others,[10,11,40] no direct evidence in the human retina for such ipRGC and MW cone has been reported. The MW cone in humans has an action spectrum[41] with a peak at around 530 nm instead of the 508 nm for the MW cone of mice.[14] Thus, if this ipRGC plus MW input-based action spectrum model for mice, with a peak at 492 nm, is applied to humans, the resultant action spectrum might be expected to have a higher peak than 492 nm.

Light-induced melatonin-suppression studies in humans[37–39] report action spectra with peak wavelengths of 504 to 514 nm, also suggested by Figure 7 for superimposed IRCs from which the Brainard et al.[27] action spectrum was constructed. The light power spectrum from 450 to 550 nm is reported as responsive.[42] Additional stimulatory effect of wavelengths of light beyond those for melanopsin action spectrum is also suggested by a study of melatonin suppression in humans with polychromatic versus monochromatic light.[43] A recent comparative study by Canadian Defence R&D[44] found that a blue–green light source of 500 nm was more effective than a blue light source of 460 nm for producing melatonin suppression and circadian phase change in human subjects. Based on their studies of effectiveness with a range of monochromatic wavelengths and their concern over potential blue-light hazard, researchers concerned with the clinical management of delayed sleep phase disorder in humans have recommended the use of light in the 500 to 530 nm range to reduce symptoms.[45] The threshold for human melatonin suppression was reported to be as low as 1.6 to 5 $\mu W/cm^2$ (approximately 6 to 17 lux) at 509 nm.[37] Irradiance of 5.5 $\mu W/cm^2$ (approximately 16 lux) provided a good melatonin-suppression response in humans at 505 nm.[46] Thus, the extension of the Dkhissi-Benyahya et al.[14] action spectrum model from mice to humans seems to be supported by these overall findings in the literature, and this action spectrum for human indeed may have a higher peak sensitivity wavelength in the vicinity of 500 nm. If this is the case, the results of the effectiveness of both the tinted IOL and untinted IOL would improve and the relative difference between their effectiveness would be lower than reported in Table 3. Figure 2 shows that the transmission curves of the untinted and tinted IOLs further reached closer values at 505 and 509 nm. For these wavelengths, the monochromatic irradiance values for threshold[39] and good[46] melatonin suppression in humans are in the range of 1.6 to 5.5 $\mu W/cm^2$ (approximately 6 to 17 lux). Considering such low irradiance requirements, both IOLs are expected to be adequately effective in the average human household illumination of 300 lux (approximately 100 $\mu W/cm^2$),[47] especially since the polychromatic light appears to be more effective than monochromatic light in regard to melatonin suppression.[43] This level of illumination also appears much higher than the required threshold. A study in Japan[48] reports good melatonin suppression in monkeys with 10 to 30 lux of polychromatic illumination. Conservatively, even for a consideration of a 100 lux dim polychromatic light environment, the higher 30 lux required for melatonin suppression yields the 233% excess reserve for circadian photoentrainment. Such excess is more than sufficient to overcome the maximum −22% difference for the tinted IOL compared with untinted IOL for the Berson action spectrum in Table 3. Thus, both IOLs are expected to be adequately effective for the circadian photoentrainment, even in such dim-light environments.

In conclusion, the wavelength at the peak sensitivity for the action spectrum primarily determined the computational results of the relative effectiveness of the photoentrainment of the circadian rhythm for all lenses. The most recent research on the action spectrum of photosensitive retinal ganglion cells and with the additional contribution by MW cones suggests peaks at around 484 nm and 492 nm, respectively. These newer action spectra support a significantly higher comparative effectiveness for the circadian rhythm for the tinted IOL than the earlier action spectra with peak sensitivity around 460 nm. The results of the computations expect the tinted IOL in 65 ± 5-year-old to 80 ± 5-year-old patients to be within +6% to −13% effectiveness of the normal adult human lens of a 30 to 39 year old for the photoentrainment of the circadian rhythm.

The difference in the relative effectiveness of the 2 IOLs was approximately −16% for sunlight and fluorescent lamp and −12% for incandescent light with the latest action spectrum of the combined contribution of the melanopsin and MW cone photopigments with a peak at 492 nm for mice. The extension of this latest action spectrum model from mice to human expects this peak to be even higher, as also suggested in the literature. If corroborated, this would reduce the difference in effectiveness between the 2 IOLs to the level of insignificance. In addition, because the average household illumination level is significantly higher than the threshold irradiance required, both the tinted IOL and untinted IOL are expected to provide adequately effective photoentrainment of the circadian rhythm.

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