

Virtual Meeting 2003/2004 Section 3 Comments

February 19, 2004

Here is the summary of discussion for Section 3, Melatonin, for the Virtual Meeting.

Please participate! To continue discussion, answer or ask questions, or raise issues, please reply to this post (r.lam@ubc.ca) or to sltbr-vm2003@yahoogroups.com .

PLEASE don't send a reply to the entire sltbr-l list, as we are trying not to overload everyone with a lot of individual emails.

*** Have you missed previous abstracts, sections and/or discussion? Everything is archived at the Virtual Meeting website at www.sltbr.org/vm/index.htm

Comment 3.9.

Re: Dr. Lam,

I was wondering about what the well-known blue-light hazard you are referring to is, if you don't mind enlightening a student about this!

*Thanks, Kathryn Roecklein
Uniformed Services University of the Health Sciences
1401 Jones Bridge Road
Bethesda, MD 20814*

The blue light hazard usually occurs with intense light sources with wavelengths centred around 440 nm. These light sources would ordinarily not include those used for light therapy, as per this citation. However, I am not sure what the issues would be for chronic light exposure if we start isolating the blue part of the spectrum for light treatment sources. I was hoping that Charlotte Reme or others could answer this question.

Regards, Raymond W. Lam

Okuno T, Saito H, Ojima J. Evaluation of blue-light hazards from various light sources. *Dev Ophthalmol.* 2002;35:104-12.

Visible light of short wavelength (blue light) may cause a photochemical injury to the retina, called photoretinitis or blue-light hazard. In this study, various light sources were evaluated for blue-light hazard. These sources include the sun, the arc associated with arc welding and plasma cutting, molten steel, iron and glass, the interior of furnaces, the arc or envelope of discharge lamps, the filament or envelope of incandescent lamps, the envelope of fluorescent lamps and light-emitting diodes. The spectral radiance of each light source was measured, and blue-light effective radiance and the corresponding permissible exposure time per day were calculated in accordance with the ACGIH (American Conference of Governmental Industrial Hygienists) standard. The sun, arc welding, plasma cutting and the arc of discharge lamps were found to have extremely high effective radiances with corresponding permissible exposure times of only 0.6-40 s, suggesting that viewing these light sources is very hazardous to the retina. Other light sources were found to have low

effective radiances under the study conditions and would pose no hazard, at least for short exposure times.

Comment 3.8.

I haven't seen any replies yet to Marc Hebert's question about the eye safety of wavelengths in the 460-480 nm range. What about the well-known blue-light hazard? Do we need to be concerned if light device manufacturers begin to selectively target these wavelengths?

Regards, Raymond W. Lam

Comment 3.7.

Re: Abstract 3.7 Melatonin rhythm free-ran at baseline and was entrained during the melatonin treatment in totally blind adults. Was it the same with sleep? Regards, Konstantin Danilenko

This is an important question. The sleep wake schedule did not free-run because the subjects attempted to maintain normal sleep/wake times. This is of course distinct from circadian sleep/wake propensity which we assume did free-run with circadian phase as we and others have demonstrated previously (1, 2). However, we did not demonstrate this with polysomnography in this study. We also assume that circadian sleep/wake propensity entrained along with all other yoked markers of circadian phase resulting in improved sleep quality, as we have also shown previously (1), but we did not demonstrate this.

1. Sack R. L., Brandes R. W., Kendall A. R. and Lewy A. J. (2000) Entrainment of freerunning circadian rhythms by melatonin in blind people. *The New England Journal of Medicine* 343: 1070-1077.

2. Lockley S. W., Skene D. J., Butler L. J. and Arendt J. (1999) Sleep and the activity rhythms are related to circadian phase in the blind. *Sleep* 22: 616-623.

Jonathan Emens, M.D.
Assistant Professor, Department of Psychiatry
Mail Code: L-469, 3181 S.W. Sam Jackson Pk. Rd.
Portland, OR 97239

Comment 3.6.

Re: Abstract 3.7 Melatonin rhythm free-ran at baseline and was entrained during the melatonin treatment in totally blind adults. Was it the same with sleep?

Regards, Konstantin Danilenko

Comment 3.5.

Re: Abstract 3.2

Would the authors please expand upon their implicit hypothesis that melatonin suppression is important for the success of light therapy? Take morning light, for example, as is being recommended for treatment of SAD, with accompanying phase advances. In one simple (simplistic?) scenario, T_{min} and the melatonin SynOff occur well before habitual wake-up time, and they coincide with the PRC crossover point. Following the SynOff, light would not suppress pineal secretion, because it has already stopped. Before the SynOff, light would engender phase delays, not advances. So, where is the therapeutic connection?

Jiuan and Michael Terman

Comment 3.4.

Re: Abstract 3.1 and 3.2

I would like to have the opinion of Dr Remé (or any other members) on the use of blue light 460-480 nm. Based on Drs Lack and Wright study, we do not really need to use blue light as green light is also quite effective (and safer according to the literature). I believe that before thinking about using blue light in human (I mean outside a research protocol) we have to prove its safety. May be I don't have all the literature on that matter, but being in an ophthalmology department, I know that blue light would not be recommended for use and it would not be approved by our ethics committee. This is a very important issue. What do we think is safe and do we have the data to prove it?

Regards, Marc Hébert
Assistant professor of ophthalmology
Laval University, Quebec City.

Comment 3.3.

Re: Abstracts 3.1 and 3.2

We do not understand how Horst Boger derived his illuminance figures for the respective wavelengths. According to our calculations, the amount of lux varied between 50 to about 890 across the wavelengths. However, when measuring monochromatic light across a considerable range of the visible spectrum (ie from 470 nm to 660 nm) it is inappropriate to use photometric measures which varies dramatically in sensitivity to actual light energy at different wavelengths (see Foster and Lucas, Biological Rhythms Bulletin, 1999 1(2) 6-9). It is more appropriate to use radiometric measures with a flat and unbiased spectral response across the entire visible spectrum. We equated for absolute light energy by using the preferred irradiance measure of microW/cm².

Similarly, we are not sure what is meant by "the illuminance must be something about 25,000 cd/m²".

In response to Dr Danileko

(1) there was no significant correlation across subjects between melatonin suppression and phase delay for any wavelength. Also, the scatter plots indicated that there was no complex or nonlinear relationship. This supports the findings of Kubota et al, 2001, Laakso et al., 1993 and Zeitzer et al. 1997. (2) Both the phase delay and phase advance study have been published. The former in Chronobiol Int 2001, 18 and the latter in J Pineal Res, 2004.

(3) The only reason we did not do a repeated measures design in the phase advance study was because it would have meant a commitment of 3 consecutive days repeated for 6 conditions with at least a week between conditions which in practice was going to be difficult to get compliance.

(4) During saliva collection the subjects sat quietly watching television, with no sudden changes in posture except for visits to the toilet that were allowed immediately after a saliva collection time. They were in dim light conditions (<25 lux).

(5) DLMO was calculated by taking the mean plus two standard deviations above the mean for the first three samples collected (Voultsios et al., 1997). From the raw data, a value that was 2 SD above the mean of the baseline values was established and the DLMO was then determined by interpolating between the first data value which consistently exceeded this value and the previous 30 minute value.

(6) We did not artificially dilate pupils as this was a 'clinically driven' study. However, in a small pilot study, under dim light conditions, we exposed 4 subjects to each light wavelength (5 minutes) and measured the pupil and iris diameter pre and during light exposure after five minutes of exposure. The order of the conditions was balanced and there was 10 minutes between each light wavelength exposure condition. We found that the 525, 497 and 470nm wavelengths produced more pupillary constriction than the longer wavelengths. Therefore, if anything, the melatonin suppression and phase change for the short wavelengths was underestimated from what it would have been had the subjects' pupils been artificially dilated. Furthermore, if the active agent for this circadian response is number of photons rather than physical light energy, our results further underestimated the strength of the shorter wavelengths. This is because shorter wavelength photons are more energetic than longer wavelengths. So with equal energy levels between our different wavelength conditions, the subjects were getting fewer photons per unit of time in the shorter wavelength condition.

(7) According to our calculations, 130 microW/cm² ranged in lux from approximately 80(470nm) to 890 (525) to 54 (660nm). Subjectively, the pairs of LEDs mounted in the glasses at 15mm from the cornea was very comparable to the brightness and extent of visual area subtended to a standard lightbox at one meter distance producing about 1000 lux. We have had the advice of several different ophthalmologists to the effect that the light from the apparatus we used is very unlikely to result in retinal damage. Nevertheless, this is an issue to which we remain attentive.

Leon C. Lack, Ph.D.

Comment 3.2.

Re: Abstracts 3.1 and 3.2.

The radiation for all conditions was 130 µW/cm². I did a calculation for the luminance and illumination. That means an illuminance of about 1.100 lx (470 nm), 3.500 lx (497 nm), 10.000 lx (525 nm), 8.500 lx (595 nm) and 750 lx (660nm). The luminance must be something about 25,000 cd/m². I think you may cause eye damage, or is there any other mistake?

Comparing the radiation between 470 nm and 700 nm, the radiation at 470 nm is more than 30 times higher than at 700 nm. So there should be more effectiveness?

Regards, Jörg Böger
Reiher GmbH

Comment 3.1.

Re: Abstract 3.1

Nice design investigating both suppression and phase shift effects of different wavelengths on melatonin. Was there a significant correlation between melatonin suppression and phase shift? Did anybody else show this association clearly?

Was this study accepted for publication? Otherwise several details of the protocol are interesting to clarify:

Why there were different protocols in the phase-delay and phase advance experiments (repeated vs. non-repeated design, 1 vs. 2 light pulses)?

What was a condition during saliva collection (posture, light intensity)? DLMO criterion? Was the pupil size controlled during the LEDs light? Any side effects during the exposure? Is 130 microW/ cm-2 approximately 400 lux?

Re: Abstract 3.3

Great result! Was the actimetry used to document no difference in sleep interruption between <5 and >3500 photopic lux conditions?

Re: Abstract 3.5

Was there a study on potential damage of 470-480 nm light?

Re: Abstract 3.7

Melatonin rhythm free-ran at baseline and was entrained during the melatonin treatment in totally blind adults. Was it the same with sleep?

Re: Abstract 3.8

By subjective ratings, patients of placebo and melatonin groups rated their getting to sleep equally at baseline, while by actimetry, sleep latency was almost twice longer in melatonin group. Why? While focusing on objective ratings and inter-group comparison, Was there a regression towards the mean among the parameters studied?

Regards,
Konstantin Danilenko