

Editorial

Blue in the face[☆]

Our understanding of retinal and circadian physiology has been profoundly transformed by the recent discovery that the ganglion cell pigment melanopsin – which had gone undetected in a century of photoreceptor research – responds to light and inputs the phase shifting mechanism of the body’s master clock in the suprachiasmatic nuclei [1]. The effect is observable in animals lacking rods and cones, which would suggest that melanopsin mediates circadian rhythm entrainment exclusive of visual sensory input. Indeed, the action spectrum of melanopsin is distinct from the well-known rod and cone spectral sensitivity curves. It peaks in the short-wavelength “blue” range below 500 nm; the cone-mediated perception of blue is irrelevant. Beyond circadian entrainment, the spectral response of light-elicited pineal melatonin suppression also tracks the melanopsin curve [2]. Maybe we were wasting light energy all these years by shifting rhythms, suppressing melatonin and treating depression with longer wavelengths tuned to photopic sensory perception.

Light therapy is now widely used for the treatment of delayed sleep phase disorder and winter depression, and several other applications look promising – from nonseasonal depression to attention deficit/hyperactivity disorder to Parkinson’s disease [3]. Light therapy apparatus is also a growing commercial industry without federal regulation. So it has not been surprising to see manufacturers quickly enter the market with clinical claims for melanopsin-tuned blue light apparatus, whether restricted to a short-wavelength narrow-band of light or mixed with longer wavelengths for polychromatic presentation. All this without standard demonstrations of safety and specific efficacy.

The story actually long predates the discovery of melanopsin and its non-image-forming functions. The earliest light therapy studies (and commercial apparatus) used “full-spectrum” fluorescent light – an ill-defined quantity that boosts short-wavelength exposure. The choice of lamp – which was inspired by industry consultants to the National Institute of Mental Health – was

not based on physiological data, but rather on the face-relevant assumption that outdoor skylight contains a lot of blue-light and therefore should be good for you by comparison with indoor artificial light. There was also a suspicion that augmentation of ultraviolet (UV) radiation from these bulbs might enhance the response to light therapy. (One manufacturer installed a UV emitter in its light box.) Concern over the UV hazard quickly led to controlled clinical trials that blocked UV [4], and the need for blue light augmentation was tested with lamps that attenuated short-wavelength emission [5]. The antidepressant response remained robust. Nevertheless, the aggressive marketing of full-spectrum light therapy continues. For one thing, the profit margin is higher than for conventional fluorescent lamps.

It has taken some time for data on the potential clinical benefits of short-wavelength exposure to appear. In a study of winter depression, bright narrow-band blue light was superior to dim red light [6]. Although this result may indicate a benefit relative to placebo, it does not demonstrate the specific efficacy of blue light. Nevertheless, this study motivated the first mass-market initiative for light therapy apparatus, using blue light-emitting diodes, with distribution including the Costco chain. Many clinicians, naïve to the issues, became enthusiasts. There was, however, concern in the ophthalmology community that such short-wavelength exposure could cause direct long-term damage to retinal structures, exacerbation of age-related macular degeneration, and a photosensitization hazard with common medications including certain psychotropic drugs [7]. The ubiquitous yellowing of the lens with age, which largely blocks short-wavelength transmission, might indeed serve a protective function. Counteracting this lens filter with massive doses of blue light in the elderly might be counterproductive. Regardless, the Food and Drug Administration declined a review.

As basic research proceeded, it became apparent that the melanopsin response in ganglion cells does not act in a vacuum. For example, the classical photoreceptors activate the same ganglion cells that subserve the melanopsin response [8]. Exposure to longer-wavelength light restores and enhances the short-wavelength melanopsin response [9]. At relatively low light intensities, and at the initiation of long-

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duration exposure to bright light, cone input predominates over melanopsin input in the suppression of melatonin [10].

Such results have been addressed with a compromise solution called “blue-enriched polychromatic [fluorescent] light” that maintains a broad spectrum, yet raises the color temperature from 3000 to 4000 Kelvin (K) (conventional white fluorescent light) and 5500 to 7000 K (the “full-spectrum” range, still white but with short-wavelength supplementation) to 17,000 K (distinctly blue with heavy weighting toward short wavelengths). I find the term “blue-enriched” an implicit advertising claim for superiority over lower color temperatures. All three ranges of color temperature include short wavelengths and – if we look across studies – can effectively elicit circadian phase shifting, melatonin suppression and the antidepressant response. Theoretically – but not necessarily – 17,000 K might be more potent at lower levels of irradiance given melanopsin’s spectral sensitivity. However, there are no comparative dose–response studies. Nevertheless, the commercial initiative is already intense (17,000 K ActiViva Active®, Philips Electronics N.V.), with “blue-enriched” bulbs more than twice the price of conventional fluorescents.

Two years ago, Marijke Gordijn and colleagues reported a controlled trial of 5000 and 17,000 K lamps at 10,000 lux for the treatment of winter depression [11]. They found no difference. To its credit, Philips summarizes the study on its website, including the authors’ conclusion that the blue component of the 5000 K light might have been sufficient to saturate the melanopsin response.

In this issue of *Sleep Medicine*, Mark Smith and colleagues [12] take the comparisons an important step further with an examination of the circadian rhythm phase shifting potency of light exposure using 4100 K at 6000 lux and 17,000 K at 4000 lux, approximately matched for irradiance ($\sim 1700 \mu\text{W}/\text{cm}^2$). Their goal was to test the lamps as they might be used for the treatment of delayed sleep phase disorder or jet-lag adjustment in the real world where these lamps are marketed. In an elegant procedural refinement, early morning bright light exposures were scheduled according to each subject’s baseline melatonin onset phase. Thus, the noisy data typical of studies that present light at a standardized clock time (*vs.* circadian time) were eliminated. With wake-up and light exposure moved one hour earlier daily for four days, the hypothesis that 17,000 K light would produce larger phase advances was not confirmed.

One reviewer actually called this study “scientifically meaningless” because it failed to identify the low irradiance threshold for phase shifting with the two lamps. The higher color temperature might win out at threshold. Yet consider the effort and expense of dose–response comparisons of phase shifting, melatonin suppression and antidepressant efficacy. Probably not worth it. Fluorescent light is complicated by idiosyncratic spectral emission profiles based on particular phosphor combinations, superimposed by a discontinuous set of mercury spikes (roughly illustrated

in Figure 2 [12]). This is not ideal for parametric investigation. Furthermore, these lamps will soon be replaced by technology that increases energy efficiency and reduces the toxic waste hazard of fluorescent tubes.

I consider this study a major accomplishment and contribution to clinical practice. Patients do not use light therapy at the lowest threshold of effect. Rather, they seek maximum response at comfortable high doses that require minimal exposure duration. By assiduous methodology that approximates the application of light therapy, the study allows us to put exaggerated, commercially inspired claims in perspective, and question whether blue light “enrichment” represents a major conceptual, technological or clinical advance.

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