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YEARLY REVIEW

BRIGHT LIGHT THERAPY FOR WINTER DEPRESSION: POTENTIAL OCULAR EFFECTS AND THEORETICAL IMPLICATIONS

Winter Depression and Light Therapy

Seasonal affective disorder (SAD*; Rosenthal *et al.*, 1984) is a syndrome of annually recurrent depression in late fall and winter. In addition to typical depressive symptoms of dysphoric mood, fatigue, and anxiety, it is marked by atypical symptoms of hypersomnia and increased appetite (especially for carbohydrates) with weight gain. Remissions occur spontaneously in spring and summer, with some patients becoming hypomanic. Population surveys indicate increased prevalence with distance from the equator, and widespread subsyndromal occurrence of the symptoms (M. Terman *et al.*, 1989a; Rosen *et al.*, 1990).

Given the temporal correlation of the depression with months between the autumnal and vernal equinoxes, reduced environmental light exposure is thought to be the main precipitating factor (Kern *et al.*, 1982). Indeed, SAD has been successfully treated with bright artificial light, with complete remissions often occurring within a few days. As the treatment was originally developed, full-spectrum fluorescent light (Vita-Lite, Duro-Test Corp.) was presented from a light box providing diffuse, direct illumination of about 2500 lux at the patient's eye level, with daily sessions lasting 2–6 h. Patients were instructed to face the light at a distance of about one meter, and, in most studies, to look into it intermittently. Scheduling of the treatment has been a primary variable of investigation, with comparisons of light given in early morning, at midday, in the evening, and twice daily in morning and evening (for cross-center review; Terman *et al.*, 1989c). In a controlled trial comparing light to the eyes or skin, it was clear that the clinical response primarily involved visual transduction (Wehr *et al.*, 1986). Ophthalmological examinations of patients treated with 2500 lux have not revealed any induced abnormalities within the acute treatment phase (Rosenthal *et al.*, 1984; Wirz-Justice *et al.*, 1986). Longer-term effects still require monitoring.

A recent treatment approach has increased light intensity—as a dosing manipulation—to approximately 10 000 lux, while reducing the average exposure duration to 30 minutes (J. S. Terman *et al.*, 1990). Because illumination level exceeds that provided by earlier devices, the ocular safety of light therapy can be conservatively assessed by examination of patients using this apparatus. As with 2500 lux systems, the lighting fixture is a metal box containing fluorescent lamps, with a reflector and plastic diffusing screen (Fig. 1). However, in contrast to the vertical position of 2500 lux units, the 10 000 lux system is positioned with a downward tilt toward the face on a 55° angle from the horizontal. The angular arrangement maximizes the exposure level while reducing the direct exposure to the eyes and glare, in comparison to vertical, straight-on illumination. Subjects receiving 10 000 lux light therapy are instructed to face the apparatus but not to look into it, concentrating instead on the illuminated work surface. Two different light sources have been employed in 10 000 lux studies (J. S. Terman *et al.*, 1990). One has been a broad-spectrum fluorescent lamp, especially designed for minimal UV radiation (Color-Gard, Duro-Test Corp.). Within the visible range, this lamp closely matches the spectrum of the Vita-Lite (Duro-Test Corp.), which has been used widely in previous research, but which does emit a "balanced" UV.

Figure 1. 10 000 lux cool-white fluorescent lighting apparatus for treatment of winter depression. (*Photo courtesy of Medic-Light, Inc., Lake Hopatcong, NJ.*)

*Abbreviations: EOG, electrooculogram; ERG, electroretinogram; PMMA, polymethylmethacrylate; SAD, seasonal affective disorder.

Secondly, standard cool-white fluorescent lamps with minimal UV have been used. Antidepressant response to 10 000 lux light treatment has been high, with 79% of subjects showing clinical remission within about one week of treatment (J. S. Terman *et al.*, 1990), a rate that equals or exceeds most prior 2500 lux/2 h studies (Terman *et al.*, 1989c).

Use of the higher intensity system, coupled with shorter exposure duration, is more compatible with patients' work-day schedules than 2500 systems. Although surface illuminance of 10 000 lux and higher is common in the outdoor natural environment, direct comparison with artificial light therapy is problematic because outdoor light incident on the eye is significantly modified by immediate surroundings. For example, reflective surfaces such as sea or snow can increase the overall light levels by 100%, whereas grass, bushes or trees may dampen effects by as much as 95%. Freely moving persons generally avoid looking into bright light, or shield their eyes or squint—protective measures that cannot be maintained over prolonged periods in the hours range, although some protection from overhead illumination is afforded by the orbital bones (Sliney, 1983).

Another experimental treatment approach mounts the lamps in a holder attached to the head, allowing relatively free movement during treatment sessions. A prototype system has used two miniature fluorescent lamps ("daylight" type; other lamps are also currently being evaluated) without a diffusing screen, yielding 4000 lux illuminance at the level of the eyes, used in 2 h treatment sessions (Brainard *et al.*, 1989). Preliminary treatment results are similar to those using a conventional full-spectrum light box. The ambulatory feature may be attractive to patients who must move about during treatment sessions. The stationary relationship between the lamps and the head serve, however, to reduce the variability of retinal illuminance (and image) given normal head movement with respect to a localized light source, thus raising a separate set of questions for future ophthalmological evaluation.

Potential for Damaging Illumination

Light therapy by no means presents an extreme of artificial light in its potential for damage to the eyes. However, given stationary exposure conditions, protection against light overexposure is lower than under natural conditions. Therefore, in order to achieve optimum antidepressant treatment as well as safety, we will consider several factors that could lead to light hazard to the eye if not carefully controlled.

Light-induced changes in ocular structures have been documented in both humans and animals. Investigations of light hazard have focused on basic mechanisms (e.g. Kremers and van Norren, 1988) as well as clinical significance for the human eye (e.g. Miller, 1987). Above and beyond direct observation of alterations of ocular structures, circumstantial evidence suggests exacerbation by light of retinal degeneration in certain patient groups (e.g. Mainster, 1987).

Certain wavelengths in the electromagnetic spectrum are absorbed within ocular tissues. The propensity is determined by tissue absorption characteristics. As summarized in Fig. 2, radiation lesions by UVB and UVA are mainly found in cornea and lens, whereas changes induced by visible light occur in the retina (Waxler and Hitchins, 1986; Andley, 1987; Roberts, 1988). In aphakic patients, UV can reach the retina and induce changes similar to visible light (Zuclic, 1984; Zrenner and Lund, 1984; Werner *et al.*, 1989). Infant and adolescent eyes transmit certain wavelengths of UV (~300 nm), a transmission window which is closed after puberty (F. Barker, personal communication). In the context of light therapy for adults, potential lesions of the retina induced by light in the visual range is of primary concern.

Whereas photochemical reactions are defined processes and occur after absorption in the UV as well as visible spectral range (Roberts, 1988), light injury to the retina involves a complex mixture of direct and indirect tissue responses. Besides generating a sensory signal, light not only modulates photoreceptor metabolism and function and circadian rhythms (Remé *et al.*, 1990a), but it can also damage or even destroy visual cells and pigment epithelium in humans and animals (for review: Lanum, 1978; Rapp and Williams, 1980; Sperling *et al.*, 1980; Lawwill, 1982; Marshall, 1983; Ham *et al.*, 1984; Lücke and Remé, 1984; Guerry *et al.*, 1985; Handelman and Dratz, 1986; Miller, 1987; Mainster, 1987; Kremers and van Norren, 1988). According to clini-

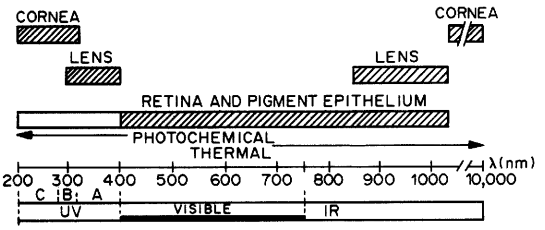

Figure 2. Spectral distribution of photochemical and thermal damage to ocular tissues. UV-induced lesions are primarily located in the cornea and lens. The open bar for retinal lesions indicates possible occurrence after lens removal, in children, and in pseudophakic eyes without UV filter in the lens implant. Photochemical lesions to the retinal pigment epithelium and photoreceptors are found in the short wavelength visible range; photochemical and thermal retinal damage may overlap in the visible range around 600 nm. With increasing wavelength, thermal damage to retinal pigment epithelium predominates. Lens damage may occur in the near and far infrared region, while corneal injury is manifested in the far infrared. It should be noted that this schematic diagram represents a simplification, and does not account for species differences and variations in exposure conditions.

cal, physiological and morphological criteria, at least two major classes of lesions are observed, both mediated by known or deduced pigments. Class I damage occurs at relatively low light intensity and exposure duration in the hours-to-days range with an action spectrum corresponding to that of the rod and cone photoreceptors. Class II damage is seen after short exposure periods with high energy radiation (Mainster, 1987; Kremers and van Norren, 1988). Both types of damage probably also occur in humans, depending on the light source, exposure conditions, and damage-enhancing factors.

Exposure of the unprotected human eye to diffuse sunlight with strong reflection by snow or water for several weeks causes a lasting reduction of visual acuity and contrast sensitivity as well as delayed and diminished dark adaptation (Clark *et al.*, 1946; Hecht *et al.*, 1948). Solar retinopathy appears funduscopically as a central edema, and in severe cases as a foveal hole with enduring central pigmental changes (Gladstone and Tasman, 1978). The question whether UV as well as visible light exacerbates or even causes retinal degeneration—especially age-related maculopathy—is controversial. However, circumstantial evidence points to visible light as a pathogenic factor among a variety of other causes (Weiter *et al.*, 1985; Mainster, 1987; Young, 1988; West *et al.*, 1989).

Application of artificial bright light can pose a hazard to the human eye. Among ophthalmological instruments, for example, the operating microscope and indirect ophthalmoscope can damage the retina, and protective measures have been proposed to reduce this possibility (Young *et al.*, 1981; Colvard, 1984; Irvine *et al.*, 1984; Jampol *et al.*, 1985; Linquist *et al.*, 1986; Khwarg *et al.*, 1987; Hoppeler *et al.*, 1988). Some specialized work-place applications of artificial light (*cf* Hughes *et al.*, 1987) also require intensities (> 10 000 lux) or spectral composition (short wavelength) that may be risky with overexposure.

Retinal damage can be exacerbated by various factors. In the context of light therapy, photosensitizing drugs are important (Table 1). These compounds have specific chemical characteristics (i.e. tricyclic, heterocyclic, or porphyrin ring systems) which enable them to absorb UV and visible light. They can act as photosensitizers if they accumulate in tissues exposed to ambient radiation, such as the skin or the eye (Dayhaw-Baker *et al.*, 1986; Lerman, 1986; Roberts, 1988). Their specific chemical characteristics enable these substances to absorb UV or visible light. The absorbed energy is transformed within fractions of a second *via* short-lived chemical intermediates. Ultimately, tissue responses result that can be classified as phototoxic or photoallergenic (Oppenländer, 1988). Modulating factors are the oxygen level and molecular composition of the tissue, as well as the availability of protective compounds or the presence of reaction-enhancing factors. A prerequisite for determining whether a drug will act as a photosensitizer in the retina is the knowledge of the drug's absorption spectrum (above 300 nm for aphakics, 400 nm for normals) and passage through the blood-retinal interface.

A well-known photosensitizer is 8-methoxypsoralen, used for treatment of psoriasis and vitiligo in conjunction with UVA exposure. Psoralens pass the blood–ocular interfaces and accumulate in both lens and retina (Lerman, 1986). Neuroleptic drugs (phenothiazines) exert photosensitizing effects in the human and animal eye (Lüllmann-Rauch, 1979; Roberts, 1984, 1988). Certain antidepressant drugs (cationic, amphiphilic with tricyclic heterocyclic ring systems)—for example, imipramine and its derivatives—induce pigment epithelial, photoreceptor, and neuro-retinal alterations in rats in a manner comparable to chloroquine (Lüllmann *et al.*, 1978). Propranolol and similar drugs perturb the metabolism of photoreceptor phospholipid membranes in rats (van Rooijen and Bazan, 1986). Knowledge of whether these widely-applied drugs act as photosensitizers in the UV or visible ranges in humans is of definite clinical relevance in the context of light therapy.

Endogenous porphyrins and porphyrin derivatives, increasingly applied for radiation treatment of various tumors, may induce phototoxic side effects to the retina (Sealey *et al.*, 1987). The diuretic and antihypertensive hydrochlorothiazide enhances operating-microscope-induced retinal lesions (Khwarg *et al.*, 1987). In rats, chronic lithium treatment significantly enhances the vulnerability of the retina to light injury; lithium selectively accumulates in the retina and perturbs the metabolism of photoreceptor membranes (Remé *et al.*, 1988; Pfeilschifter *et al.*, 1988; Remé *et al.*, 1990c). In the human eye, both psychophysical and electrophysiological changes occur after chronic lithium treatment (Kaschka *et al.*, 1987). In rats, the hormone prolactin as well as the neuro-modulator melatonin enhance light damage to the retina (O'Steen, 1979; Leino *et al.*, 1984; Bubenik and Purtill, 1980).

In hyperprolactinemic women subtle changes of cone dark adaptation have been noted (Fulton, 1989). It remains to be determined whether these hormones increase light hazard to the human eye. Compounds with distinct photosensitizing effects on the skin include tetracyclines, sulfonamides, antimalarial agents, non-steroidal anti-inflammatory drugs, chlorpromazine, retinoids, and others. These drugs may exert similar effects on the eye (Dayhaw-Baker, 1986; Fraunfelder, 1989), and thus light-treated patients using them should be closely monitored.

Animal research indicates that the application of bright light at early dawn or late evening may increase the risk of light damage in comparison to midday illumination: in the rat retina, the susceptibility to damage shows a distinct diurnal variation with peak sensitivity at night and in the early morning (Duncan and O'Steen, 1985; White and Fisher,

Table 1. Effects of photosensitizing drugs on the eye

Compound			Site of damage		Spectrum		References
Chemistry	Generic name	Class	Lens	Retina	UV	Visible	
Tricyclic, heterocyclic ring	Phenothiazine	Neuroleptic	+ H	+ H,A	+ H	+ H,A	Lüllmann-Rauch, 1979 Lerman, 1986 Roberts, 1988
	Imipramine	Antidepressant	o H,A	o H,A	o H,A	o H,A	Lüllmann *et al.*, 1978 Kari *et al.*, 1988
Porphyrin ring	Porphyrin	Tumor therapy	+ H,A	+ H	+ A	+ H	Roberts, 1984, 1988 Lerman, 1986
Furocumarin, heterocyclic	8-Methoxypsoralen	Photodermatology	+ H	+ H	+ H	+ H	Lerman, 1986 Souêtre *et al.*, 1988, 1989
Indoleamine	Melatonin			+ A		+ A	Bubenik and Purtill, 1980 Leino *et al.*, 1984
Tryptophan	Tryptophan		+ H,A		+ H,A		Dillon, 1985 Andley, 1987
Quinoline, heterocyclic	Chloroquine	Antimalarial Antirheumatic		+ H,A		+ H,A	Lerman, 1986
Thiazide heterocyclic	Hydrochlorothiazide	Diuretic		+ H		+ H	Khwarg *et al.*, 1987
Monovalent cation	Lithium	Antimanic Antidepressant		+ A		+ A	Remé *et al.*, 1988, 1990a Pfeilschifter *et al.*, 1988
+, known; o, inferred; H, human; A, animal.							General: Dayhaw-Baker *et al.*, 1986 Fraunfelder, 1989.

1987), approximately paralleling the peak period of visual sensitivity in the rat (Terman and Terman, 1985) and in humans (Bassi and Powers, 1986). In circadian phase-delayed SAD patients melatonin—a known photosensitizer—may reach its nocturnal peak in the early-morning hours at which light therapy is scheduled. Photoreceptor transducin levels follow a similar nocturnal pattern in the rat (Brann and Cohen, 1987). The intermission of darkness between damaging light exposures causes an exacerbation of lesions in the rat retina (Organisciak *et al.*, 1989). Investigation of such factors in context of bright light exposure to humans has high priority.

In rats, previous light history is an important determinant of the susceptibility to light damage. An animal raised under low illuminance levels is significantly more susceptible than one raised in a bright environment and shows a general elongation of rod outer segments and increased rhodopsin content ("photostasis"; Penn and Williams, 1986; Williams *et al.*, 1988). It is not yet known whether the human retina shows a similar response. The previous light history of SAD patients may prove to be a determinant of susceptibility to light damage as well as to the beneficial therapeutic effects of light. If, for example, patients' retinal response to dim winter lighting conditions were an exaggerated elongation of the rod photoreceptors, with accumulation of higher rhodopsin levels than in summer, susceptibility to damage by bright-light exposure could be heightened. On the other hand, rod-shortening due to deficient photostatic adjustment has been hypothesized in SAD (Remé *et al.*, 1990b).

Estimating Phototoxicity to the Retina

Whereas in the adult eye UV radiation is absorbed in the lens and cornea (Marshall, 1983), one must assess the effects of visible radiation when judging risk to the retina from therapeutic light exposure. In gauging potential thermal and photochemical insult, one must consider the actual amount of energy reaching the retina—the retinal irradiance—and the duration of the exposure. There is evidence (Mainster, 1987; Kremers and van Norren, 1988) that reciprocity factors of energy × duration lead to two classes of photochemical damage from visible light: Class I damage appears at the photoreceptor level and follows large-field exposure at relatively low irradiances, whereas Class II damage is found in both photoreceptors and the pigment epithelium, and usually follows more limited exposure of small retinal areas to much higher irradiances. Many variables alter the actual retinal irradiance, including angle of incident light, ocular transmittance, refractive index and focal length of the eye, pupillary diameter and, most significantly, the spectral distribution of the light source.

A number of investigators have devised methods for calculating irradiance taking many of these factors into account (e.g. Calkins *et al.*, 1980; Sykes *et al.*, 1981; Sliney, 1984). In applying a method to estimate energy reaching the patient's retina, one must balance accuracy of measurement with the need to generalize the finding to a clinical setting where, due to patient movement, angle of incident light will vary, as will moment-to-moment illuminance levels and, perhaps, pupil diameter (Sykes *et al.*, 1981). Methods such as those of Sliney and Calkins, which require careful radiometric measurements of the light source for a given angle of incidence, are more applicable to situations involving lasers, ophthalmoscopes, and other sources which cast a discrete image on the retina (M. Waxler, personal communication). For the purpose of assessing the risk involved in presentation of a large, more diffuse light source, we estimate retinal irradiance from a method presented by Sykes *et al.* (1981):

$$Er = Ec \times dr^2/fl^2$$

where Er is retinal irradiance (W/cm^2), dr is pupil radius (using 0.1 cm in the expectation that the pupil may dilate slightly during a light therapy session > 15 min), fl is focal length of the eye (1.7 cm), and Ec is corneal irradiance in W/cm^2.

Corneal irradiance was calculated from cosine-corrected illuminance measurements at patient eye position converted to radiometric units using conversion factors for cool-white and "full spectrum" fluorescent sources (for λ = 290–770 nm; Hughes *et al.*, 1987). Although this method does not take into consideration either the increase in irradiance contributed by ocular refraction or the minimizing factor of incomplete transmittance, in assuming a constant value of corneal irradiance based on a nominal maximum illuminance measure (which will be attenuated by changes in patient angle of gaze, head motion, eye closure, etc.) the result is, we believe, a reasonable and conservative estimate of retinal irradiance applicable to clinical situations. When the irradiance value is multiplied by the time (in seconds) of the exposure per treatment session:

$$Hr = Er \times t$$

the irradiance (E) in W/cm^2 is transformed to irradiant dose (H) in J/cm^2.

Kremers and van Norren (1989), using focused white light, found a threshold irradiant dose for Class II photoreceptor damage in primates to be 230 J/cm^2 for exposures ranging from 10 min to 12 h. Sykes *et al.* (1981), by contrast, found a threshold for cone photoreceptor damage in the primate following diffuse white light exposure for 12 h to be ~9 to 16 J/cm^2. Cone threshold appeared to be lower than rod threshold. The considerable threshold differences reported by these studies probably reflect differences in experimental procedure, including damage assessment.

The values of ~0.000009 W/cm^2 and ~0.016 J/cm^2 we have calculated for 10 000 lux cool-white

light per 30 min therapy session are well below these levels. Furthermore, they are well below the dose at which thermal damage—as is seen in laser applications—would be expected to occur (Marshall, 1983). Other common illumination methods for light therapy are 2500 lux cool-white light for 2 h (Er = 0.000002 W/cm^2, Hr = 0.016 J/cm^2 per session) and 2500 lux "full-spectrum" light (Er = 0.000003 W/cm^2, Hr = 0.022 J/cm^2 per session). Given the relatively short exposure durations of the 30-min to 2-h therapy sessions, and the 22-h recovery period that intervenes, Class I damage (Sykes, 1981; Kremers and van Norren, 1988) would not be expected.

By comparison, the retinal irradiance provided by the indirect ophthalmoscope can range from 0.069 to 0.125 W/cm^2 (Calkins *et al.*, 1980) well within the range of thermal and Class II damage induction. Calculations by Young *et al.* (1981) showed that the retinal irradiance delivered by the indirect ophthalmoscope is about 300 times that required for full visual acuity (of the observer) and, thus, could be lowered significantly, perhaps by a factor of 2 or 3.

It appears that there is little risk to an eye free of photosensitizing agents (Table 1) of either thermal injury or photochemical injury of either Class I or II from the light sources used to this point for therapy of winter depression. Studies of albino rats—although a highly vulnerable preparation—suggest, however, that the determinants of damage threshold and susceptibility have yet to be clarified: Class I type alterations of photoreceptors with concomitant biochemical changes have been noted in albino rats after exposures ranging from 100 to 1000 lux for 30 min (Pfeilschifter *et al.*, 1988; Reme *et al.*, 1988). Threshold lesions were reversible within the following 24 h, but greater alterations persisted for up to 6 days (longer durations were not studied). In albino as well as pigmented rabbits, Class II type lesions occurred after light exposures ranging from 5 to 35 min of 25 and 46 mW/cm^2 irradiance, respectively. Long-term observations revealed irreversible lesions after 2 months (Hoppeler *et al.*, 1988). Although the pigmented primate and human retina may be less vulnerable to this type of photochemical lesion, it is possible that pathological changes would be expressed after several years of exposure to such conditions. In pseudophakic humans, for example, cone damage was observed after several years of ambient near-UV exposure (Werner *et al.*, 1989) and in normal subjects after repeated use of lasers (Berninger *et al.*, 1989). Conceivably, visible blue light might have contributed to the observed lesions. Another cautionary principle may be derived from data on rats showing the extent of retinal damage to depend upon level of dark adaptation prior to illumination (Noell, 1980). For example, a dark adaptation period of 36 h is sufficient to induce vulnerability of the rat retina to 30 min of 100 lux illumination (Pfeilschifter *et al.*, 1988). It may therefore be beneficial for light therapy patients to pre-adapt to low photopic levels of illumination in the morning, following dark adaptation during sleep, prior to exposure to therapeutic levels of light. Such early adaptation to the dynamic dawn twilight signal may itself be therapeutic (Terman *et al.*, 1989b; Terman and Schlager, 1990). It is not known whether damaging effects, if any, would be potentiated by administering additional doses of bright light during the diurnal recovery cycle. Multiple light therapy sessions per day (e.g. morning plus evening light; *cf.* Terman *et al.*, 1989c) might pose an increased challenge.

Comment on the ultraviolet component in light therapy. The strong antidepressant response to 10 000-lux cool-white fluorescent light exposure suggests that the active treatment involves light within the visible spectrum. Nonetheless, some preliminary investigations (Docherty *et al.*, 1988; Lam *et al.*, 1989) have suggested heightened clinical effects when the UV-component of full-spectrum fluorescent light has been made available; others have not (e.g. Lebegue and Brown, 1989). In phakic patients little UV will reach the retina (but see Fig. 1), though in aphakics UV damage to the retina has been demonstrated in both humans (Zrenner and Lund,1984) and primates (Zuclic, 1984). Additionally, pseudophakics may be vulnerable to UV-induced blue-cone damage (Werner *et al.*, 1989). The further risk of cumulative skin exposure to UV—beyond the scope of this review—warrants additional caution. Some SAD patients have indeed shown erythemic responses under full-spectrum fluorescent light, not present under cool-white light (M. Terman, unpublished observation). Given that complete remission of SAD symptoms is possible without UV exposure, it should be eliminated from routine light therapy procedures as a precautionary measure.

Light Sensitivity and Pathogenesis of Winter Depression

Predisposing factors for winter depression have not yet been established (*cf.* Terman, 1988). State changes or trait abnormalities in retinal light transduction may be involved. It should be noted that light sensitivity assessed by the threshold for pineal melatonin suppression—a central rather than peripheral marker—appears to be normal in SAD patients (Murphy *et al.*, 1989; A. J. Lewy, personal communication), although one study has shown strong suppression to illuminance as low as 500 lux (Gaddy *et al.*, 1989). Most tests of nocturnal melatonin suppression in humans have utilized bright photopic stimulation, whereas physiological response of the circadian system may be triggered at scotopic and mesopic twilight levels (Terman and Schlager, 1990). Thus, winter depressives may prove to be abnormally sensitive—or insensitive—to low-level, threshold stimulation. Indeed, one pilot study

(Oren *et al.*, 1989) has suggested supersensitivity of light detection in the first 10 min of dark adaptation, during the period of cone function recovery. This result must be considered tentative pending tests of larger groups, firmer definition of the magnitude of effect, and analysis of the threshold shift, if any, following bright light therapy.

Two contrasting hypotheses merit investigation in the context of retinal involvement in pathogenesis of the disorder. Beersma (1990) posits that the critical function of the circadian pacemaker—a hypothalamic mechanism with monosynaptic connection to retinal input—is to transduce daylength by discriminating night from day in a binary manner. Such detection occurs at twilight rather than supra-sunrise levels. If the SAD patient is supersensitive in winter, the transition from "day" to "night" would occur after the dusk twilight transition because low ambient room light intensities in the late evening would serve artificially to extend daylength. As a result, circadian phase delays are often observed in depressed SAD patients (Lewy *et al.*, 1987; Terman *et al.*, 1988). The pacemaker mistakenly interprets the objectively short winter day as summer-like, with pathogenic consequences that are normalized by light therapy.

In contrast, Remé *et al.* (1990b) posit retinal subsensitivity as the triggering factor for SAD, based on animal data that show degraded photoreceptor function in winter or low-light conditions. Two potential mechanisms involve (a) deficient photostatic adjustment (Penn and Williams, 1986) to reduced winter light, and (b) reduced availability of photoreceptive material and dampening of metabolic activity, as has been observed in autumn in squirrels, preceding and during hibernation (Remé and Young, 1977). As noted earlier, photostatic adjustment to dim ambient light normally promotes increased rod length, conserving the daily total photon catch; if deficient in SAD, the result would be reduced light input to the central nervous system. The "hibernation response", which could occur concurrently with or independently from photostatic dysregulation, also serves to reduce light input. Circadian phase delays could result from weakened entrainment by the light-dark cycle in subsensitive patients with long underlying pacemaker period. A. J. Lewy (personal communication) has hypothesized such period lengthening in SAD. Both photostatic and hibernation mechanisms, however, are thought to react to bright artificial light with rapidly stimulated synthetic activity that exceeds degradation (e.g. Korenbrot and Fernald, 1989). Consequently, photoreceptor outer segments would elongate and increase their visual pigment content, with normalization of light sensitivity and remission of depressive symptoms. The postulated metabolic changes are not vision-related, and they require exposure times of far longer duration (in the minutes-to-hours range) than that necessary to elicit visual detection, as does light therapy.

Pre- and Posttreatment Assessment of Winter Depressives

Experiments assessing the ocular safety of long-term use of bright light therapy are currently in progress at several centers (N.E. Rosenthal, pers. comm.; A. Wirz-Justice, pers. comm.), and final results are still pending. Our group is following SAD patients treated with 10 000 lux fluorescent light, seeking to detect changes in visual function or retinal state that might be induced by antidepressant light exposure (P.F. Gallin and colleagues, in progress). Because SAD patients represent a new clinical group in the practice of ophthalmology as well as psychiatry, we identified possible risk factors and developed screening procedures whereby patients with pre-existing ocular damage or predisposition towards it would be excluded from treatment or given ophthalmological monitoring. As a precaution, we have denied treatment to patients with any acute or chronic severe eye diseases, including corneal-, uveal tract-affections, cataract, glaucoma, or retinal pathology. The test battery, administered at the pretreatment baseline and after 2–6 weeks of treatment, includes corrected and uncorrected far and near visual acuity, color vision screening test using the American Optical or Ishihara plates, functional macular examination with the Amsler grid, the macular stress test, and static visual field evaluation with the Humphrey Automatic Perimeter (full-field 81 point screening test). Slit lamp examinations have been performed to evaluate the anterior segment and Goldmann Applanation tonometry to test the intraocular pressure. After pupil dilation, a fundus photograph of the central 30° has been taken.

Pretreatment examinations have been unremarkable, except perhaps for a relatively high incidence of best-corrected mild and moderate myopia (mild, 1–5 diopters; moderate, 6–10 diopters) observed in 41% of the 34 patients thus far studied. Past medication with potentially photosensitizing antidepressant drugs has been noted for 29% of patients, with several of them taking more than one compound (tricyclics, phenothiazines, or lithium). As might be expected, we are finding an increase in past use of potential photosensitizers among older patients. Thus far, however, no subject has shown any acute alteration that could be attributed to light therapy.

Prolonged application of bright light within one treatment period or recurrent light therapy over many years has not yet received systematic ophthalmological evaluation. Although the light levels used in our study are within the lower range of outdoor daytime illuminance—and thus would seem to involve no more than naturally-occurring risk—it remains to be determined whether long-term accumulation of subthreshold photochemical lesions occurs more frequently in light therapy patients than in controls. Ophthalmological examinations in coor-

dination with light therapy would enable screening for early diagnosis of tumors or other eye diseases without distinct symptomatology, such as chronic open-angle glaucoma, whether or not they are connected with the treatment.

Ophthalmological Monitoring of Light Therapy

Although the risk factors of light exposure in humans are still not completely understood, and evidence to date indicates no retinal sequelae in standard ophthalmological tests, it is important to specify potential damage-enhancing factors in each patient and, conservatively, to withhold treatment given specific pre-existing ocular disorders or other medical conditions in which bright light exposure would be contraindicated. In some cases, the potential risk needs to be gauged against the benefits of antidepressant treatment, especially when medications cannot be tolerated or have proved ineffective. In such cases light therapy should be administered only with the patient's informed consent.

We outline three stages of ophthalmological evaluation below, which probe a range of visual functions that require documentation for (a) intake screening, (b) follow-up testing, and (c) research on subtle effects and underlying neurophysiological response to light exposure. We propose that all prospective patients receive a minimal screening battery (Table 2, Part 1), whether treated openly or in controlled research trials.

Presumed risk conditions for light therapy

The retinal/ocular pathologies listed in Table 2, Part 2, summarize those conditions that might be exacerbated by light treatment. However, because risk factors in light therapy are not completely understood, this tentative list may be substantially modified in the future. A patient suffering from acute retinal detachment obviously will first be treated for this condition before entering a light therapy program. Detachment and reattachment pose a trauma at least to the outer retina (Guérin *et al.*, 1989) and thus light treatment of a patient with past history of detachment might stress the photoreceptor–pigment epithelial interaction. A retina bearing various vascular or inflammatory diseases might react more sensitively to normally non-traumatic light exposure. Light has been shown to acutely and chronically influence several biochemical processes involved in photoreceptor metabolism

Table 2. Basic ocular screening examination for light therapy

Part 1: Core Test Battery

- Best-corrected visual acuity
- Amsler grid
- Ocular motility (9 cardinal directions of gaze)
- Stereopsis
- Pupillary reactions (direct and indirect)
- Slit lamp examination (note chamber angle width)
- Intraocular pressure (note time of day)
- Ocular fundus (preferably indirect with mydriasis)

Part 2: Specific Diagnoses

RETINA
- Retinal detachment
- Diabetic retinopathy
- Retinal vasculitis/ Chorioretinal inflammation
- Vascular retinopathies
- Central serous retinopathy
- Degenerative disease of the macula
- Tapeto-retinal degenerations
- Solar/radiation retinopathy
- Drug-induced retinopathy
- Post-traumatic retinopathy

OTHER
- Inflammatory diseases of anterior segment/uveal tract
- Glaucoma
- Cataracts
- Optic nerve affections

Part 3: Relevant Symptoms and Medications

EYE COMPLAINTS
- Photophobia
- Glare
- Dry eyes
- Blurred vision
- Metamorphopsia
- Color vision
- Night vision
- Other

CURRENT MEDICATIONS
- Antidepressants (tricyclic)
- Neuroleptics (phenothiazine)
- Lithium
- Psoralens
- Antimalarial/antirheumatics
- Diuretics (hydrochlorothiazide)
- Porphyrins
- Tetracycline
- Sulfonamides
- Other photosensitizers

(e.g. Schmidt, 1983; Pfeilschifter *et al.*, 1988; Penn *et al.*, 1989). The role of light in promoting central (maculopathies) or peripheral (retinitis pigmentosa) degenerations is controversial (Weiter *et al.*, 1985; Young, 1988; West *et al.*, 1989). Considering the distinct effects of light on photoreceptor renewal (Remé *et al.*, 1990a), precaution in severe cases may be warranted (e.g. Dorey *et al.*, 1989). The causes of central serous retinopathy are not clearly understood, but, theoretically, additional light exposure might enhance the subretinal serous exudate, because a similar alteration is also observed in radiation lesions, including solar retinopathy. Drug-induced retinopathy may be exacerbated by light, particularly when photosensitive drugs are involved. In cases of uveitis, patients might not tolerate light therapy, due to photophobia. Whether glaucomas, cataracts, or optic nerve diseases pose contraindications for light therapy remains unclear at this point, and thus opthalmological evaluation is required during light treatment.

Light-treated patients may complain of increased sensation of glare if there is an of alteration of tear film composition, reduced corneal integrity, edema, or various types of lens opacities and vitreous opacities. The resulting light scatter, we believe, probably does not significantly increase retinal irradiance. Aphakic patients should be carefully monitored and their eyes protected by UV- and blue-filtering glasses. The transmission characteristics of intraocular lens implants (i.e. lens material such as polymethylmethacrylate [PMMA]) need to be fully evaluated vis à vis light therapy applications. Many of these lenses are equipped now with complete UV filters, but transmit strongly in the blue region. Subjective complaints of visual difficulties as well as the light exposure history of a patient should be monitored, and current medications noted (*cf.* Table 2, Part 3).

Recommended core battery of eye examinations

A basic screening program for documenting eye status and detecting potential retinal pathology is provided in Table 2, Part 1. The outcome of this examination, together with psychiatric evaluation, will determine the eligibility of a patient for light treatment.

Researchers who wish to pursue analyses of retinal changes that might be observed during or after the acute treatment phase with light, as well as clinicians monitoring any sequelae in patients at suspected risk, should supplement the core examination with pre- and posttreatment fundus photography, and tests of retinal thresholds to visible light, contrast sensitivity (e.g. Vistech 6000), color vision (e.g. Farnsworth panel D15, or, if possible, Farnsworth 100 hue), the macular stress test (*cf.* Pavan-Langston, 1987), and Amsler grid testing. Ideally, these tests would be performed before and during the acute treatment phase (weeks), and within six-month (summer) and annual follow-ups. For the evaluation of potential visual field changes, threshold programs revealing subtle alterations are recommended. For example, the Humphrey perimeter program, "central 30/2" (corresponding to the Octopus 31/32), includes ample rod and cone testing, but requires about 15 min per eye. The Humphrey macular threshold test (corresponding to the Octopus M1), by contrast, requires about 5 to 6 min per eye and is restricted to about the central 4°, thus including fewer rods for analysis.

Exploring the possible retinal mechanisms of light therapy effects will require more detailed and extensive ophthalmological examinations, which are not feasible for routine clinical testing and are typically unavailable except in major university eye clinics. The photopic and scotopic full-field flash electroretinogram (ERG) would detect overall functional alterations of photoreceptors, the pigment epithelium, or the neural retina. In animal experiments, for example, the b-wave amplitude correlates with the amount and spectral sensitivity of chronic light damage (Williams and Howell, 1983). The pattern ERG probably arises at the level of retinal ganglion cells and detects subtle pathology within this area, which might not be of primary relevance for light therapy. The electrooculogram (EOG) specifically monitors pigment epithelial alterations that may lead to disturbed photoreceptor/pigment-epithelial interactions. Conceivably, a phagocytic overload in the pigment epithelium induced by repeated light-elicited disk shedding could lead to long-term functional disturbances. Dark adaptometry monitors the time course of the threshold of visual detection in cones and rods after a bleaching light exposure. Elevated thresholds have been observed in military personnel after exposure to strong environmental light (Clark *et al.*, 1946; Hecht *et al.*, 1948). Fundus reflectometry or densitometry analyzes bleaching and regeneration of visual pigments in small fundus areas (van Norren and van de Kraats, 1981). Light-induced disturbances have been observed in primate retina (Kremers and van Norren, 1989). Tapeto-retinal degenerations cause distinct alterations of visual pigments in humans.

If light therapy alters the functional state of the retina—acutely or chronically—such testing will reveal subtle changes. Conclusive results would require testing before and after light therapy, ideally monitored at similar times of day (i.e. morning or afternoon) to control for diurnal variations of psychophysical and electrophysiological responses and fatigue effects. Such measurements may also serve to elucidate ocular mechanisms of light therapy on a neurophysiological level.

Conclusions

Bright light therapy for winter depression (Seasonal Affective Disorder) is a rapidly spreading method used by patients with clinical diagnosis, sub-

syndromal sufferers of "winter doldrums", as well as in exploratory applications for non-seasonal circadian phase adjustment (sleep timing, jet lag, shift work). Although ophthalmological examinations of winter depressives treated with relatively high-intensity (10 000 lux) fluorescent light have thus far revealed no induced abnormalities, precaution is warranted because cumulative formation of subthreshold photochemical damage cannot be ruled out without more detailed, longer-term testing. Furthermore, several conditions are known to enhance UV- and visible-light-induced lesions that might coincide with light treatment in individual cases, such as use of photosensitizing antidepressant drugs. Such interactions, as well as ocular diseases, should be evaluated using a standard comprehensive screening examination, as outlined here, before initiation of light therapy, and patients at risk should receive follow-up examinations.

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