

Light Treatment and Biological Rhythms

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Report from the 9th Annual Meeting of the SLTBR

The first Canadian-hosted meeting of the SLTBR was held June 7-9 in Vancouver, British Columbia. Vancouver, located on a harbor which looks toward Vancouver Island and the Pacific Ocean and bordered to the north and east by snow-capped mountains, is arguably one of the most beautiful cities in North America. The fact that the meeting's organizers, Ray Lam and David Schlager, arranged for several days of 70-80 F temperatures and blue skies (with which to fully appreciate the long photoperiod) may have, of course, contributed to that impression. The banquet was held at the University of British Columbia Anthropology Museum. Before dinner we were treated to guided tours of the museum, its wooden carvings, totem poles, pottery, and other artifacts. Following libations, a gourmet dinner featured salmon and ended with a dessert plate of both a chocolate torte and a lemon tart. (The mere memory triggers Pavlovian salivation). After dinner, though well past 10 P.M., it was yet light enough to take in a panoramic view of the harbor and mountains.

The banquet speaker was Martin Zatz of the NIMH. Marty started off by promising a mix of humor and science, and, after a brief struggle with the microphone and slide projector, delivered on both. To the clinical researchers who might, in today's climate, be feeling only slightly less dated than the above-mentioned native American artifacts, he suggested repackaging their research by renaming their division the "Division of Molecular Molecular Molecular". That, he promised, would make the grant money flow. On a scientific note, Marty expounded on the advantages of studying the chick pineal over the rat pineal, one of them being the former's *in vitro* activity. He also explained that the enzyme SNAT, and hence melatonin synthesis, are influenced by light via two parallel pathways, one involving cAMP and the other involving the clock gene.

Young Investigator Award

This year's Young Investigator Award was awarded to Boris Pinchasov from the Siberian branch of the Russian Academy of Medical Sciences. His entry, entitled "Effects of midday kinesitherapy and light therapy on mood, physical performance, and oxygen consumption in women with depression", was presented in absentia via poster, discussed enthusiastically by

Norman Rosenthal, and awarded a prize of \$500, the latter provided by Apollo Light Systems. One hopes that the recognition and money will serve to sustain his and other future recipients' continuing research. In what seems to have become an SLTBR tradition (perhaps a phase marker of an annual rhythm), Norman Rosenthal provided an excellent overview of the meeting's 27 posters. Regarding the content of the posters, space does not permit them to be covered in this summary. Suffice it to say that there were a great many excellent posters, and that anyone who was unable to attend the meeting would be well-served by purchasing a copy of the abstract booklet in which they are covered in detail.

Presentations and Papers

The meeting included five invited presentations, each 45 minutes in length and ranging in topic from basic to applied and back. From Larry Morin we learned that the neuroanatomical pathways involved in regulating the circadian system are more complex than previously appreciated. He described routes by which photic information can gain access to the circadian clock. There is a direct path from retina to SCN via the retinohypothalamic tract and an indirect route from the intergeniculate leaflet via the geniculohypothalamic tract. However, there is extensive visual input into the subcortical visual system with most of the subcortical visual nuclei connecting to the intergeniculate leaflet. Thus, multiple pathways by which light, somatosensory and auditory stimuli might reach the circadian clock are present. Vinnie Cassone gave a comparative phylogenetic perspective on melatonin. In addition he reviewed emerging data showing a notably widespread distribu-

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tion of melatonin receptors in the avian brain. Such receptors appear to be found in all nuclei of the bird visual system and, therefore, are much more pervasive in the bird CNS than in the mammal. The present indications are that melatonin may modulate sensitivity to visual stimuli. Tom Wehr, in his talk "Biological Night in the SCN", reviewed evidence from animal studies for the existence of separate E (evening) and M (morning) oscillators. He also presented evidence suggesting that this two-oscillator system may be operational in humans as well. This evidence, which included bimodal melatonin profiles among several subjects recently studied at the NIMH, should give melatonin researchers pause. One implication is that, when we use melatonin secretion as a phase marker, we should consider that melatonin's offset may be just as important, if not more important, than its onset. Al Lewy presented evidence for and against the phase-shift hypothesis of winter depression. Al went on to present a fleshed-out (more data points) version of his (DLMO-based) melatonin PRC, and pointed out that the PRC for melatonin is 180° out of phase with the PRC for light. Based on such melatonin-PRC evidence, Lewy outlined his

ongoing efforts to administer afternoon/evening exogenous melatonin to treat winter depression by way of eliciting a corrective phase advance. Finally, Michael Terman presented elegant work, in both animals and humans, using his dawn/dusk light simulator. He walked us through a 3-dimensional graph illustrating that season and latitude affect not only daylength, but also the duration and "shape" (i.e., progression of instantaneous rate) of illuminance change during dawn and dusk. He showed evidence that a gradual twilight transition is more chronobiologically active than a suddenly switched on/off light. The animal work employed an apparatus in which a rat could choose to expose himself to light or to stay in a darkened "burrow". Michael showed data from 2 rats, one "long-tau" (i.e., >24 hours) and the other "short-tau" (<24 hours). The former appeared to synchronize its daily rhythm, despite intrinsic phase delay tendencies, by preferential self-exposure to phase-advancing dawn light whereas the latter, conversely, "treated" its phase-advancing tendency by self-exposure to the delaying effects of dusk.

Three oral paper sessions included 15 presentations. Anna Wirz-Justice presented data showing that 3 mornings of dawn simulation (DS) can phase-advance the dim-light melatonin onset (DLMO) by a half-hour; the first exposure to DS seemed to have the greatest effect, causing an advance in the DLMO of about 20 minutes. In light of Wehr's presentation, it might be interesting to see whether and how DS affects melatonin offset; and, to digress, one wonders whether a PRC for melatonin offset might look different from the current one which is based on its onset. Anna also presented data on behalf of her colleague Kurt Krauchi, who Anna said only attends meetings in more exotic locales, and that the United States didn't qualify as one of those. Rumor has it that the Bill Clinton quickly got on the red phone to reassure an agitated Brian Mulroney that an attempt by the U.S. to annex Canadian territory was not, in fact, underway. On a more scientific note, the Krauchi/Wirz-Justice study addressed the complex issues around the relative effects of melatonin versus light on thermoregulation and circadian phase.

Michael Terman presented a paper first-authored by his collaborator Robert Spitzer, reviewing results of a large, placebo-controlled treatment study of orally administered melatonin as treatment for jet-lag. This study of 257 subjects, mostly Norwegian physicians traveling home after a work-related trip to New York City, revealed no significant therapeutic effect of melatonin, either 5mg or 0.5mg, taken at either local (Norwegian) bedtime or in the early evening on a shifting schedule, compared to placebo. Furthermore, no effects of melatonin were observed within subgroups expected to be more likely to show such effects, namely those free of jet-lag prior to the home-bound flight and those with moderate or greater severity of jet-lag during the first or second day post-travel. Overall, the negative findings from this large, well-designed study are in conflict with several prior, though smaller, studies and must give pause to reexamine both treatment and research on melatonin for jet lag.

Dan Oren presented some further support for the possibility that light may exert antidepressant and chronobiologic effects via a countercurrent vascular mechanism of diffusion and

concentration (similar to that in the kidney's nephron) between ophthalmic venous blood and cerebral arterial blood. As first presented at last year's meeting, Oren suggests that such a system might transduce ambient retinal light reception into meaningful chronobiologic information via pathways separate from previously described neuronal tracts like the retino-hypothalamic. (Will the glove finally fit? Stay tuned.). Dan's work reminded us, should we have forgotten, that all those undergraduate and graduate courses, from biochemistry to physiology to histology to gross anatomy, were more than just a rite of passage.

Martin and Eastman reported significant circadian adaptation to simulated night-shift work using a conventional nighttime light/daytime dark regimen but finding that medium intensity nighttime light - i.e. 1230 lux - was no less effective than high intensity - i.e. 5700 lux - in producing circadian shifts in core body temperature and reducing fatigue. Marc Hebert presented his finding of decreased retinal sensitivity of subsyndromal SAD patients in the wintertime. He also reported that the degree to which one's retinal sensitivity changed with the seasons correlated with the degree of seasonal change in SAD symptoms (as measured by the GSS or SPAQ score). Women had lower retinal sensitivities than men. This prompted Al Lewy to wonder aloud how this could be reconciled with findings that women show an increased sensitivity to melatonin suppression by light.

Two PET studies of SAD were presented by the NIMH group. Jeff Matthews presented a study of the acute effects of bright light on brain blood flow, while Erick Turner (yours truly) presented a study which looked at the effects of (the serotonergic agonist) m-CPP on brain metabolism. Neither study was able to replicate the baseline decrease in global activity reported in the only prior PET study of SAD patients by Cohen, et. al. With respect to regional findings, both studies found increased (baseline) activity in the temporal lobes of SAD patients compared to controls. Alex Neumeister presented a nice review of tryptophan depletion studies, including his replication of earlier work by Ray Lam and colleagues in which the antidepressant effects of light were reversed by wintertime tryptophan depletion. In a further study done with Siegfried Kasper in Austria, Alex tryptophan-depleted SAD patients in the summertime, when they were of course euthymic, and induced a brief relapse of their depressive symptoms. (Hmmm. What would happen if you tryptophan-depleted a manic patient?) Dan Kripke warned us that, before we prescribe light therapy to treat circadian disturbances, we should not assume that a given patient necessarily has a normal, or even stable, phase position. Older people, he demonstrated, seem particularly vulnerable to phase dispersion and thus risk, during conventional therapeutic regimens, getting light exposure to portions of their phase response curve that are likely to produce unintended effects. Another notable finding was that the magnitude of sleep disturbance did not correlate well with age, gender, or volume of melatonin, but it did correlate well with the degree of phase dispersion. Kripke's slides, as always, merit special mention.

Ray Lam extended previous work by Barbara Parry by showing that evening light therapy effectively treated premenstrual syndrome symptoms, noting that the superiority of active

over placebo light therapy emerged only in the 2nd cycle, and that it would have been missed if the study had been confined to a single cycle.

Speaking of placebo, Paul Arbisi showed that a positive response to placebo light therapy was associated with an MMPI personality dimension known as Absorption. This suggests a possible screening method for excluding research volunteers whose tendency for placebo response might obscure a real difference between active and placebo conditions. This work also represents another contribution to the growing body of work on placebo effects in light treatment for SAD (see letters to the editor this issue and LTBR, 1997; 9:19-21). It might be interesting to see whether the degree of absorption predicts tendency to respond to placebo in pharmacological studies, also, in which the active and placebo conditions (pills in this case) would be indistinguishable, at least in terms of their appearance.

Namni Goel, who works with the Terman's, presented a new instrument designed to address the understudied "upside" of mood, energy, etc. which certain (perhaps many) SAD patients seem to experience in the spring and summer. The HIGH-R (the "R" stands for retrospective) might be thought of as a hybrid between the SPAQ, which measures primarily depressive symptoms but does so retrospectively, and the HIGH-SAD, which measures hypomanic symptoms in detail but only for the time period immediately preceding the interview.

The oral paper sessions concluded with two studies of the epidemiology of SAD, one done by Anthony Levitt in Ontario and the other by Erin Michalak in Wales. Levitt, in contrast to the 1989 Rosen study, did not find an association between latitude and prevalence of SAD. On the contrary, he found that the severity of SAD, as measured by the GSS, actually decreased, though not significantly, with increasing latitude. This study was most impressive in terms of its magnitude and N. However, it, like many other epidemiological studies of SAD, was not designed to measure light actually received by subjects. Ideally, one should want to correlate each individual's GSS with his/her degree of light exposure/deprivation. This would mean taking into account percent possible sunshine (David Avery's point), presence/absence of snow cover, and how much time patients spend out of doors. (Anna Wirz-Justice pointed out that this was the main discriminator in her Swiss SPAQ study).

Rewarding Experience

As we departed for home, many of us by way of the impressive new Vancouver International Airport, whose glass walls allowed a parting view of the mountain peaks, one could only leave with the sense of having been through an intellectually and esthetically rewarding experience.

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MELATONIN: NATURE'S SOPORIFIC?

The recent explosion of articles on the use of melatonin have led to heated discussions as to its actions on sleep and sleepiness in humans (e.g., at the 1995 APSS/WFSRS meetings). Indeed, the discussants appear to use the same terminology to describe different effects, or different terminology to describe similar effects. The confusion is evident (see Hughes et al., 1995). Careful attention to definitions may help to clarify what acute melatonin administration actually does to subjective and objective sleep and vigilance, and careful attention to timing is particularly necessary so as not to confound circadian with homeostatic mechanisms. Any natural sleep-inducing and hypothermic function of endogenous melatonin must be limited to diurnally active mammals. In nocturnally active mammals, melatonin cannot have these direct actions.

The populist suggestion that melatonin may be administered as a sleeping pill available to all and sundry is far too simplistic. The inference is that we are dealing with problems such as psychophysiological and idiopathic insomnia (Thorpy, 1990). However, many insomnias are associated with neurological, psychiatric, and medical conditions, with mood, anxiety and panic disorders being foremost (Thorpy, 1990). Prevalence of psychophysiological insomnia has been estimated at 15%, while insomnia associated with psychiatric disorders is 35% (Buysse and Reynolds, 1990). At present, Circadian Rhythm Sleep Disorders (Thorpy, 1990) are the appropriate major focus for discussion of melatonin's use.

Definitions

What are the official definitions? A hypnotic is defined as a drug which produces drowsiness and facilitates the onset and maintenance of a state of sleep that resembles natural sleep in its EEG characteristics, and from which the recipient can be aroused easily (Goodman and Gilman, 1996). General use of the term hypnotic refers to a heterogeneous group of drugs that improve subjective and polysomnographic sleep measures, and are usually prescribed for the management of insomnia. The consequences of a hypnotic on decreasing subsequent wakefulness must also be considered. A typical benzodiazepine hypnotic shortens sleep latency and slightly lengthens total sleep time, diminishes the number of awakenings and the duration of waking after sleep onset (all of which contributes to its subjective effect), but may reduce REM sleep and slow wave sleep (and power in the EEG spectra in the delta and theta range). It can decrease alpha activity in the waking EEG. Thus, the classical hypnotics themselves do not conform to the definition of inducing 'natural' sleep and a refreshed day following it.

The duration of activity of a hypnotic depends on its absorption, distribution, and elimination (Nicholson, 1994). A very rough estimate of duration of action according to half-life has been made to categorize hypnotics for treatment indications: ultra-rapid (c. 2 h) to ameliorate sleep onset insomnia, short-

acting (c. 5 h) to promote sleep maintenance and control terminal insomnia, and long-acting (>10 h) with daytime anxiolytic effects (Nicholson, 1994). Were melatonin with its half-life of c. 0.5 h found to be hypnotic, it might even be designated as "super-rapid".

A drug which decreases activity, moderates excitement, and calms the recipient is a sedative (Goodman and Gilman, 1996). Sedatives usually refer to the older generation of drugs such as barbiturates and chloral hydrate, though this definition also partially fits the benzodiazepines. A tranquilizer belongs to a large class of drugs in widespread use since the 1950s for the reduction of tension or anxiety and the treatment of psychotic states (Oxford English Dictionary, 1986). The idea of the pineal gland being a tranquilizing organ (Romijn, 1978) has not stood the test of time. None of the more recent studies of melatonin (that use < 5 mg) have called it a tranquilizer or sedative.

Since sleepiness is the sleep propensity or probability of falling asleep in a given situation at a particular time (see Johns, 1993, for informed discussion), the most appropriate term for a drug inducing or tending to induce sleep (make drowsy, sleepy, somnolent) is a soporific (Oxford English Dictionary, 1986). This term is seldom used in the scientific literature. Melatonin does increase subjective sleepiness about 1 h after administration in most studies to date, independent of time of day (Arendt et al., 1984; Waldhauser et al., 1990; Dollins et al., 1994; Tzischinsky and Lavie, 1994; Nave et al., 1995a; Zhdanova et al., 1995). This sleepiness can be objectively documented in specific changes in the waking EEG spectra (enhanced theta/alpha activity) (Cajochen et al., 1996).

A chronobiotic is defined as a chemical substance capable of therapeutically re-entraining short-term dissociated or long-term desynchronized circadian rhythms, or prophylactically preventing their disruption following environmental insult (Short and Armstrong, 1984; Dawson and Armstrong, 1996). Crucial in this definition is the timing of the treatment to match the timing (or mix-timing) of the disorder. Thus, for example, melatonin in blind subjects with delayed sleep phase syndrome could only advance sleep onset and stabilize sleep phase within a certain circadian window (Sarrafzadeh et al., 1990; Tzischinsky and Lavie, 1994).

Melatonin a Chronobiotic

Melatonin is demonstrably a chronobiotic (e.g. (Arendt et al., 1984; Armstrong, 1991; Attenburrow et al., 1995; Krauchi et al., 1995; Dawson and Armstrong, 1996)). Melatonin's phase shifting ability follows a phase response curve (Lewy et al., 1992; Zaidan et al., 1994). This chronobiotic characteristic has been practically demonstrated by the many controlled studies successfully using melatonin to combat jet lag (Short and Armstrong, 1984; Arendt et al., 1987; Petrie et al., 1989; Nickelsen et al., 1991; Claustrat et al., 1992), and entrain circadian-related sleep disturbances in some blind persons (Folkard et al., 1990; Sarrafzadeh et al., 1990; Sack et al., 1991; Tzischinsky et al., 1992) and severely retarded children (Palm et al., 1991; Jan et al., 1994; Lapierre and Dumont, 1995). In sleep studies to date, chronobiotic and putative hypnotic properties of melatonin have been intractably confounded. Theoretically, studies designed to document the purely hypnotic effects of melatonin

should avoid times at which phase shifts occur. Few studies have actually established circadian phase prior to melatonin treatment.

For scientists who have been self-administering melatonin for many years to combat jet-lag (anonymous personal communications), the claims that melatonin has hypnotic properties (Waldhauser et al., 1990; MacFarlane et al., 1991; Dollins et al., 1994; Garfinkel et al., 1995; Haimov et al., 1995; Wurtman and Zhdanova, 1995; Zhdanova et al., 1995) as distinct from mild soporific ones come as a complete surprise. If the hypnotic effects are so potent, how had all these vigilant scientists missed them? This raises the issue: how good is the sleep EEG evidence for melatonin's hypnotic action (reviewed in Dawson and Encel, 1993)?

The effect of melatonin (< 5 mg) in healthy subjects is rather small and often occurs only after several days of administration. Melatonin can reduce sleep latency when given in the daytime or early evening (Dollins et al., 1994; Hughes et al., 1994; Nave et al., 1995), but not necessarily (Dijk et al., 1995). A shortened sleep latency has been found after night-time administration in some studies (Zhdanova et al., 1995) but not in all (James et al., 1988; Cajochen et al., 1995). A time-dependency of melatonin's capacity to advance sleep propensity has been very nicely demonstrated (Tzischinsky and Lavie, 1994). Some, but not all, investigations in insomniac populations have found improved sleep after melatonin (James et al., 1989; Waldhauser et al., 1990; MacFarlane et al., 1991; Garfinkel et al., 1995; Wurtman and Zhdanova, 1995; Ellis et al., 1996). In these few studies the interval between melatonin intake and sleep onset has not always been the same, nor the time of day chosen, not to mention the additional factor of number of hours of prior wakefulness, plus presence or absence of endogenous melatonin secretion. It has been suggested that hypnotic effects of melatonin may only be manifested when circulating levels of endogenous melatonin are low (Dawson and Encel, 1993). If this were found to be the case, melatonin's clinical usefulness as a sleeping pill would be severely curtailed.

In healthy volunteers tested in a midday nap, the effects of 5 mg melatonin on EEG spectra were mildly benzodiazepine-like, i.e., suppression of low-frequency activity and enhancement of spindle frequency activity (Dijk et al., 1995). However, the increase induced was in the 13-14 Hz band and not the 12-13 Hz band as seen after benzodiazepines and their analogues. Low dose melatonin (0.1-0.3mg) given before an early evening nap suppressed low-frequency activity and enhanced power in the beta band (15-19Hz); higher doses (3 and 6 mg) in a similar protocol additionally enhanced power in the 12-14Hz range (Lavie et al., personal communication; Nave et al., 1995b). In contrast, EEG spectra remained unchanged during nocturnal sleep 5 h after melatonin ingestion in the early evening, even though melatonin concentrations were still >7 times placebo levels at sleep onset (Cajochen et al., 1996). Thus, EEG spectral analysis differentiates melatonin substantially from the classical hypnotics and provides an important tool to definitively do so.

Whatever further studies reveal about the sleep-inducing properties of melatonin, there are still certain consequences. Subjects need to be warned that driving a motor car or carrying out tasks that require adequate vigilance could be contraindicated for several hours after intake. The interaction with other medications administered to neurological, psychiatric and medical patients becomes paramount.

Proper Dosing

Dosing parameters are particularly confusing. There may be complex interactions between age of the subjects and dose required for a given response. It may be the changes in melatonin levels which influence sleepiness (in particular, the initial rise after a period without melatonin secretion), and not the actual concentrations (e.g. Cajochen et al., 1996). Should the endogenous melatonin profile be mimicked using low doses (and possible sustained release) as a form of 'replacement' therapy? Or, are higher pharmacological doses necessary to induce the prerequisite physiological changes preparatory for sleep? One important such change is the pronounced and dose-dependent hypothermic response to melatonin (Cagnacci et al., 1992; Dawson and Encel, 1993; Hughes et al., 1994; Deacon and Arendt, 1995; Krauchi et al., 1995). This larger effect may be required in order to treat jet lag or shift work disturbances.

Levels or Timing?

It is still not clear whether a person's endogenous melatonin levels (as opposed to its timing) may predispose to sleep problems. Case studies are available of patients with very high melatonin (hypogonadotrophic hypogonadism, delayed puberty, amenorrhea (Brezinski et al., 1988; Luboshitzky et al., 1995) or very low or absent nocturnal secretion (pineal tumor, pinealectomy, old age, major depression, some insomnias, e.g. Claustat et al., 1985; Petterborg et al., 1991; Haimov et al., 1994; Etzioni et al., 1996; Attenburrow et al., 1996). The former do not manifest sleep abnormalities; the latter may do so. However, the evidence for a so-called "hypomelatonin syndrome" is still rather sparse.

A final point in this comparison still needs clarification. In the clinical use of benzodiazepines for insomnia, particularly psychophysiological insomnia, the anxiolytic properties often play a crucial role in permitting sleep (Morin, 1993). There is no evidence, as far as we know, that melatonin is an anxiolytic agent, nor evidence for benzodiazepine-like muscle-relaxant or anti-epileptic properties. It does not appear to have any effect on mood (Arendt et al., 1984; Dollins et al., 1994; Cajochen et al., 1996).

Clinical Consequences

These dissections of definitions are not mere academic arguments. They have clinical consequences such as to how to treat insomnias-of-the-circadian-kind with melatonin, analogous to their treatment with bright light (Terman, 1995). For example, early morning awakening insomniacs lengthen their sleep in response to timed evening bright light treatment (Lack and Wright, 1993), as do sleep maintenance insomniacs (Campbell et al., 1993). Delayed (DSPS) and advanced (ASPS) sleep phase syndrome and irregular sleep/wake cycle disorder (Thorpy, 1990) are traditionally misdiagnosed as sleep onset insomnia, terminal insomnia, and sleep maintenance insomnia.

DSPS in particular may be far more common than hitherto supposed, particularly in a milder form (which should be designated as sub-DSPS; Armstrong, 1991). Both early evening administration of melatonin (Dahlitz et al., 1991) and early morning administration of light (Terman, 1995) have a phase-advancing effect on DSPS.

In irregular sleep/wake cycle disorder, loss of the 24-hour rhythm is thought to be due to decreased amplitude of (Thorpy, 1990), and possible desynchrony within, the circadian pacemaker (Armstrong, 1991). This disturbance is most commonly found in the elderly, and a recent study has shown that their sleep responds well to melatonin administration (Haimov et al., 1995). The most likely interpretation is that melatonin 'replacement' therapy re-organizes the circadian sleep/wake cycle at the level of the circadian pacemaker (Armstrong, 1991) and not that melatonin acts as a sleeping pill in the conventional sense for sleep maintenance insomnia (Wurtman and Zhdanova, 1995). There is no data to document melatonin's improvement of sleep maintenance insomnia, similar to the short-acting benzodiazepines. In other words, will melatonin still induce sleep after the sleep debt has been partially met after 4 h of sleep? It may do so only with long-release formulations taken prior to bedtime (Garfinkel et al., 1995).

Pivotal to the evidence that melatonin is a chronobiotic is the dense concentration of high-affinity melatonin binding sites (Vanacek et al., 1987) in the biological clock, the suprachiasmatic nucleus (SCN) of rodent, sheep and human brain; furthermore, a high-affinity G protein-coupled melatonin receptor [designated Mel 1a] has been cloned and shown to be expressed in the human SCN (for review see Weaver et al., 1991). The receptor is found in very few other functionally discrete brain areas (primarily the hypophyseal pars tuberalis, and a second Mel 1b receptor primarily in the retina (Reppert et al., 1995)), and these are not known to be sites integral to sleep regulation. The demonstration of such a site could help elucidate a putative hypnotic role for melatonin. It remains possible that the more widespread low-affinity melatonin binding sites are involved in sleep mechanisms. To date, the status of these low-affinity binding sites remains obscure (for review see Morgan and Williams, 1989).

Conclusion

Thus, the quandary is that melatonin is a natural hormone which in part fits the definition of a hypnotic, since it induces sleepiness and facilitates the onset of a 'natural' sleep EEG (when given in the evening). Melatonin is clearly not a tranquilizer in the classical sense, nor a sedative drug, and there is no evidence for any anxiolytic characteristics. Melatonin has minor effects on sleep stages. More information is needed about its effect on EEG spectra at different times of day. The lack of adverse side-effects, at least in the short term, suggests that melatonin should be separately defined. However, we do not yet have any evidence in humans for long-term effects of chronic melatonin administration on sleep. Does tolerance occur? Is endogenous melatonin synthesis down-regulated? Are there withdrawal symptoms after cessation? Are there side-effects on other functions (e.g. retina, reproduction). All the above lead to the conclusion that it is premature to classify melatonin as a hypnotic. Those aspects of melatonin which are deemed

hypnotic may be better termed soporific. We suggest that this term is more accurate and we advocate its usage to discuss the sleepiness-inducing characteristics of melatonin, while retaining parallel use of the term chronobiotic when a shift in sleep timing is an important factor. Note that such dual definitions already exist: a benzodiazepine administered during the day is usually called a tranquilizer, a benzodiazepine taken during the night called a hypnotic. Until more laboratory and field trials provide answers to the issues we have raised, melatonin remains a chronobiotic with soporific properties. The latter represent the icing on the cake.

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Anna Wirz-Justice, *Chronobiology and Sleep Laboratory, Psychiatric University Clinic, CH-4025 Basel, Switzerland.*

Stuart Maxwell, *Armstrong Brain Sciences Institute, Swinburn University of Technology, PO Box 218, Hawthorn 3122 Victoria, Australia*

The following are letters to the editor and response pertaining to Charmane Eastman's piece "What the placebo literature can tell us about light therapy for SAD", published in the last issue of this bulletin (LTBR 1997; 9:19-21).

Dear Sirs:

In the early 70's, Thomas Kuhn (Kuhn, 1970) caused a bit of philosophical trouble when he suggested that science might be less logical than scientists would like. Kuhn argued that entities derived from different theories are literally incommensurable and, worse still, that what is called scientific progress is actually better understood in psychological and social terms. I was reminded of this argument when reading Dr. Eastman's excellent article (Eastman, 1997) on the placebo issue in the recent SLTBR bulletin. In the study of SAD, as elsewhere in science, there is a strong tendency for individual researchers to deny, oversimplify or ignore dimensions of a scientific problem which are beyond their expertise or interests. Dr. Eastman suggests that this phenomenon has occurred with the placebo issue, with good research on the placebo effect remaining strangely invisible to many researchers. Beyond the useful summary of relevant placebo literature contained in the excerpts, two things struck me as important about Dr. Eastman's article. Firstly, it acknowledges some of the personal realities of the scientific endeavor. For example, Dr. Eastman refers to her own difficulty in dealing with the diversion of the placebo literature in the face of her primary interest in circadian rhythms. She also takes account of emotions such as embarrassment and disdain as motivators in research. The second important thing about Dr. Eastman's article is that it was published in the LTBR bulletin. The placebo issue is, for obvious reasons, a hot topic in SAD research and the fact that it receives this type of study attests to the maturity of the field. In fact, the published article exemplifies a partial solution to the relativistic dilemma proposed by Kuhn: scientific fields can make rational progress when they develop a discourse which attends to both the formal conclusions derived from experiment and the psychology of the research endeavor.

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Greg Murray, *B.Sc., B.A. (Hons) M. Psych.*

Dear Sirs:

Charmane Eastman (1997) puts up straw men and asks others to shoot them down. This is good for the field since it makes everyone else pay better attention to what they do and say. Indeed, I find her maverick point of view refreshing, if annoying. Whether she has substantively added to our knowledge is another matter.

Eastman tries to differentiate spontaneous remission/recovery from "placebo effects." I have always considered spontaneous remission/recovery to be one possible mechanism for "placebo effects". Since in psychiatric disorders there is no underlying pathophysiology to measure, I see no way to differentiate spontaneous remission/recovery from other putative nonspecific causes of improvement, such as life events, entry into a supportive relationship and the like. If we are interested in demonstrating that a touted treatment has specific efficacy, the important distinction is demonstrating superiority of the touted treatment relative to a "placebo", not among the possible causes of response in the placebo group. It thus becomes and empty exercise and possibly misleading to define "placebo effect" as improvement not attributable to spontaneous remission/recovery.

Eastman's discussion of "Does bright light work?" seems confused. She asserts that this is really two questions. But the questions she cites appear to be the same. "Whether bright light significantly reduces symptoms" means to me that I can attribute the symptom reduction to the light. Thus, bright light produces more symptom reduction than can be attributable to "placebo effects" Obviously, it is a mistake to attribute symptom reduction to whatever happened to be going on at the same time unless it occurred significantly more or significantly more often on purported active treatment than with some comparison condition, a point she correctly makes later in her discourse.

Eastman appears to commit her own sin of misattribution in citing the Lasagna (1958) data. She implicitly attributes the improvement he found to the placebo pill, without considering the possibility that increased attention, suggestion or spontaneous remission could have played a role. Since there was no "placebo" for the placebo pill – e.g., a no-pill group – we cannot attribute the improvement to the pill itself.

An important point that she makes later in the article is that just because there is an apparent dose-response relation does not necessarily mean that the treatment is active, since it has been shown that there is a dose-response relationship for placebo – the more pills, the better the response! However, she seems to argue that because there is a possible alternate explanation, we should pay no attention to the data. Applying this logic to her own argument, one can provide an alternative explanation to her assertion that light therapy is all "placebo

effect." Does that mean we should not pay attention to her "placebo" arguments? This really becomes *reductio ad absurdum*. Rather, we need to weigh the strength of the data and reach what appears to be the most reasonable conclusion. Eastman appears to argue that since we cannot be 100% certain of the efficacy of lights that therefore we should consider its effects to be not demonstrated. She is correct that we should not be 100% convinced. But, then, one never has 100% certainty, since even in the perfect experiment there is a 5% chance of making mistaken inferences. The question is not whether we can be 100% convinced, but what mistakes are we willing to live with? Eastman asserts that we made a mistake to assert the efficacy of bright light based on significantly different reductions in symptoms in patients treated with bright light versus some placebo condition since she can demonstrate that placebo response can be manipulated and, perhaps, that the placebo response was differently manipulated in the bright light condition. She is correct. My problem, however, is that she makes no estimate of the likelihood of her alternative explanations, how to go about assessing them, or what the likelihood is that rejecting these light therapy studies will lead us astray. Would Eastman recommend that we place a heavy bet in Las Vegas that bright lights are just an elaborate placebo? Would she recommend that her SAD-afflicted sister spend her last \$300 on a light therapy box?

Where does all this leave us? I do not think that Eastman has addressed what is wrong with the statement "[The] response rate to bright light is higher than virtually all other published reports and may be inflated". Ditto, "Light therapy is probably not just a placebo because the response rate for improvement is unusually high", and "A method for distinguishing between placebo and real responses is to use the [discrete remission] criteria of Terman et al." She seems to argue out of both sides of her mouth, first stating that placebo effects are long-lasting then that they quickly abate. Her point, however, is that without showing that a supposed active condition differs from "sham" treatment, no assertions of causation can be made.

I find her final statement most apt: "Scientists.. must continue to try to tease apart placebo effects from specific treatment effects, in order to learn more about the causes of SAD and to develop new treatments." She well fits her own view of a scientist.

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Dr. Eastman replies:

Reply to Jonathan Stewart

Dear Jon,

You're not really listening to me! You may think you are, but you're not! You're twisting my words! You're telling people I said things I never did! That's why I have to answer your letter.

I strive to write clearly and in an easy-to-understand fashion. Obviously, I'm a complete failure, at least with you. I could write 10 pages explaining how you've misinterpreted me in almost everything you said, but I won't. My husband says I shouldn't spend more than a day on this. So, I'll just try to make a few points.

1. Let's start with the quotes from various papers that I found, disguised a little, and then stuck in various places in my old (1990) paper "What the Placebo Literature Can Tell Us About Light Therapy for SAD." I didn't explain what was wrong with *any* of the quotes. It was supposed to make you think, and one clue was derived from *where* within the paper I stuck the quote. Two of the quotes you mentioned were "Light therapy for SAD is probably not just a placebo because the response rate for improvement is unusually high" and "A method for distinguishing between placebo and real responses is to use the criteria of Terman et al. The latter responses should bring the Hamilton Rating score to less than 8 points and to less than 50% of the baseline rating." These quotes are wrong wrong, wrong! You cannot assume that light treatment is not just a placebo because it produces a very good response. These quotes were under the heading PLACEBO RESPONSES ARE UNDERRATED. This was the clue. Just because you get a large, dramatic improvement with bright light, does not prove that it's more than a placebo, because placebo treatments can do this also. Jon, I'm really surprised at you. I know you know this. Are you trying to confuse people?

The point of the third quote you mentioned is a little more subtle. That quote was under the heading "PLACEBO CONTROLS REDUCE ACTIVE TREATMENT RESPONSE." It said "What's Wrong with This Statement from a Bright Light Study with No Control Treatment? - This response rate to bright light is higher than virtually all other published reports and may be inflated." The point is that response rates depend on the design of the study. When there are no placebo control treatments, response rates to the active treatment are usually higher than when the design includes a placebo control. To state that the response rate to bright light in a study is "high" and may be "inflated," may make the reader think that there is only one "true" response rate to a particular treatment.

2. I never said that placebo effects "quickly abate." Where did you get that from? I said on page 19 that "long term studies usually show that patients maintained on placebos continue to improve, although perhaps not as much as with active treatment." The point is that placebo responses *do not* wear off.

3. I never made the "assertion that light therapy is all placebo effect." Nor did I ever say that "since we cannot be 100% certain of the efficacy of lights that therefore we should consider its effects to be not demonstrated." I never said that "we make a mistake to assert the efficacy of bright light based on significantly different reductions in symptoms in patients treated with bright light versus some placebo condition." In fact, what I was getting at is that *this is exactly what we have to do* to determine whether bright

light treatment is better than a placebo. But we have to use a good placebo control treatment. As I said on page 18 "the only scientific demonstration of incremental effectiveness for a treatment is comparison with a placebo condition. Furthermore, that placebo condition must be as identical as possible to the "active" treatment, to equate the non-specific factors and expectations which can be so powerful. The same attention, enthusiasm, and effort should be applied to the placebo treatment as to the active treatment." I've discussed this specifically with regard to bright light treatment in other publications (e.g., A comparison of two different placebo-controlled SAD light treatment studies. In: Wetterberg, L. (ed) Light and Biological Rhythms in Man, Pergamon Press, 1993). But apparently you didn't read that one.

Somehow, you must have also missed our latest abstract from the last SLTBR meeting "Light Therapy for Winter Depression is More Than a Placebo." In this 6-year study, testing 96 patients, we compared bright light treatment to a placebo that had the same non-specific factors as light treatment (such as, a regular sleep schedule, 1.5 hours of treatment sitting time, high patient and staff expectations for improvement, etc.) Light was better than placebo after 3 weeks of treatment. So, to answer your question of whether I would recommend that my SAD-afflicted sister spend her last \$300 on a light therapy box, the answer is no. I would give her one!

Now I've run out of time, and have to end this. I hope I've undone some of the damage you did, and maybe we've helped others who are interested in thinking about the placebo problem. It felt good to write this, but you were very nasty, and I'm still not satisfied. So, please send me your photo for my dart board.

Insurance Reimbursement Notices

Mixed news on the reimbursement front. The first entry, contributed by Michael Terman, is a letter written by a Medi-Cal official to a California Assemblyman in response to the latter's attempt to help a constituent with SAD obtain insurance coverage for a light box. After that, an update from Switzerland contributed by Anna Wirz Justice.

The Honorable William Hoge
Member of the Assembly
625 Fair Oaks Avenue, Suite 383
South Pasadena, CA 91030

Dear Assembly Member Hoge:

This is to acknowledge your inquiry on March 18, 1996, regarding the Department of Health Services (Department) policy on phototherapy services for Medi-Cal beneficiaries and specifically related to the constituent, Mr. X. Mr. X's physician, Dr. Y, sent a letter to the Department, which was received by the Los Angeles Medi-Cal Field Office on February 14, 1996, to inquire about the use of phototherapy to treat his recurrent major depression. The Department considers phototherapy for the treatment of seasonal affective disorder, e.g., winter depression, as not primarily a medical service. The light used in this therapy contains all of the wave frequencies present in sunlight. There has been no published data on what frequency of light waves are "healing"; therefore, full-spectrum light, i.e., sunlight, is usually employed. Moreover, safety and long term efficacy have not been formally evaluated, nor has light therapy been tested against other potentially active treatments, such as medication, psychotherapy, or the combination. Since controversy remains in the medical community about this therapy, we must conclude that it remains an investigational service...

Sincerely,

Virgil J. Toney, Jr., Chief
Medi-Cal Operations Division

Switzerland

On April 1, 1996, light therapy for SAD was officially recognized by the Government Agency regulating the list of medical treatments accepted by insurance companies. Thus, reimbursement is now compulsory. After further discussions, reports, and the due slow process of such deliberations, the next step of legal implementation - definition of tariffs - has been completed. As of January 1, 1998, 800.- Swiss Francs will be paid towards the cost of a light treatment apparatus for SAD patients; light box rental is fixed at 2.- Swiss Francs /day for a maximum of three months / year. The doctor's consultation for diagnosis etc. follows the usual tariffs. This decision is now a country-wide law. One of our arguments in the tariff discussion compared the cost of antidepressants for 4-5 months / year: a light box is paid off after two winters. We hope that this information can be of use in other countries in the slow and difficult process of implementing insurance reimbursement.

Anna Wirz Justice

Highlights of the SLTBR Board Meeting June 7, 1997 Vancouver BC, Canada

The President, Ray Lam, presented his report on the launch of the new website and the discussion list. He noted the progress of LTBR and that there were nearly 100 attendees at this meeting. Talks with SRBR have been initiated recognizing joint efforts. Membership still needs to be built. Scott Campbell and Sonia Ancoli-Israel have completed their Board terms.

Treasurer, Sonia Ancoli-Israel reported a closing net of \$4,380 for 1996 which is a turnaround from 1995's loss.

Membership and the need for an aggressive campaign were discussed. It was decided to develop a campaign with an incentive to current members who enlist new members.

New publications and the expansion of the LTBR were discussed.

It was agreed to meet jointly with the SRBR in Amelia Island in 1998.

New Board members are Michael Young, Treasurer and Juana Terman, Board member.

Raymond W. Lam, MD

Redux (dexfenfluramine) Recalled

On September 15, 1997, fenfluramine and dexfenfluramine were voluntarily withdrawn from the American market by their manufacturer Wyeth-Ayerst Laboratories. The latter drug, dexfenfluramine (brand named Redux), had been approved for use in the long term treatment of obesity but had also been found effective, in a placebo controlled trial, for winter depression (O'Rourke et al., 1989; see also Schlager, 1997).

In the letter announcing the drugs' withdrawal, the company cited "preliminary information regarding abnormal heart valve findings in patients using these medications" either alone or in combination with phentermine. The association between fenfluramine exposure and abnormal heart valves had been reported in the August 28th, 1997 issue of *The New England Journal of Medicine* (Connelly et al., 1997; Kurfman, 1997) and in a subsequent unpublished communication from the FDA which summarized findings from a five center study of *asymptomatic* patients who had been treated with either drug. In this study "abnormal echocardiogram findings were reported in 92 of 291 subjects evaluated, including 80 reports of aortic regurgitation (mild or greater) and 23 reports of mitral regurgitation (moderate or greater)." It is important to note that such observations follow prior published reports of an association between fenfluramine use and a yet a different medical condition, Primary Pulmonary Hypertension (Abenhaim et al., 1996, Manson and Faich, 1996; Mark et al., 1997; also see Schlager, 1997), an often fatal condition of the lungs and heart.

In light of these findings, patients previously treated with dexfenfluramine should be referred for medical evaluation to rule out such cardio-pulmonary abnormalities. In places where dexfenfluramine is still available, its off-label use in winter depression is unjustified in light of the accumulating evidence of risk and the availability of alternative safer treatments.

For further medical information on fenfluramine call the Wyeth-Ayerst Medical Affairs Department at 1-800-513-7897.

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SLTBR Young Investigator Award

The Society for Light Treatment and Biological Rhythms offers a \$500 award for the purpose of stimulating international research in clinical aspects of biological rhythms and light therapy by young investigators. The 1997 winner was Boris B. Pinchasov of the Institute for General Pathology and Human Ecology, Novosibirsk, Russia for his paper on "Effects of Midday Kinesitherapy on Mood, Physical Performance, Metabolism and Leukocyte Count in Patients with Seasonal and Nonseasonal Depression."

GUIDELINES

1. Candidates shall not have passed their 35th birthday on January 31, 1998. If a senior investigator is listed as a co-author, the senior author must supply an accompanying letter indicating the degree of independence represented by the candidate's contribution.
2. Although the research is not to be judged in comparison with the work of the more senior investigators in the field, special consideration will be given to the originality of the approach and independence of thought evident in the submission.
3. The candidate must still be actively involved in the field.
4. The submission should be in the form of a manuscript that describes empirical studies. The studies and data must not have been published at the time of submission.
5. The winning author will be invited to present a scientific abstract and to receive his/her award at the 10th Annual Meeting of the Society in 1998.
6. Submission will be welcomed from young investigators in any country.
7. Candidates need not be current members of the SLTBR.

INSTRUCTIONS

1. All guidelines above must be strictly followed.
2. Submit six copies of a 10 to 20 page (excluding references) double-spaced manuscript.
3. Submit six copies of a brief biographical sketch with the manuscript.
4. The deadline for receipt of submissions is February 1, 1998.
5. Submissions should be sent to Young Investigator Award, SLTBR, 10200 W. 44th Avenue, Suite 304, Wheat Ridge, CO 80033-2840.

SPONSOR

The SLTBR gratefully acknowledges the continued sponsorship of this award by Apollo Light Systems, Orem, UT.



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