SLEEP AND BIOLOGICAL RHYTHMS
THE JAPANESE SOCIETY OF SLEEP RESEARCH

Sleep and Biological Rhythms 2010; **8**: 161–162 doi:10.1111/j.1479-8425.2010.00444.x

PREFACE

Chronotherapeutics: An example of translational research for sleep and mood disorders

The catch-phrase of the decade in government ministries, granting agencies, and plenary sessions at scientific conferences is "translational research," which seems to have replaced "from bench to bedside" – perhaps because it sounds more impressive. It links research from the basic sciences with clinical investigation, and facilitates the results of clinical trials to be incorporated into clinical practice. In our field of sleep and biological rhythms, we are already doing an enormous amount of translation, yet we scarcely advertise this fact. My first question is, why are we not more energetic in recognising our achievements, to obtain attention from the policy makers?

I focus here on chronotherapeutics as a prime example. This field encompasses a set of treatments directly derived from research in circadian biology. Chronotherapeutics can be defined as controlled exposure to environmental stimuli such as light, which act on biological rhythms, and direct manipulations of sleep, both with strong therapeutic effects. The pineal hormone melatonin, exogenously administered, belongs to this field, since it can, like light, synchronise circadian rhythms and also induce sleep.

Light and melatonin, our non-pharmaceutical therapeutic tools, are important zeitgebers for maintaining rhythmic stability – crucial for good sleep and mood. Darkness (as defined in clinical trials as 14-h winter nights) is a surprisingly effective treatment for mania or rapid cycling.

Some in Pharma have awakened to the novel therapeutic potential of melatonin as a sleep-promoting agent, and developed low dose slow-release preparations of the natural product (Circadin) or its agonists (Tasimelteon, Ramelteon). The melatonin agonist and $5HT_{2c}$-antagonist (Valdoxane) is marketed as an antidepressant with sleep-stabilising properties. We do not yet have light in a pill.

The discovery of a novel circadian photoreceptor in the retinal ganglion cells, which contain the photopigment melanopsin sensitive to blue wavelengths, has led rapidly to blue-enhanced or pure blue light therapy devices. Theoretically a logical development, they have been placed on the market without appropriate clinical trials showing superiority over white light and consideration of long-term safety issues. Blue light is considered as contributory to certain retinopathies. The basic research finding of the blue-sensitive photoreceptor has also led to a simple tool to block the circadian light input in certain patients – amber-coloured eyeglasses. These are useful adjuncts to treating patients with light or melatonin for their circadian sleep disorders. By wearing the filters at the appropriate time of day (evening for DSPS (delayed sleep phase syndrome), morning for ASPS (advanced sleep phase syndrome)) unwanted phase shifting can be easily prevented. The filters are also helpful for shift workers coming home after the night shift, so as not to interfere with daytime sleep and functioning.

In sleep medicine, sleep restriction is conventionally used to counter the habit of going to bed too early or staying in bed too long, whilst expecting to fall asleep immediately and stay asleep the entire night. However, attempts to shift pathological sleep timing as in DSPS and ASPS are often ineffective without timed light and/or melatonin to support entrainment at the targeted circadian phase. Most blind persons who free run cannot reentrain without carefully timed melatonin.

In mood disorders, the close relationship between depression and sleep disorders is well known. What is less known, and much less used, is the paradoxical effect of taking away a night's sleep from such depressed patients: two-thirds improve their depression within hours. Alas, recovery sleep or even a nap usually

reinstates the depressive state; as a counter-move, newer studies have developed methods to maintain the rapid response – light therapy, lithium for bipolar patients, phase advance of the sleep–wake cycle. Phase advancing sleep itself maintains improvement much longer than sleep deprivation on its own.

So we have a set of unusual methods – total or partial sleep deprivation in the second half of the night, phase advance of the sleep–wake cycle, light therapy, dark therapy or blue-blocking sunglasses, melatonin. These are well-documented treatments that indeed fulfil the goals of translational research.

Now I come to the next question – why aren't these treatments wider known and more generally used? This is Phase 3 of the translational research progression (Phase 1, at the bench; Phase 2, clinical trials). Given the rapid action of chronotherapeutics, lack of side effects, and easy combination possibilities, how can we educate sleep physicians and psychiatrists about their use?

Obviously, treatments that are not patentable do not make profits for industry, thus denying the commercial marketing model used for drugs. Because they do not go through official clinical trial registration at federal regulatory agencies, treatments are off the list for insurance reimbursement. The simplicity of our treatments contrast with high-tech medicine, and for this reason are often not taken seriously.

Finally, there is still rather widespread ignorance among doctors and patients about circadian sleep disturbances. Given our methodological toolbox, how can we proceed with wider dissemination? First, enterprising doctors should try them out. Only with first-hand experience does the reality of efficacy and response emerge. Second, the techniques should be taught in medical school and during residency – since it is the younger generation that is most open to change and cogent alternatives to medication. Through its societies, our field needs to advocate recognition for reimbursement. The nonprofit, multilingual patients' website www.cet.org and clinicians' website www.chronotherapeutics.org illustrate some first attempts meet this Phase 3 educational challenge.

Anna WIRZ-JUSTICE
Centre for Chronobiology, Psychiatric Hospitals, University of Basel, Switzerland
anna.wirz-justice@unibas.ch
www.chronobiology.ch

FURTHER READING

1 Wirz-Justice A, Benedetti F, Terman M. *Chronotherapeutics for Affective Disorders. A Clinician's Manual for Light and Wake Therapy*. S. Karger AG: Basel, 2009.