

## Appendix A16

### Abnormalities of Sleep and Non-pharmacological Therapies for Affective Illness

To supplement the discussion of the neurobiology of sleep and circadian rhythms in Chapter 16, here we provide further discussion of some of the genetic contributions to abnormalities of sleep, and brief descriptions of two non-pharmacological therapies for affective illness.

#### *Advanced Sleep Phase Syndrome (ASPS)*

Familial advanced sleep phase syndrome (ASPS) is characterized by persistent advanced sleep onsets and offsets (that is, falling asleep and waking occur earlier than desired), while delayed sleep phase syndrome (DSPS) is characterized by persistent delayed sleep onsets and offsets (where sleeping and waking occur later than desired). Jones and colleagues (1999) describe three families with a preponderance of ASPS and a shorter-than-normal circadian period, suggesting a genetic basis for this syndrome. Affected individuals are “morning larks” with a striking 4-hour advance of sleep, melatonin, and temperature rhythms. Those with ASPS appear to segregate with an autosomal-dominant mode of inheritance (Reid et al., 2001). The familial ASPS gene was localized near the telomere of chromosome 2q, the same area where *hper2*, the human homologue of *Drosophila dper2*, is localized. (The ASPS can be attributed to a mutation in a *clock* component, *hPER2*. This mutation results in the replacement of serine with glycine in a critical region of the *hPER2* protein, which in turn results in deficient phosphorylation of *hPER2* in the cytoplasm that could impair its degradation and/or accelerate its entry into the cell nucleus. This impairment would phase-advance the rhythm of *hPer2*, perhaps in part by increasing transcription of *Bmal1* (Toh et al., 2001). Based on the phase-advance theory of nonseasonal major depression, it would be of interest to compare depression rates and mood regulation among subjects with ASPS and normal individuals. For more discussion on the genetics of sleep in affective illness, see Chapter 13 of *Manic-Depressive Illness 2E*.

#### *Smith-Magenis Syndrome (SMS)*

An extreme abnormality in circadian rhythm, a phase reversal, occurs in Smith-Magenis syndrome (1 in 25,000 births), characterized by mental retardation, hyperactivity, attention deficit, tantrums, aggressive self-injurious behavior, and sleep disturbance, and caused by the deletion of

a portion of chromosome 17 (first described by Smith and Lapp, 1986). Sleep disturbances include daytime sleepiness with sleep attacks at the end of the day, early awakening, and difficulty falling and staying asleep at night. The most striking feature of Smith-Magenis syndrome, however, is the reversal of melatonin secretion, which occurs in daylight rather than at night. Tantrums also tend to occur during the daytime, when melatonin rises. The administration of acebutolol, a  $\beta_1$ receptor antagonist, suppresses the inappropriate daytime secretion of melatonin and alleviates napping and tantrums.

## **Non-pharmacological Therapies for Affective Illness**

### *Chronotherapeutics and Light Therapy*

Light treatment and sleep-wake manipulation (chronotherapeutics) are non-pharmacological therapies which could be powerful adjuvants to pharmacological treatment of mood disorders (Wirz-Justice et al 2005). These interventions are affordable and obtainable, and appear no less potent than available drugs (Wirz Justice et al 2004). Many people favor non-pharmacological treatments, and Wirz Justice and colleagues write that light treatment and sleep manipulations are not to be considered “alternative medicine”—that is, unproved or soft. Rather, these therapies provide opportunities for adjuvant or augmenting treatment for maximizing therapeutic effect.

Sleep manipulations for depression include therapeutic sleep deprivation (wake therapy), phase advance of sleep-wake rhythms, and dark therapy.

Light therapy is another treatment for depression that can be accomplished even more easily than sleep deprivation. The most obvious point at which to employ light therapy is when the depressive phase occurs during the winter months, but it can also be helpful at other times of year, probably because of nonspecific activating effects on the one hand (it can be especially effective against daytime somnolence that can be associated with mood stabilizers) and, on the other hand, because it can help synchronize the circadian cycle, thereby contributing to the stabilization of sleep. For a review of efficacy of light treatment for seasonal and nonseasonal depression, see the meta-analysis of Golden et al 2005. The authors’ conclusion was that when only randomized controlled studies are included, light treatment for both seasonal and nonseasonal depression is safe and efficacious, with effect size equivalent to those in most antidepressant trials.

After a decade of research, the precise timing of daily light exposure necessary for maximum benefit for winter depression in the majority of individuals has been established, and it is first thing in the morning. Certainly early-morning exposure is required for normalizing a phase-delay sleep disorder in which the patient gets to sleep late and then finds it difficult to get up in the morning. No advantage of broad-spectrum light over more typical cool white florescent light has been demonstrated. Current recommendations are for at least 30 minutes of exposure to 5,000–10,000 lux, respecting the specific “distance from the eye” recommendations of the manufacturer. All patients with a seasonal pattern to their mood symptoms, as well as those with phase-shifted sleep patterns, should probably invest in their own phototherapy light box, as should all psychiatric inpatient units. Side effects include headache, eyestrain, jitteriness, and insomnia. It

has been suggested that prolonged exposure to full-spectrum light in the absence of a mechanism to screen out ultraviolet wavelengths (which most light boxes have) poses a risk for the development of cataracts and skin cancer. There have also been case reports of the induction of manic symptoms from phototherapy (Terman and Terman, 1999). Nevertheless, the side effects of light treatment compare favorably with those associated with medication.

The World Health Organization has placed emphasis on the need for interventions that are effective, sustainable *and affordable*. Sleep manipulations and light treatment could fulfill these WHO standards.

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