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EDITORIAL

Chronotherapeutics (light and wake therapy) in affective disorders*

The Committee on Chronotherapeutics was recently formed by the International Society for Affective Disorders (ISAD), which has asked us to provide a consensus review of chronotherapeutics (light and wake therapy) in affective disorders. We consider these non-pharmaceutical, biologically based therapies to be potentially powerful adjuvants ready for clinical application. We also stress the need for additional studies, both in-patient and out-patient, to broaden the evidence base for indications and efficacy.

The theme of adjuvant therapy is of increasing interest. Many of the lectures at the 2nd ISAD Meeting (Cancun, Mexico, March 2004) emphasized that combination treatments – such as cognitive behavioural therapy added to antidepressants (Paykel, 2004; Scott, 2004) – could help treat the residual symptoms that indeed portend relapse (Thase, 2004). The meeting highlighted expansion of interest in the development of new concepts for treating depressive illness (i.e. drug targets other than monoamines) – to wit: 'New antidepressants are needed and they are on their way' (Pinder, 2004). On a pragmatic plane, the World Health Organization (WHO) has placed emphasis on the 'need to demonstrate that interventions are not only effective and sustainable, but also affordable' (Chisholm, 2004). The meeting symposia shared the realization that the long-sought, faster-acting, relapse-preventing antidepressants are still not at hand, and that the field must continue to pursue combinations of psychological and pharmacological interventions.

Missing from discussion, however, was consideration of light therapy and sleep deprivation, whose well-demonstrated efficacy – alone or in combination (Berger, 2004; Benedetti *et al.* 2004*a*; Martiny *et al.* 2004; Terman, 2004; Wu, 2004) – could fulfil the WHO mandates of affordability and sustainability. The apparent blindness to these treatments by the psychiatric mainstream most likely stems from the prevailing neuropharmacological paradigm, and – if we may face realities – the commercial drawback that they cannot be patented (Studwell, 2004). In spite of many fascinating recent advances in development of new classes of antidepressant drugs (Holden, 2003), they are not yet ready for clinical use. By contrast, chronobiological interventions are already available and offer prospects no less potent than any candidate drug (Wirz-Justice *et al.* 2004).

Chronotherapeutics – treatments based on the principles of circadian rhythm organization and sleep physiology – offers mental health practitioners a set of non-pharmaceutical, rapid and effective antidepressant modalities for monotherapy or as adjuvants to conventional medication. Here, we consider supplemental light exposure and sleep deprivation (more positively known as 'wake therapy') as first-line treatments for major depression.

Light therapy was first developed and has been established as the treatment of choice for winter seasonal affective disorder (SAD; Partonen & Magnusson, 2001). The use of light therapy has expanded beyond SAD (Lam, 1998), with evidence for efficacy in premenstrual (Lam *et al.* 1999) and antepartum (Epperson *et al.* 2004) depression, bulimia nervosa (Blouin *et al.* 1996; Lam, 1998; Braun *et al.* 1999), as well as sleep–wake cycle disturbances [delayed and advanced sleep phase syndromes (Abbott, 2003; Reid *et al.* 2004) and Alzheimer's dementia (Skjerve *et al.* 2004)].

Evidence for the usefulness of these treatments for non-seasonal major depression is less clear, with both positive (Yamada *et al.* 1995) and lack of effects (Mackert *et al.* 1991) on record. Most studies have been of much shorter duration than required for testing new antidepressants, even

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though an early study found a significant 18% net benefit relative to placebo after only 1 week (Kripke *et al.* 1992). Controlled trials of light therapy for non-seasonal depression have been reviewed (Kripke, 1998) and are the focus of two recent meta-analyses (Tuunainen *et al.* 2004; Golden *et al.* in press). Cautious in their recommendations ('light therapy offers modest though promising antidepressive efficacy, especially when administered during the first week of treatment, in the morning, and as an adjunctive treatment to sleep deprivation responders' (Tuunainen *et al.* 2004, p. 1), these overviews emphasize the need for further studies. The first positive data for this next generation of studies is beginning to appear, e.g. light therapy in chronic depression (Goel *et al.* 2003; Terman, 2004) and bipolar depression (Benedetti *et al.* 2004*a*). The completion of the largest controlled, double-blind clinical trial to date of adjuvant bright light in non-seasonal major depression is auspicious (Martiny, 2004).

Neither drugs nor psychotherapy has overcome a time lag of at least 2 weeks before onset of clinically significant effect (Bech, 2002). In contrast, wake therapy, whether administered over the whole night or restricted to the second half of the night, provides astonishing responses – within hours – in approximately 60% of patients with major depression, independent of diagnostic subgroup (Wu & Bunney, 1990; Leibenluft & Wehr, 1992; Wirz-Justice & Van den Hoofdakker, 1999; Berger *et al.* 2003). Wake therapy has been extensively studied since it was first reported more than 30 years ago, yet it has suffered a fate similar to that of orphan drugs (Wirz-Justice, 1998). Its antidepressant effect is usually brief; indeed, full or partial relapse usually follows recovery sleep or even short naps. Psychiatrists who tested wake therapy were surprised and impressed by the rapidity and the magnitude of response, particularly in patients with severe melancholia, but relegated the method to a back corner because of the burden of administration and almost certain rapid relapse. 'Should one show them paradise and then take it away?' one leading psychiatrist at the ISAD Meeting commented disparagingly. Nevertheless, the key finding of remarkably rapid major improvement remains important and unique. It is surprising that no drug company has sought a novel fast-acting antidepressant in this model of extended wakefulness.

Over the last decade, the Milano psychiatrists have carried out systematic studies of repeated all-night wake therapy to find a way to prevent relapse. The antidepressant response was successfully maintained with lithium salts (Szuba *et al.* 1994; Benedetti *et al.* 1999*a*), the 5-HT_{1A} antagonist pindolol (Smeraldi *et al.* 1999), phase advance of the sleep-wake cycle (Benedetti *et al.* 2001*a*) and morning light therapy (Neumeister *et al.* 1996; Colombo *et al.* 2000). Wake therapy combined with light has been successfully self-administered by out-patients on concomitant antidepressant medication (Loving *et al.* 2002).

These studies demonstrate rapid and sustained antidepressant response in unipolar and – most strikingly – bipolar depressed patients. The switch rates to mania or hypomania are not exacerbated, and are similar to those observed with newer antidepressants (Colombo *et al.* 1999). In a collective with unipolar depression, the Freiburg group has focused on single-night wake therapy followed by a sleep phase advance with a 5-day stepwise return to normal sleep time. This strategy prevented relapse in two-thirds of wake-therapy responders, and, in a randomized, controlled trial, was more effective than sleep phase delays (Riemann *et al.* 1999). To make this kind of protocol more practicable, the phase advance has been reduced to 3 days, with similar results (Voderholzer *et al.* 2003). Given that sleepiness is quite high after a night awake, going to sleep earlier on the first night (17:00 hours) is easy for patients, and the protocol then shifts bedtime to 19:00 and 21:00 hours on subsequent nights. The method is now being used in a clinical trial that assigns patients to 'treatment as usual' or augmentation of single-night wake therapy with the 3-day sleep phase advance protocol combined with daily morning light. Initial results are promising (Wu, 2004).

Selective serotonin reuptake inhibitors (SSRIs) are effective in approximately 70% of patients with a major depressive episode, but usually require at least 2 weeks for significant clinical improvement. The combination of wake therapy and fluoxetine (Benedetti *et al.* 1997) or morning light and citalopram (Benedetti *et al.* 2003*a*) hastens and magnifies the antidepressant response, showing that both wake and light therapy are compatible with, and reinforce the effect of,

Table 1. *Circadian and sleep therapies for major depression*

	Therapeutic latency	Response duration
Total sleep deprivation (TSD)	Hours	~1 day
Partial sleep deprivation (PSD) (2nd half of the night)	Hours	~1 day
Repeated TSD or PSD	Hours	Days/weeks
Repeated TSD or PSD with antidepressants	Hours	Weeks/months
Phase advance of the sleep–wake cycle	~3 days	1–2 weeks
TSD followed by sleep phase advance	Hours	1–2 weeks
Single or repeated TSD or PSD followed by light therapy	Hours	Weeks
Single or repeated TSD or PSD followed by phase advance and light therapy	Hours	Weeks
Single or repeated TSD or PSD combined with lithium, pindolol, or SSRIs	Hours	Months
Light therapy (winter seasonal MDD)	Days	Weeks/months
Light therapy (non-seasonal MDD)	Weeks	Weeks/months
Light therapy with SSRIs (non-seasonal MDD)	1–2 weeks	Weeks/months
Dark or rest therapy (for rapid cycling or mania)	Days	Throughout maintenance of treatment

serotonergic antidepressants. Indeed, many biological studies of light therapy in winter depression have addressed the importance of the role of classical neurotransmitters in addition to circadian phase advance shifts for therapeutic response (Sack *et al*. 1990; Terman *et al*. 2001), providing solid evidence for both mechanisms of action (Lam *et al*. 2001). Genetic variations of the serotonin transporter exert similar influences on the response to serotonergic drugs (e.g. Smeraldi *et al*. 1998), wake therapy (Benedetti *et al*. 1999*b*) and light therapy (Benedetti *et al*. 2003*b*). Individual genetic characteristics of the molecular mechanisms of the biological clock are also determinants of the same core features of mood disorders, including age at onset (Benedetti *et al*. 2004*b*), recurrence (Benedetti *et al*. 2003*c*), response to wake therapy (Benedetti *et al*. 2004*b*), and depressive insomnia (Serretti *et al*. 2003) and its response to drugs (Serretti *et al*. in press). Such parallel findings point to an intimate relationship between the neurotransmitter systems targeted by drugs and the circadian rhythms targeted by chronotherapeutics.

The latest large controlled study compares 5 weeks of adjunctive bright white light with placebo dim red light in sertraline-treated patients with non-seasonal major depression (Martiny, 2004). With a response rate of 66·7% *v*. 40·7%, and remission rate of 41·7% *v*. 14·8% for bright *v*. dim light, we now have convincing evidence of specific efficacy using stringent clinical trial methodology. We hope this will provide impetus to other researchers to investigate the potential of light therapy as an adjuvant in their depressive populations.

The various chronotherapeutic modalities (and their combinations) studied thus far are summarized in Table 1. Initial intriguing studies showing that long dark nights can stop rapid cycling (Wehr *et al*. 1998; Wirz-Justice *et al*. 1999) or diminish manic symptoms (Barbini *et al*. 2005) may add another chronobiological treatment to the repertory.

The public zeitgeist favours non-pharmaceutical treatments. Patients accept and often prefer them. Unlike many touted remedies, however, wake and light therapy are not alternative, unproved, or soft. Wake and light therapy provide flexible opportunities for multimodal treatment as adjuvants with negligible side-effects or untoward interactions with ongoing medication. The few systematic reports of side-effects suggest that these treatments are safe, with only relative counterindications that can be evaluated with careful psychopathological and somatic diagnosis and observation throughout treatment. In these days of managed care, their speed of action is an important consideration. Indeed, length of hospitalization can be reduced. Retrospective examination of more than 800 in-patients treated for bipolar depression in a common psychiatric

hospital setting found that the combination of multiple wake therapy with usual drug treatment led to discharge an average of 3 days earlier than with drug treatment alone (F. Benedetti, unpublished data). Mere increased exposure to natural light in sunny hospital rooms has also resulted in an average 3-day advantage compared with dimmer rooms (Beauchemin & Hays, 1996; Benedetti *et al.* 2001*b*).

It is time for wake and light therapy to be incorporated into mainstream psychiatry. To consider them mere curiosities outside the paradigm wastes resources and prolongs suffering. Building on the example of the American Psychiatric Association (Golden *et al.* in press), national psychiatric associations should exert clinical leadership and develop standards of practice for chronotherapeutics. It would be a shame to wait for the insurance industry to impose these measures based purely on the cost considerations of managed care.

SUMMARY

The Committee on Chronotherapeutics, delegated by the International Society for Affective Disorders (ISAD), makes the following recommendations after reviewing the evidence as of November 2004.

(1) Wake therapy is the most rapid antidepressant available today: approximately 60% of patients, independent of diagnostic subtype, respond with marked improvement within hours. Treatment can be a single or repeated sleep deprivation, total (all night) or partial (second half of the night). Relapse can be prevented by daily light therapy, concomitant administration of SSRIs, lithium (for bipolar patients), or a short phase advance of sleep over 3 days following a single night of wake therapy. Combinations of these interventions show great promise.
(2) Light therapy is effective for major depression – not only for the seasonal subtype. As an adjuvant to conventional antidepressants in unipolar patients, or lithium in bipolar patients, morning light hastens and potentiates the antidepressant response. Light therapy shows benefit even for patients with chronic depression of 2 years or more, outperforming their weak response to drugs. This method provides a viable alternative for patients who refuse, resist or cannot tolerate medication, or for whom drugs may be contraindicated, as in antepartum depression.
(3) Given the urgent need for new strategies to treat patients with residual depressive symptoms, clinical trials of wake therapy and/or adjuvant light therapy, coupled with follow-up studies of long-term recurrence, are a high priority.

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DECLARATION OF INTEREST

None.

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EDITORS' ADDENDUM

Included in this issue is a paper by Goel *et al*. (2005), accepted in March 2005 after the Editorial had already been published online, which reports a study of the kind which it advocates. Goel *et al*. undertook a three-group controlled trial of light therapy, high-density negative air ions and a control procedure of low-density ions, in patients with chronic non-seasonal depression. Both active treatments were found superior to the control procedure.

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