MORNINGNESS-EVENINGNESS QUESTIONNAIRE (revised)[1]

Name: _____ Date: _____

For each question, please select the answer that best describes you by checking the corresponding box. Make your judgments based on how you have felt in recent weeks.

Leave this section blank:

1. *Approximately* what time would you get up if you were entirely free to plan your day?

   - ❑ 5:00 a.m. – 6:30 a.m. 5
   - ❑ 6:30 a.m. – 7:45 a.m. 4
   - ❑ 7:45 a.m. – 9:45 a.m. 3
   - ❑ 9:45 a.m. – 11:00 a.m. 2
   - ❑ 11:00 a.m. – 12 noon 1

2. *Approximately* what time would you go to bed if you were entirely free to plan your evening?

   - ❑ 8:00 p.m. – 9:00 p.m. 5
   - ❑ 9:00 p.m. – 10:15 p.m. 4
   - ❑ 10:15 p.m. – 12:30 a.m. 3
   - ❑ 12:30 a.m. – 1:45 a.m. 2
   - ❑ 1:45 a.m. – 3:00 a.m. 1

3. If you usually have to get up at a specific time in the morning, how much do you depend on an alarm clock?

   - ❑ Not at all 4
   - ❑ Slightly 3
   - ❑ Somewhat 2
   - ❑ Very much 1

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[1]Some stem questions and item choices have been rephrased from the original instrument (Horne and Östberg, 1976) to conform with spoken American English. Discrete item choices have been substituted for continuous graphic scales. Prepared by Terman M, Rifkin JB, Jacobs J, and White TM. New York State Psychiatric Institute, 1051 Riverside Drive, Unit 50, New York, NY, 10032. Supported by NIH Grant MH42931. *See also:*
automated version (AutoMEQ) at www.cet.org.

Horne JA and Östberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. International Journal of Chronobiology, 1976: 4, 97-100.

Leave this section blank: _____

4. How easy do you find it to get up in the morning (when you are not awakened unexpectedly)?

   - ❑ Very difficult 1
   - ❑ Somewhat difficult 2
   - ❑ Fairly easy 3
   - ❑ Very easy 4

5. How alert do you feel during the first half hour after you wake up in the morning?

   - ❑ Not at all alert 1
   - ❑ Slightly alert 2
   - ❑ Fairly alert 3
   - ❑ Very alert 4

6. How hungry do you feel during the first half hour after you wake up?

   - ❑ Not at all hungry 1
   - ❑ Slightly hungry 2
   - ❑ Fairly hungry 3
   - ❑ Very hungry 4

7. During the first half hour after you wake up in the morning, how do you feel?

   - ❑ Very tired 1
   - ❑ Fairly tired 2
   - ❑ Fairly refreshed 3
   - ❑ Very refreshed 4

8. If you had no commitments the next day, what time would you go to bed compared to your usual bedtime?

   - ❑ Seldom or never later 4
   - ❑ Less that 1 hour later 3
   - ❑ 1-2 hours later 2
   - ❑ More than 2 hours later 1

9. You have decided to do physical exercise. A friend suggests that you do this for one hour twice a week, and the best time for him is between 7-8 a.m. Bearing in mind nothing but your own internal "clock," how do you think you would perform?

Leave this section blank: _____

- ❑ Would be in good form 4
- ❑ Would be in reasonable form 3
- ❑ Would find it difficult 2
- ❑ Would find it very difficult 1

10. At *approximately* what time in the evening do you feel tired, and, as a result, in need of sleep?

- ❑ 8:00 p.m. – 9:00 p.m. 5
- ❑ 9:00 p.m. – 10:15 p.m. 4
- ❑ 10:15 p.m. – 12:45 a.m. 3
- ❑ 12:45 a.m. – 2:00 a.m. 2
- ❑ 2:00 a.m. – 3:00 a.m. 1

11. You want to be at your peak performance for a test that you know is going to be mentally exhausting and will last two hours. You are entirely free to plan your day. Considering only your "internal clock," which one of the four testing times would you choose?

- ❑ 8 a.m. – 10 a.m. 6
- ❑ 11 a.m. – 1 p.m. 4
- ❑ 3 p.m. – 5 p.m. 2
- ❑ 7p.m. – 9 p.m. 0

12. If you got into bed at 11 p.m., how tired would you be?

- ❑ Not at all tired 0
- ❑ A little tired 2
- ❑ Fairly tired 3
- ❑ Very tired 5

13. For some reason you have gone to bed several hours later than usual, but there is no need to get up at any particular time the next morning. Which one of the following are you most likely to do?

Leave this section blank:

- ❑ Will wake up at usual time, but will not fall back asleep 4
- ❑ Will wake up at usual time and will doze thereafter 3
- ❑ Will wake up at usual time, but will fall asleep again 2
- ❑ Will not wake up until later than usual 1

14. One night you have to remain awake between 4-6 a.m. in order to carry out a night watch. You have no time commitments the next day. Which one of the alternatives would suit you best?

- ❑ Would not go to bed until the watch is over 1
- ❑ Would take a nap before and sleep after 2
- ❑ Would take a good sleep before and nap after 3
- ❑ Would sleep only before the watch 4

15. You have two hours of hard physical work. You are entirely free to plan your day. Considering only your internal "clock," which of the following times would you choose?

- ❑ 8 a.m. – 10 a.m. 4
- ❑ 11 a.m. – 1 p.m. 3
- ❑ 3 p.m. – 5 p.m. 2
- ❑ 7p.m. – 9 p.m. 1

16. You have decided to do physical exercise. A friend suggests that you do this for one hour twice a week. The best time for her is between 10-11 p.m. Bearing in mind only your internal "clock," how well do you think you would perform?

- ❑ Would be in good form 1
- ❑ Would be in reasonable form 2
- ❑ Would find it difficult 3
- ❑ Would find it very difficult 4

Leave this section blank: _____

17. Suppose you can choose your own work hours. Assume that you work a five-hour day (including breaks), your job is interesting, and you are paid based on your performance. At *approximately* what time would you choose to begin?

- ❑ 5 hours starting between 4:00 – 8:00 a.m. 5
- ❑ 5 hours starting between 8:00 – 9:00 a.m. 4
- ❑ 5 hours starting between 9:00 a.m. – 2:00 p.m. 3
- ❑ 5 hours starting between 2:00 – 5:00 p.m. 2
- ❑ 5 hours starting between 5:00 p.m. – 4:00 a.m. 1

18. At *approximately* what time of day do you usually feel your best?

- ❑ 5:00 a.m. – 8:00 a.m. 5
- ❑ 8:00 a.m. – 10:00 a.m. 4
- ❑ 10:00 a.m. – 5:00 p.m. 3
- ❑ 5:00 p.m. – 10:00 p.m. 2
- ❑ 10:00 p.m. – 5:00 a.m. 1

19. One hears about "morning types" and "evening types." Which one of these types do you consider yourself to be?

- ❑ Definitely a morning type 6
- ❑ Rather more a morning type than an evening type 4
- ❑ Rather more an evening type than a morning type 2
- ❑ Definitely an evening type 0

Total: _____

NCPA 2014
Workshop on
LIGHT THERAPY
with
Michael Terman PhD
and
Gregory Sahlem MD

RESOURCE FOLDER

LITERATURE

1. Terman M, Terman JS (2013) Chronotherapeutics: Light therapy, wake therapy, and melatonin. In *Clinical Handbook for the Management of Mood Disorders*, Mann JJ, Roose SP, McGrath PJ, eds. Cambridge, Cambridge University Press, pp. 332-344
2. Wirz-Justice A, Benedetti F, Terman M (2013): *Chronotherapeutics for Affective Disorders* – Flyer and Contents
3. Terman M, McMahan I (2013): *Reset Your Inner Clock* – Flyer and Contents
4. Sahlem G et al (2014, in press): Adjunctive triple chronotherapy … rapidly improves mood and suicidality in suicidal depressed inpatients. *J Psychiatric Res*

ASSESSMENT

1. Preliminary screening questionnaire for light therapy outpatients
2. Terman M, Williams JBW (1993) Personal Inventory for Depression and SAD
3. Morningness-Eveningness Questionnaire, Self-Assessment Version (MEQ-SA)
4. The Columbia Eye Exam for Users of Light Treatment
5. Remé CE, DeLeo V: Bright Light Exposure Risks

PROTOCOL

1. Instructions [to patients] for conducting light therapy sessions
2. How To Position Your Light Box (Daylight Classic 10,000 lux, Model 930)
3. Daily Sleep, Mood, and Energy Log
4. Simplified Daily Log
5. Saliva Melatonin: Home Collection Procedure

EQUIPMENT & SUPPLIES

1. Resources for purchase of chronotherapy equipment and supplies
2. Light box insurance reimbursement endorsement

Chapter 26

Chronotherapeutics

Light therapy, wake therapy, and melatonin

Michael Terman and Jiuan Su Terman

Introduction

Antidepressant chronotherapy uses light, dark, and sleep interventions that impact the circadian timing system. The human hypothalamic inner clock is genetically programmed to time a cycle that deviates from 24 hours, with outputs to a host of physiological endpoints. Primary examples are body temperature, sleep and wakefulness, and cortisol and melatonin hormone production. The clock conforms to the solar day by sensing the pattern of light and darkness, creating cohesive temporal organization of physiological function. Multiple factors can disturb this harmony, however, among them sleep disturbance, work schedules, seasonal changes in day length, and artificial lighting. Sleeping out of synchrony with the circadian clock is closely tied to mood disorders (Wirz-Justice *et al.* 2009a). The goal of chronotherapy is to bring the ensemble of external and internal cycles into alignment.

Light therapy

Light therapy, first explored in the late 1970s (Kripke *et al.* 1983, Rosenthal *et al.* 1984) is the first somatic antidepressant treatment to have been born of a biological hypothesis rather than discovered by serendipity in the course of drug testing or brain stimulation (Wirz-Justice *et al.* 2004). The hypothesis arose from the observation of photoperiodism in animals – for example, seasonal variation in reproductive behavior tied to the length of the night and the duration of pineal melatonin production. There seemed to be a parallel in unipolar and bipolar patients who show more depression in winter than summer. It was plausible to hypothesize that daylight manipulations would affect mood state. By lengthening the day (shortening the night) with artificial light exposure, there were rapid remissions from winter depression (Rosenthal *et al.* 1984, Terman *et al.* 1989b).

Hotly debated for several years, a placebo explanation was hard to rule out, since, by definition, the active treatment is visible. Four kinds of controls provided supporting evidence, equating for subjects' expectations: dim or colored light vs. bright white light; brief vs. longer sessions; evening vs. morning light exposure; and a nonphotic, inert comparator treatment using deactivated or low-density negative air ionizers (Wirz-Justice, 1998).

Light therapy has seen increasing use in clinical practice, often in conjunction with antidepressant medication, but also as monotherapy. At the start of citalopram treatment, for example, augmentation with light therapy can expedite improvement (Benedetti *et al.* 2003) and prevent relapse under drug maintenance (Martiny *et al.* 2004). Light therapy is useful not only for seasonal affective disorder, but also for nonseasonal chronic, recurrent, bipolar, premenstrual, and gestational depression (Terman, 2007). The treatment protocol is similar in all cases.

Light therapy devices and the mode of administration are unregulated, however. This has made it popular for unsupervised self-treatment, with the attendant liabilities of unskilled, arbitrary dosing, unsupervised combination with drug treatment, absence of monitoring, and risky outcome. Inappropriate administration can exacerbate depression and sleep disturbance, and trigger adverse events such as headache, nausea, and agitation. Clinical guidance is important. Although the protocol is not complicated, it requires that clinicians learn the principles of circadian timing in order to supervise effectively.

Clinical Handbook for the Management of Mood Disorders, ed. J. John Mann, Patrick J. McGrath, and Steven P. Roose. Published by Cambridge University Press.

Wake therapy

That a night of sleep deprivation resulted in immediately improved mood state was first reported by a patient in the 1960s who would ride her bicycle all night to lift her depression (Schulte, 1966). Hundreds of cases have since been studied, with a majority showing improvement after a single night awake – *the fastest turnaround known to psychiatry* (Wirz-Justice *et al.* 1999). Rapid relapse upon recovery sleep, however, made the protocol useless in clinical practice.

The key, discovered 30 years later, was the application of two new chronotherapeutic methods immediately following nights of sleep deprivation (now rechristened *wake therapy*): *morning light therapy* coupled with *earlier recovery sleep* (also called sleep phase advance) (Wirz-Justice *et al.* 2009b). The combined protocol is termed *triple chronotherapy*. The overnight remission was sustained, and the course of inpatient treatment completed in a week or less, with durable maintained response.

Benedetti (2007) provides a comprehensive review of the components of triple chronotherapy, their efficacy in various patient populations, and their neurochemical, anatomical, and genetic mechanisms of action, which parallel the action of antidepressant drugs, but on an accelerated time course. For example, Wu *et al.* (2009) found that depression in bipolar patients was significantly improved relative to a medication control group after a single night awake followed by 3 days of phase-advanced recovery sleep and morning light therapy. At the 7-week endpoint, 63% of patients maintained remission. Similar results were obtained for patients with unipolar depression who began duloxetine treatment with a course of three wake therapy nights interspersed with earlier recovery sleep and initiation of daily morning light therapy, compared with a medicated control group that engaged in daily exercise (Martiny *et al.* 2012).

An earlier study of bipolar depression that combined wake and light therapy without sleep phase advance found 57% maintained remission after 9 months in patients without a history of drug resistance, but a far lower success rate of 17% in drug-resistant cases (Benedetti *et al.* 2005). Two studies of bipolar (Benedetti *et al.* 2001) and unipolar (Voderholzer *et al.* 2003) patients without light therapy demonstrated the benefit of the sleep phase advances across 3 nights following a single night of wake therapy, with remission sustained at the end of the 7-day hospital stay.

Melatonin

Above and beyond its role in photoperiodism, this hormone – a nocturnal product of the pineal gland – is temporally associated with sleep, although it does not trigger sleep in the same sense as pharmaceutical hypnotics (Wirz-Justice and Armstrong, 1996). Use of melatonin as a hypnotic shortly before bedtime is generally ineffective because it overlaps pineal melatonin production.

Recent research on melatonin administered before pineal production begins has revealed its potent function as a *chronobiotic* that acts directly on the circadian timing system to shift the internal clock earlier when taken in the afternoon or evening. When administered early in the morning, it shifts the clock later in a symmetrical fashion (Lewy *et al.* 1998, Burgess *et al.* 2008). Exogenous melatonin serves essentially as a complement to timed light administration, but without direct antidepressant effect. For patients with major sleep phase delays, the combination of low-dose melatonin in the evening with light therapy in the morning can expedite the course of treatment (Terman and Terman, 2010a, Figure 149–4).

Light therapy

Figure 26.1 outlines diagnostic steps, dosing strategy, and treatment management.

Preparatory diagnostics

Before beginning light therapy, triple chronotherapy, or melatonin administration, the clinician needs to estimate circadian rhythm status and its relation to the current sleep pattern – information key to all the procedures.

Circadian phase assessment

Although impractical for clinical use, the laboratory standard for circadian phase determination is *pineal melatonin onset*, obtained by saliva sampling over several hours before habitual sleep onset, and analyzed by radioimmunoassay. As an expedient, a 19-item chronotype questionnaire (Terman *et al.* 2001) is used to assess the daily pattern of behavior changes that reflect the underlying circadian rhythm. The chronotype score provides an estimate of melatonin onset, with a large effect size of about $r = 0.75$ (Terman and Terman, 2010a). The chronotype score range of

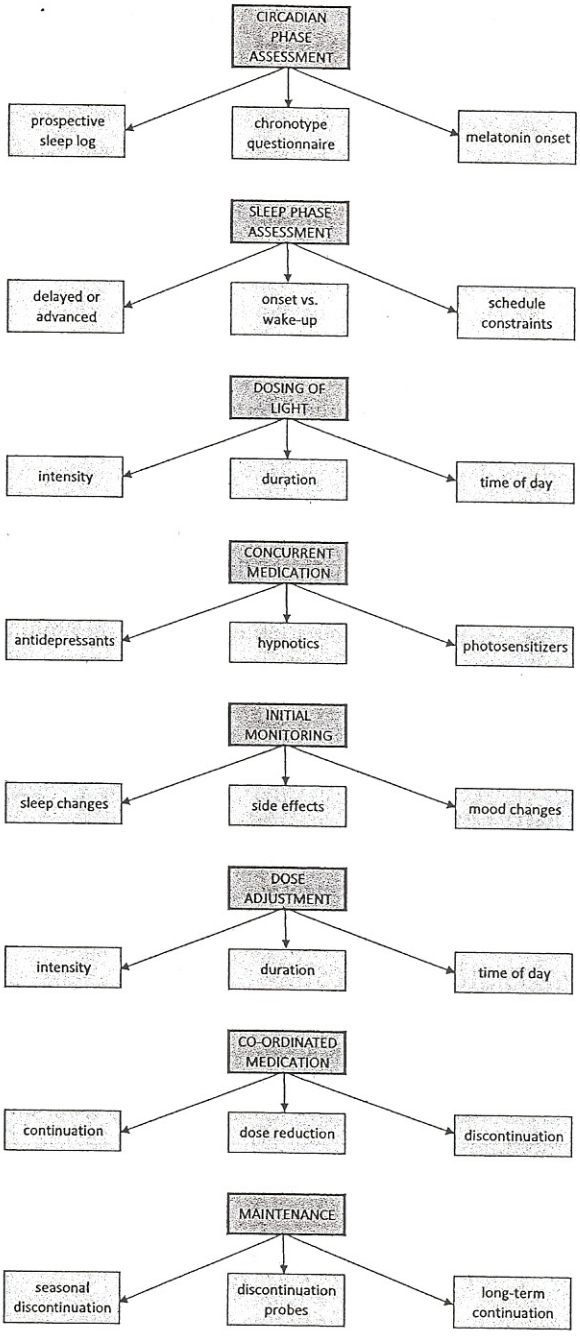

Figure 26.1 Management sequence for light therapy administration

16 to 84 corresponds to a melatonin onset range of 6 PM to 12 AM (higher score, earlier onset). The score is used to specify the optimum time to begin morning light therapy and promote circadian rhythm phase advances – about 8.5 hours after melatonin onset. The questionnaire is most easily completed on the Web (Terman and White, 2003), which provides instant scoring and interpretation, and a printout summary for the patient to bring to the appointment. A patient's score may fall at any point along the spectrum of early to late chronotype – it need not be at the late end to use morning light therapy. (An exception is for unusual patients with advanced sleep phase disorder who fall asleep in the evening with final awakening in the middle of the night.)

Sleep phase assessment

Mere description of the generalized sleep pattern is often uninformative, with distorted retrospective generalizations (even for the past week) that are not useful for setting the schedule of light therapy. For 7 to 10 days before the appointment, the patient prepares a daily sleep log in graphic format (Wirz-Justice *et al.* 2009b, Appendix 5) that can be quickly reviewed in the office. The clinician notes and discusses the reasons for variability in sleep onset, night-time interruptions, duration, wake-up time, and napping. For example, extended weekend sleep may result from forced early awakening on workdays. Late bedtime may be the consequence of evening activities, meals, and light exposure, with sleep debt that accumulates toward the weekend.

Sleep timing in depressed patients may be advanced or delayed relative to the 11 PM to 7 AM norm. The delay tendency is seen most frequently in seasonal, atypical, and bipolar depression. The determination of sleep phase is easily confounded by depressive hypersomnia, when the patient goes to sleep far earlier than when in remission, awakens far later, or both. Late wake-up requires caution: light therapy should not begin more than 1 hour before current wake-up time, or it may exacerbate the delayed sleep pattern.

Although the circadian clock heavily influences sleep timing, actual bedtime is complicated by social pressures, work schedules, medications, ... and depression itself. Since the efficacy of light therapy is anchored to circadian timing, chronotype is key to establishing the treatment schedule. But the clinician needs to reconcile mismatches of the sleep pattern with the patient's chronotype, and sometimes coach sleep hygiene in preparation for light therapy.

Table 26.1 A patient's response to variations in intensity, duration, and timing of light therapy

Light intensity/Condition	Session duration	Session time of day	Depression severity score[a]
Baseline	–	–	41
2500 lux	2 hours	Evening	43
2500 lux	2 hours	Morning	8[b]
2500 lux	1 hour	Morning	15
2500 lux	30 minutes	Morning	33
10 000 lux	30 minutes	Evening	33
10 000 lux	30 minutes	Morning	2[b]
Final withdrawal	–	–	37

[a] *Structured Interview for the Hamilton Depression Rating Scale – Seasonal Affective Disorder Version* (SIGH-SAD) (Williams *et al.* 2002). This instrument has been updated as the *Structured Interview for the Hamilton Depression Rating Scale with Atypical Depression Supplement* (SIGH-ADS) (Williams and Terman, 2003).
[b] Meets remission criteria (at least 50% improvement to a SIGH-SAD score of 8 or less).

Dosing and timing strategy

Light

The three major dosing parameters that comprise the treatment regimen – which are mutually interactive – are light intensity, exposure duration, and the circadian time of the daily session. Circadian time is specified as the interval between evening melatonin onset and the start time of the morning light therapy session. As a generalization, higher light intensity – measured as illuminance in lux – requires shorter exposure duration. The circadian rhythm and antidepressant effects of these lighting parameters are strongly modulated by the time of day of treatment, with the impact waning after the early morning hours.

In contrast to common drug-dosing strategy, light therapy does not require increments from the low end of dosing range to find the optimum level for individual patients. Because of the favorable side-effect profile, quicker progress is made by starting in the middle range and working in either direction, as the case dictates. A common starting point is 10 000 lux white light, the highest level that has been verified for safety and efficacy, in 30-minute sessions. Duration is then adjusted downward (as far as 10 minutes) if there are side effects, or upward (as far as 60 minutes) if progress is slow. If the patient experiences glare sensations or other visual discomfort at 10 000 lux, the level can be reduced as low as 2500 lux by varying the distance of the light box from the eyes, but this will require compensatory lengthening of session duration.

A single-case research example demonstrates the effect of dosing manipulations, which have been verified in group studies (Terman *et al.* 1989b, Terman *et al.* 1990). The 28-year-old patient had experienced a multi-year, unmedicated history of fall–winter depression, which remitted with euthymia in spring and summer. She underwent a series of 10-day light therapy and withdrawal phases throughout the winter, in which the intensity, duration, and time of treatment were varied in a randomized sequence. Light intensity was 2500 or 10 000 lux; session duration, 30 minutes to 2 hours; with morning sessions upon habitual awakening or evening timing 2 hours before bedtime. When she showed a positive response in any condition, she discontinued treatment and the next condition was delayed until relapse occurred. Table 26.1 summarizes the results.

As morning session duration decreased from 2 hours to 30 minutes at 2500 lux – the intensity used in the earliest clinical trials (Terman *et al.* 1989b) – the antidepressant effect waned. And regardless of intensity, evening light was not beneficial.

The dosing strategy for light is more cautious for bipolar I than for bipolar II and unipolar disorders, given the risk of switching. Switches to mania are exceedingly rare for patients using lithium or other stabilizing medication – although one study has noted mixed states that resolved with reductions in light dose (Sit *et al.* 2007). A bipolar I patient may begin at 7000 lux for 10 minutes at midday. If tolerated, the session can be moved earlier, the duration lengthened, and the light intensity increased to 10 000 lux.

Light therapy in seasonal, nonseasonal, and bipolar depression appears most effective when administered about 8.5 hours after evening melatonin onset, shortly after awakening (Terman *et al.* 2001). The chronotype questionnaire estimates melatonin onset and specifies

the time of the morning light therapy session (as specified in the printout summary). For example, session time for a low chronotype score of 35 would be 7:30 AM, while a score of 55 would shift the session earlier to 6:15 AM (Terman and White, 2003). For patients who sleep longer than 7 hours, the treatment schedule requires earlier wake-up; in some cases, the need for sleep is reduced as the antidepressant response emerges, while in others the patient compensates with earlier bedtime. The treatment time may seem too early to manage for some patients, in which case it can be delayed for up to an hour. However, treatment should never be started *earlier* than the time specified by the questionnaire result, because – falling into the circadian night period – it risks a countertherapeutic *delay* in circadian rhythms, similar to what occurs with evening light exposure. Patients with irresistible late awakening can gradually shift the morning light session earlier as the circadian phase advances take hold.

For patients with late insomnia – waking far too early, as in the classic melancholic pattern – the priority after wake-up is to *restrict* light stimulation, with light therapy delayed to later in the morning. The same is true for patients with enforced early awakening due to their work schedule. In both cases, it is useful to wear blue-blocking glasses (see the section on Resources) to reduce the countertherapeutic effect of prematurely early light exposure, and not to remove the glasses until light therapy would have been scheduled. (Unlike sunglasses, the blue-blockers maintain clear visibility.)

If the patient is already at work when light therapy is scheduled, treatment may need to be postponed. It can begin on weekends or days off as a boost toward phase-advancing the circadian rhythm. Adjustment can be expedited with microdose, controlled-release melatonin, and blue-blockers in the evening hours before bedtime (see section on Melatonin as a chronobiotic, below). Daily light therapy can then begin when wake-up adjusts to the targeted circadian time.

Medication

There are few contraindications to the use of light therapy, which is compatible with most psychiatric medications. As a rule, we do not alter the drug regimen when starting light therapy, but rather wait to see if there is distinct improvement after introducing the treatment. If a patient is on an established medication regimen, it should not be tapered or discontinued in preparation for light therapy. (Note, however, that hypnotic or sedating psychotropic drugs can impose a sleep pattern that presents a problem for scheduling light therapy according to the circadian clock (see below).) If improvement under light therapy is dramatic, it is reasonable to consider drug tapering. Sometimes discontinuation is possible, while other times the dose can be reduced. Frequently, in cases of polypharmacy, drugs suspected of inaction can be dropped with others maintained.

Antidepressants

Case evidence demonstrates that patients who have discontinued antidepressant medication because of nonresponse can then respond to light therapy, while partially responsive or drug-resistant patients can respond in full with adjunctive light therapy (Papatheodorou and Kutcher, 1995, Beauchemin *et al.* 1997, Terman, 2007). Patients often seek to reduce their medication burden if light therapy works, but lacking clinical trials, clinicians often prefer to maintain combination treatment.

Frequently, patients seek light therapy, or the clinician may suggest it, because ongoing medications have been inadequate, the sleep pattern is obviously delayed, or there is extreme difficulty awakening, suggestive of a circadian rhythm disturbance. On the other side of the coin, if light therapy shows only partial benefit – especially after attempts at increased session duration and timing – medication can be added, with the caution that it may interact with light therapy and require lower dosing than otherwise.

When medication is indicated, light therapy can serve as a booster at drug start-up, accelerating improvement until the delayed drug effect sets in. At that point, light therapy might be discontinued (Martiny *et al.* 2012). While some patients perceive the morning light session as a schedule burden (and would prefer medication if effective), others enjoy the routine (quiet time, e-mail time, newspaper time, breakfast time), and are relieved to be free of medication.

Drug-naïve patients who show rapid, lasting remission with light therapy demonstrate that monotherapy can succeed, as exemplified by numerous studies of winter depression that excluded the use of antidepressant drugs (Terman *et al.* 1989, Wirz-Justice, 1998). In our experience, about 30% of patients seeking chronotherapy at our clinic have never used antidepressants, and we withhold that option until light therapy has been tested.

Hypnotics

Hypnotic medication complicates the dosing strategy for light therapy because it forces sleep out of synchrony with the circadian activity/rest rhythm. While early insomnia can have multiple causes including anxiety and depression, it often arises from delayed circadian rhythms. The patient might fall asleep easily at 2 AM, for example, but is pressured to sleep earlier because of the workday schedule. Chronotype estimates and sleep log data are distorted by the masking effect of hypnotics, which interferes with optimum scheduling of light therapy.

Patients want to be freed of hypnotics, but tapering usually is infeasible as preparation for morning light therapy. If, under hypnotic medication, the patient sleeps from 11 PM to 7 AM, pineal melatonin onset at the start of the circadian night might occur well after sleep onset, and the circadian signal for awakening might occur well after 7 AM. Light therapy upon awakening – in the middle of the circadian night – would further delay the rhythm, magnifying the problem. Short of abandoning light therapy, it can be scheduled later in the morning and gradually moved earlier until the sensation of sleepiness precedes taking the sleeping pill. At that point, the medication taper can begin with lower risk of insomnia relapse.

Photosensitizers

Several medications – psychiatric and nonpsychiatric – are known to induce damaging photosensitization of the skin, retina, or lens at the short-wavelength, violet-blue end of the visible spectrum – a major component of white light. This effect differs from ultraviolet photosensitization, which is controlled by the diffusion filter on the light box. Blue photosensitizers include the following drug groups: neuroleptic, porphyrin, psoralen, antiarrhythmic, antimalarial, and antirheumatic. In addition, St. John's Wort (*Hypericum*) photosensitizes in the longer-wavelength, green spectral range. When such photosensitizing drugs cannot be replaced with a benign alternative, light therapy should be avoided.

Treatment management

Initial monitoring

Light therapy often has accelerated action compared with the rate of response to antidepressant drugs. This creates a need for frequent clinical monitoring in the week or two after start-up. Apart from side effects seen in about 5% of cases (mainly mild nausea, headache, and agitation; Terman and Terman, 1999), the clinician needs to look for the emergence of awakening more than 30 minutes before the scheduled light therapy session. Such early awakening indicates too large of a circadian rhythm phase advance, and can lead to increased sleep debt, or a bipolar switch, and greatly concern the patient even if mood is improving.

Changes in mood state and sleep can occur within a day, so the standard schedule of office visits will not serve. To ensure vigilance, the patient continues the daily sleep log prepared for the initial evaluation, noting the light therapy session times, medications, and mood and energy ratings. The form is e-mailed or faxed to the doctor's office as frequently as twice a week to detect major sleep disruption, resumption of sleep after the light therapy session, or labile mood. The patient also submits log updates immediately if there is any sudden change. This initial feedback is critical for making rapid adjustments of the three dosing variables – intensity, duration, and time of day. The patient is instructed not to change these conditions without consulting, and to avoid inadvertent overdose. For example, unless instructed otherwise, patients with initial positive response may start extending session duration and become overexcited.

Dosing and timing adjustment

If the depression does not improve, session duration can be increased from 30 to 45 minutes, and then to 60 minutes, but not faster than every 4 days. If there are adverse effects, the first move is a reduction in session duration, a switch to lower light intensity, or both. Intensity level may be switchable on the device, or the screen can be moved farther from the eyes. The distance factor is sensitive, since lux falls off rapidly – not linearly – with distance from the light source.

Adjusting the time of day of the light therapy session is more of a challenge than adjusting intensity or duration, because there is no direct information about changes in circadian rhythm phase once treatment has begun. We aim for solid sleep until 15 minutes or less before the scheduled session. If the patient starts waking far earlier, the session should be delayed about an hour. This may be difficult if the patient needs to leave hours beforehand, in which case reducing session duration (e.g., from 30 to 20 minutes) or light intensity (e.g., from 10 000 to 2500 lux) may suffice.

When dealing with a very late sleep pattern, the aim to is move wake-up and the light therapy session

toward a normal sleep/wake pattern. Often this can be achieved with 30-minute steps earlier, every 3 to 5 days, with complete adjustment in 2 weeks or less. If the progression earlier is too fast, it may trigger a relapse into the delayed state. In such cases, the process needs to start again with a slower progression.

Clearly, management of time of day of treatment requires that the patient comply with the schedule, noting "real" (rather than ideal) times of treatment on the log, and avoiding day-to-day variations as much as possible. In the absence of self-control it is difficult for the clinician to guide timing adjustments. The first few days of light therapy are often the hardest, especially when the patient finds earlier waking not the priority of moment. Encourage the patient that this challenge will pass as the treatment effect sets in. When convenient – and especially when oversleeping seems uncontrollable – it helps to have a family member monitor waking for the light therapy session for the first week.

Maintenance

Every patient asks how long it will be necessary to continue treatment once there is a positive response. For winter depression, the answer – from experienced patients who have continued with self-treatment – is fairly clear: the end of April at northerly US latitudes, by which time most people are waking up to daylight (Terman *et al.* 1994). The exception is for patients who historically show unusually early spontaneous remission (for example, in February, as the solstice period ends), or those who break the cycle with a vacation south in March.

There is little downside to attempting discontinuation of light therapy, since resuming the treatment rapidly recaptures the effect. Tapering is unnecessary, and does not improve outcome. Within the winter depression season, if a patient achieves complete remission, it becomes important to know whether a weekend or a week away from light therapy is possible without slumping or relapse. This has been tested early in the season following initial response in a 1-week trial (Terman *et al.* 1994). Some patients slumped noticeably within a day, most showed a relapse into a major depressive episode within a week, and a small number coasted as long as 3 weeks before relapse, but not longer. Ultimately, a maintenance schedule is needed.

The required dose of light can vary within an episode, and patients learn to sense changing needs without guidance. January and February are usually the most difficult months, even when the seasonal relapse occurred earlier in the fall. Long after the supervised start-up period, patients may sense, for example, that 30 minutes at 10 000 lux at 6:30 AM is losing effectiveness, with noticeable fatigue and malaise short of relapse. By switching to 45-minute sessions, the slump immediately resolves. By mid-March, 45 minutes may feel "too much," with onset of sleep interruptions and morning irritability. Switching back to 30 minutes can fix the problem in a few days.

The ultimate goal of light therapy is intelligent self-treatment. The clinician cannot be there to micromanage.

Patients with nonseasonal depression who have responded to light therapy should maintain treatment for at least 2 months before attempting discontinuation. Again, resumption is simple, and it should not wait for a relapse, but rather an anticipatory slump. Patients sometimes "forget" their light therapy and fall back into depression within 3 days, to the point that they do not "remember" to resume treatment. Family members should watch out for such lapses and take initiative – the patient may no longer be in active contact with the clinician.

Of course, the clinician may have to be contacted when such relapses occur. It is very difficult to make specific recommendations without a current assessment of the sleep/wake pattern. The best one can advise is resuming the same schedule as before the treatment lapse. This may not be optimal, because sleep, circadian rhythm phase, or both may have drifted into a new pattern – with respect to time of day as well as to each other. Thus, patients should maintain their logs for at least half a year. Some have logged for years; they find it fascinating and instructive. To quote one, "When things fall apart and I'm in a state of confusion, I look back into my logs to see how we handled this in the past, and that works."

Triple chronotherapy

Light therapy has been used successfully with hospitalized patients in conjunction with standard medications and electroconvulsive therapy when the latter have produced insufficient improvement (Terman, 2007). On admission, prospective sleep logs will be unavailable, so decisions for timing must be made from the interview evaluation of the sleep pattern and

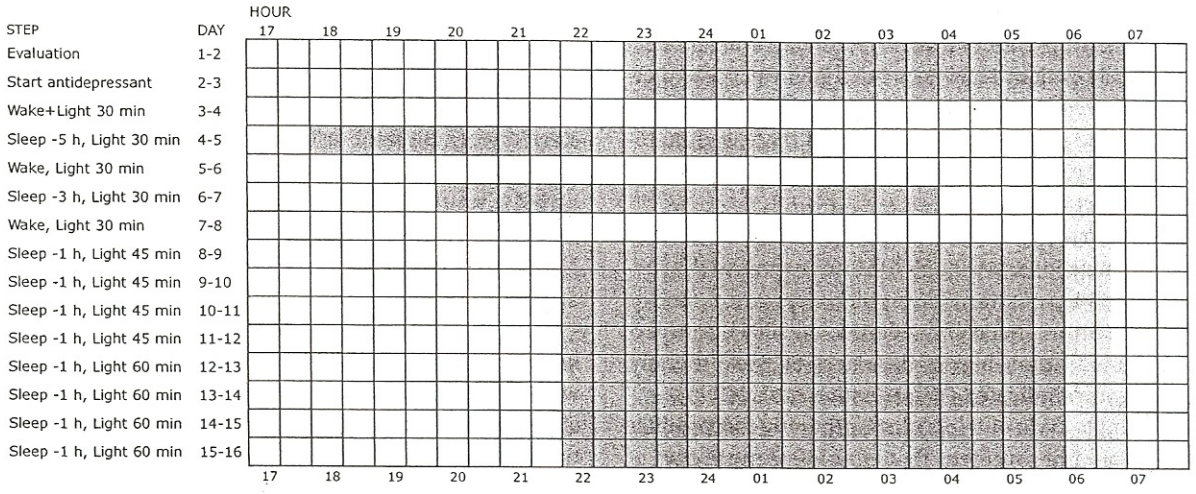

Figure 26.2 Inpatient protocol for a three-cycle sequence of wake therapy, light therapy, and sleep phase advance. The need for repeated wake therapy depends on the speed of improvement, and can be limited to one or two cycles if there is rapid remission. Dark gray spaces, sleep; light gray spaces, light therapy

the chronotype score. Importantly, the staff need to allow the patient to maintain the habitual sleep pattern regardless of the unit's standard lights-out and lights-on schedule, withhold early-morning vital signs when the patient is still asleep, and allow flexible mealtimes. The staff also need to begin an observational sleep log to guide dosing adjustments of light therapy. Alert patients can begin a self-report log.

Light therapy on the hospital unit is just one of a set of chronotherapeutic techniques that together can form the primary intervention. The elaborated protocol is termed *triple chronotherapy*, and includes:

- *Wake therapy.* Patients stay awake through the night, which can present a challenge. (See Wirz-Justice *et al.* 2009b for tips on avoiding sleep.) When the morning arrives, it becomes easier to remain awake because the circadian clock has signaled daytime wakefulness. The objective is for patients to remain awake up to 34 hours or longer despite accumulating sleep deprivation.
- *Recovery sleep with phase advance.* Toward the end of the day, but several hours *before* their usual bedtime, they go to sleep, compensating for their sleep loss the night before. Then, after sleeping about 8 hours, they wake up earlier, in the second half of the night
- *Light therapy.* Starting on the morning after the first wake therapy night, they do 30 minutes of light therapy, scheduled 60 minutes earlier than their baseline wake-up time.

The primary manipulation is *wake therapy* (less enthusiastically termed sleep deprivation), which has long been known to produce overnight remission of depression in a majority of hospitalized patients with bipolar or unipolar depression (Wirz-Justice and van den Hoofdakker, 1999). Although this is the fastest known therapeutic reversal of clinical state known to psychiatry, it comes with a liability: the next night's recovery sleep is likely to produce a relapse. By itself, then, wake therapy is not clinically useful.

Triple chronotherapy was developed to forestall the next day relapse and facilitate an enduring remission within a week. The initial response is maintained with daily light therapy starting at the end of the first wake therapy night, and a progression of earlier recovery sleep periods that converge on a normal sleep pattern over the week. Figure 26.2 outlines the protocol.

At entry, the patient is allowed to sleep habitual hours. Timing of the chronotherapies is anchored to habitual sleep time and the chronotype score. Treatment begins with a night of wake therapy followed by the first light therapy session, and light therapy continues each morning. Bedtime the next day is 5 hours earlier than normally (a sleep phase advance), with wake-up during the second half of the night, and light therapy in the morning. The remaining protocol varies individually, based on remission, partial improvement, nonresponse, worsening, or relapse following transient remission. With partial or no improvement, the

patient receives a second night of wake therapy followed by sleep 3 hours before habitual bedtime. If necessary, the patient receives a third night of wake therapy followed by sleep starting 1 hour before habitual bedtime. Light exposure duration is increased in 15-minute steps, up to 60 minutes if response continues to fall short of remission.

Concurrent medication during triple chronotherapy is discretionary, though lithium magnifies the success rate in patients with bipolar depression, and is highly recommended (Benedetti *et al.* 2001). Antipsychotic medication blocks the effect of wake therapy, and is contraindicated (Wirz-Justice *et al.* 2009b).

A single cycle of triple chronotherapy can produce such rapid improvement that after a few more days of observation the patient can be discharged. Others may need a second or third cycle of wake therapy – but the expected course of acute treatment can be completed within a week. The risk of bipolar switching, about 5%, is no higher than for serotonergic antidepressants (Wirz-Justice *et al.* 2009b). Duration of remission – up to 9 months or longer – compares favorably with standard treatment (Benedetti *et al.* 2005). Maintained light therapy has yet to be tested in controlled studies, but in principle it should reinforce the remission.

Case vignette: triple chronotherapy at an accelerated pace

Mr. B, aged 21, a patient of John F. Gottlieb, MD (Northwestern University), was a college student who experienced his first manic episode as a freshman after flying across time zones on winter vacation. He recovered in hospital. Later that year, he fell into depression, and was drinking, keeping irregular sleep hours, and ultimately not getting out of bed.

He began a course of triple chronotherapy – not in hospital, but supervised by clinic staff in a Chicago hotel suite. At entry, he scored 29 points on the SIGH-ADS scale (Williams and Terman, 2003). A rotation of nurses and graduate assistants stayed with him throughout the wake therapy phases, beginning with admission at 11 PM. Later, he recollected the experience (Terman and McMahan, 2012), "It was rough. It was really hard to do. I drank coffee, and I had cigarette breaks, and I was splashing water on my face." Starting the next morning, he used a 10 000-lux light box for 30 minutes at 7:30 AM, the time specified by his chronotype score (Terman and White, 2003). Recovery sleep began the next evening at 6 PM. He was awakened at 1 AM, with next sleep at 8 PM to 3 AM, and bedtime the following day at 10 PM (the target bedtime for maintenance).

"It was cool, the way it shocked my system. It started working a lot faster than I thought it would. I realized that I was feeling better in 24 hours. I was surprised I would be going home (so soon)." (His wake therapy monitors noted improvement in 18 hours.) He left in complete remission, with a SIGH-ADS score of 2.

Mr. B continued light therapy after discharge. "I know it's a big deal about wake-up time, and I always wake up at the same time and I try to be very good about that. I do the lights every morning (except sometimes). Sometimes I don't. If I've not done it for a few days, I'm a little more sluggish. But if I'm late for work in the morning, I only do 10 minutes instead of half an hour – but 10 minutes helps."

Melatonin as a chronobiotic

Hormone production and circadian timing

Pineal melatonin is produced on a nocturnal cycle triggered by the internal circadian clock, which in turn is synchronized to the day/night cycle by appropriately timed light exposure. The hypothalamic suprachiasmatic nuclei (SCN), home to the circadian pacemaker, are rich with melatonin receptors, creating a negative feedback loop (SCN/pineal/SCN) that stabilizes the body's rhythms. For late chronotypes – as we often see in depressive illness with early insomnia and difficulty awakening – the SCN-onset signal to the pineal gland occurs hours later than the norm, with sleep delayed another 2 hours. While the average onset of melatonin production is about 9:30 PM, patients can show onsets well past midnight – indeed, as late as early morning.

Considering the close association of melatonin production and sleep, it is not surprising that synthetic tablet melatonin (and recently developed pharmacologic agonists) have been used as sleep promoters, although not very effectively. The major reason for this failure is timing shortly before bedtime (as when using hypnotics). With endogenous pineal production having started far earlier than tablet ingestion, the hormone is already in circulation, and the exogenous dose has limited additional effect.

The circadian feedback loop holds the key to the solution. For tablet supplementation to expedite sleep

onset, it must be taken hours before spontaneous pineal production, when the daytime hormone level is at or near zero. The SCN responds by shifting its cycle toward the time of tablet ingestion. Optimum timing to achieve this effect is about 6 hours before current sleep onset (Lewy *et al.* 1998). Typical over-the-counter doses (0.5 to 5 mg), however, place far more hormone into the bloodstream than the pineal itself produces, and if taken 6 hours before bedtime can have a rapid hypnotic effect. Furthermore, controlled-release formulations at such high dose bleed over into the next day with a risk of hangover.

The therapeutic "microdose" regimen

The solution is to use a controlled-release microdose of melatonin 6 hours before bedtime. It binds to SCN receptors without producing sleepiness. As the circadian cycle shifts earlier, sleep onset also shifts, relieving the insomnia. The action is *chronobiotic* rather than hypnotic or soporific. The optimum physiologic dose is about 0.2 mg (see section on Resources). There is no perceptible sensation after taking the tablet, and the formulation ensures early-morning washout.

The endogenous melatonin cycle is intimately connected to the day/night pattern of light exposure, and thus to light therapy. Light therapy at the end of the circadian night serves to shift the internal clock earlier. Microdose melatonin acts the same way, but in *antiphase* with light – displaced by about 12 hours. It shifts the clock earlier when taken in the *evening*. In cases of extreme delayed chronotype – for example, with sleep onset at 3 AM – the combination of evening melatonin and morning light therapy can expedite response. The interval between presleep melatonin and morning light should not be shorter than 11 hours. As sleep moves earlier, melatonin and light administration can be moved earlier as an ensemble. After achieving a normalized sleep pattern, melatonin usually can be discontinued and the positive effect maintained with light therapy alone.

As a night-time hormone and physiological signal of darkness, melatonin circulates in the retina to support scotopic vision in dim light; exposure to bright light after taking the tablet can cause retinal photosensitization, while also working against the therapeutic circadian phase-advancing effect. Therefore, several additional measures are important after taking the melatonin tablet in the evening:

- Bright evening room and screen light (computer, screen reader, television) is contraindicated because it acts on the circadian cycle to delay rather than advance the sleep cycle. Room light fixtures should be placed on dimmers to allow visual comfort without excess illumination. Without dimming, low-color-temperature, soft-white bulbs rated at 2700 or 3000 K should be used. Computer displays should be controlled by a software program that reduces short-wavelength exposure while maintaining sharp visibility (see section on Resources). Screen-reader and television screen brightness should be reduced to the lowest comfort level.
- If going into bright artificial light, the action of melatonin can be protected by wearing blue-blocking glasses, whether singly or as fitovers on prescription glasses (see section on Resources).
- Caffeine should be avoided.
- Strenuous physical activity (for example, gym workouts) should be avoided.
- Dinner should be completed at least 3 hours before bedtime.

Future directions

Dawn simulation

Morning light therapy, with its antidepressant and circadian phase-shifting effects, is like walking outside into the sun after waking up. In fact, however, the action of morning light begins even earlier, during the twilight period preceding sunrise, when we are usually still asleep. Brought into the bedroom by lighting technology, the simulation of dawn triggers the same responses as post-awakening light therapy.

As we have seen, light exposure during the evening and morning has opposite effects on the circadian rhythm. Evening light leads to a delay, and morning light to an advance. Importantly, these effects are magnified when light is presented at different points during the night. (By "night," we mean the interval between sunset and sunrise, including the twilights.) As night-time progresses, phase delays to light exposure increase. Then at a certain point toward the end of the night, the process reverses, and light exposure leads to the largest *advance* shifts in the circadian cycle. This ability to phase advance then gradually tapers off as the morning hours proceed. Therefore, to achieve equivalent phase advances, less

light is needed before we wake up than later in the morning.

The graded circadian response to light at different times of day suggested to us that a mimic of dawn illumination in the bedroom, while the patient still sleeps, could produce an antidepressant response similar to post-awakening bright light therapy (Terman *et al.* 1989a). Our translucent, closed eyelids still transmit light to the retina.

We devised a bedroom apparatus to simulate a gradual springtime dawn with sunrise around 6 AM, while it remained dark outside in midwinter. Depressed mood improved within 1 to 2 weeks, even when patients slept through until the artificial sunrise. In parallel, their melatonin cycle shifted earlier. We replicated these effects in controlled trials, with no significant difference from post-awakening bright light therapy in an independent group (Terman and Terman, 2006, 2010b).

These findings led to a spate of untested commercial "dawn alarm clocks" that differ, however, from the clinical trial device by presenting a narrow field illumination at the side of the bed, which is easily missed by turning away on the pillow. Such alarm clocks have no demonstrated efficacy. A key to successful dawn simulation is broad-field diffuse illumination from *above* the bed. Such a system can be configured from current commercial components – a programmable controller coupled with an overhanging incandescent fixture that projects diffuse light toward the pillow (see section on Resources). Development of an integrated unit is underway. Initial installations will be installed in a group of residential facilities for the elderly, in Switzerland (Terman and McMahan, 2012).

Optimum dosing parameters have yet to be established for the rate of increase of the dawn signal from darkness and the overall level of the dawn signal compared to outdoor levels. The data show that an attenuated dawn signal is sufficient, rising at sunrise to standard room light level of about 300 lux.

Potential advantages of dawn simulation are its automated presentation during sleep, which eliminates the need to reserve a morning period for light therapy. It is useful also for patients vulnerable to drug photosensitization and those suffering retinal degenerative diseases for which bright light exposure is contraindicated. A disadvantage is for bed partners who want or need to sleep later than the simulated dawn.

Antimanic light protection

Switching to hypomania or mania is a common springtime event even in patients without seasonal affective disorder. This implicates the seasonal increase of early morning light exposure. A study of patients who had undergone long-term lithium therapy found reduced retinal sensitivity to light (reversible, not pathologic) – as if they were wearing "pharmacologic sunglasses" (Wirz-Justice *et al.* 1997). In an exploratory antimanic intervention, patients were restricted to a dark bedroom for 14 hours, and symptoms abated within the session – a time course similar to that when using antipsychotic medication (Barbini *et al.* 2005).

Exposure to short-wavelength light in the violet to blue-green range may contribute to manic switching. This is the same spectral range that has maximal effect on the circadian-timing system. Phase advances – accompanied by early awakening – have long been associated with mania. In an exploratory test, we have had patients in both euphoric and agitated manic states wear blue-blocking glasses (see section on Resources) throughout their waking hours, while maintaining standard sleep hours in a dark bedroom. They were calmed within one day. Controlled trials are still pending, but there is little downside to wearing blue-blockers as an adjunct to standard care.

Clinical pearls

- Bright light therapy acts in three inter-related ways: as an acute energizer, as a circadian rhythm phase-shifter, and as an antidepressant.
- Light exposure upon awakening acts to reduce early insomnia, stabilize irregular sleep patterns, and discourage oversleeping. Excessive light exposure in the evening, and light in the bedroom at night, has the opposite effect.
- The circadian timing system responds as if it were night to filtered light that eliminates the short-wavelength, blue range of the visible spectrum.
- A night awake can immediately terminate a depressive episode. Starting the next day, morning light therapy and earlier bedtime protect against relapse.
- For patients with a delayed sleep pattern, low-dose melatonin taken hours before sleep can act synergistically with morning light therapy

to reset circadian rhythms and expedite the antidepressant response.

Resources

The professional organization for clinicians using and learning chronotherapy is the Society for Light Treatment and Biological Rhythms (http://www.sltbr.org), which offers a CME course at its annual meeting. The nonprofit Center for Environmental Therapeutics (http://www.cet.org) offers the following resources:

- Recommended chronotherapy products (light box, dawn simulation system, blue-blocker glasses, blue-blocking computer screen software, and microdose melatonin).
- Guides to ocular safety and light box design standards.
- Online questionnaires for seasonality, chronotype, and depression severity, with personalized feedback.
- Clinical assessment instruments from the Columbia group (including structured interviews for depression and hypomania; diagnosis of chronotype, seasonality, and atypical depression; treatment-emergent effects; a sleep log; and a structured eye exam).
- A privacy-protected discussion forum for clinicians, at http://www.chronotherapeutics.org.

Patients value background understanding when entering chronotherapy, because of its novelty. For a layperson's overview of the literature and procedures, with interview-based case reports, see Terman and McMahan (2012).

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References

Barbini, B., Benedetti, F., Colombo, C. *et al.* (2005). Dark therapy for mania: A pilot study. *Bipolar Disorders*, 7, 98–101.

Beauchemin, K.M. and Hays, P. (1997). Phototherapy is a useful adjunct in the treatment of depressed patients. *Acta Psychiatrica Scandinavica*, 95, 424–427.

Benedetti, F., Barbini, B., Campori, E. *et al.* (2001). Sleep phase advance and lithium to sustain the antidepressant effect of total sleep deprivation in bipolar depression: New findings supporting the internal coincidence model? *Journal of Psychiatric Research*, 35, 323–329.

Benedetti, F., Colombo C., Pontiggia, A. *et al.* (2003). Morning light treatment hastens the antidepressant effect of citalopram: A placebo-controlled trial. *Journal of Clinical Psychiatry*, 64, 648–653.

Benedetti, F., Barbini, B., Fulgosi, M.C. *et al.* (2005). Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: Acute response and long-term remission rates. *Journal of Clinical Psychiatry*, 66, 1535–1540.

Benedetti, F., Barbini, B., Colombo, C. *et al.* (2007). Chronotherapeutics in a psychiatric ward. *Sleep Medicine Reviews*, 11, 509–522.

Burgess, H.J., Revell, V.L., and Eastman, C.I. (2008). A three pulse phase response curve to three milligrams of melatonin in humans. *Journal of Physiology*, 586, 639–647.

Kripke, D.F., Risch, S.C., and Janowsky, D. (1983). Bright white light alleviates depression. *Psychiatry Research*, 10, 105–112.

Lewy, A.J., Bauer, V.K., Ahmed, S. *et al.* (1998). The human phase response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. *Chronobiology International*, 15, 71–83.

Martiny K., Lunde M., Simonsen, C, *et al.* (2004). Relapse prevention by citalopram in SAD patients responding to 1 week of light therapy: A placebo-controlled study. *Acta Psychiatrica Scandinavica*, 109, 230–234.

Martiny, K., Refsgaard, E., Lund, V. *et al.* (2012). Nine-week randomized trial comparing a chronotherapeutic intervention (wake and light therapy) to exercise in major depression. *Journal of Clinical Psychiatry*, 73, 1234–1242.

Papatheodorou, G. and Kutcher S. (1995). The effect of adjunctive light therapy on ameliorating breakthrough depressive symptoms in adolescent-onset bipolar disorder. *Journal of Psychiatry and Neuroscience*, 20, 226–232.

Rosenthal, N.E., Sack, D.A., Gillin, J.C. *et al.* (1984). Seasonal affective disorder: A description of the syndrome and preliminary findings with light therapy. *Archives of General Psychiatry*, 41, 72–80.

Schulte, W. (1966). Kombinierte psycho- und pharmakotherapie bei melancholikern. In Kranz, H. and Petrilowitsch, N., eds., *Probleme der Pharmakopsychiatrischen Kombinations und*

Langzeitbehandlung. Basel: Rothenberger Gespräch, Karger, 160–169.

Sit, D., Wisner, K.L., Hanusa, B.H. *et al.* (2007). Light therapy for bipolar disorder: A case series in women. *Bipolar Disorders*, 9, 918–927.

Terman, J.S., Terman, M., and Amira, L. (1994). One-week light treatment of winter depression at its onset: The time course of relapse. *Depression*, 2, 20–31.

Terman, J.S., Terman, M., Schlager, D. *et al.* (1990). Efficacy of brief, intense light exposure for treatment of winter depression. *Psychopharmacology Bulletin*, 26, 3–11.

Terman, J.S., Terman, M., Lo, E.S. *et al.* (2001). Circadian time of morning light administration and therapeutic response in winter depression. *Archives of General Psychiatry*, 58, 69–75.

Terman, M. (2007). Evolving applications of light therapy. *Sleep Medicine Reviews*, 11, 497–507.

Terman, M. and White, T. (2003). *Automated Morningness-Eveningness Questionnaire* (AutoMEQ) [online]. New York: New York State Psychiatric Institute. Available: http://www.cet.org (accessed April 15, 2012).

Terman, M. and Terman, J.S. (1999). Bright light therapy: side effects and benefits across the symptom spectrum. *Journal of Clinical Psychiatry*, 60, 799–808.

Terman, M. and Terman, J.S. (2006). Controlled trial of naturalistic dawn simulation and negative air ionization for seasonal affective disorder. *American Journal of Psychiatry*, 163, 2126–2133.

Terman, M. and Terman, J.S. (2010a). Light therapy. In Krieger, M.H., Roth, T., and Dement, W.C., eds., *Principles and Practice of Sleep Medicine, Fifth Edition*, St. Louis: Elsevier/Saunders, 1682–1695.

Terman, M. and Terman, J.S. (2010b). Circadian rhythm phase advance with dawn simulation treatment for winter depression. *Journal of Biological Rhythms*, 25, 297–301.

Terman, M. and McMahan, I. (2012). *Chronotherapy: Resetting Your Inner Clock to Boost Mood, Alertness, and Quality Sleep*. New York: Avery/Penguin.

Terman, M., Terman, J.S., and Ross, D.C. (1998). A controlled trial of timed bright light and negative air ionization for treatment of winter depression. *Archives of General Psychiatry*, 55, 875–882.

Terman, M., Schlager, D., Fairhurst, S. *et al.* (1989a). Dawn and dusk simulation as a therapeutic intervention. *Biological Psychiatry*, 25, 966–970.

Terman, M., Terman, J.S., Quitkin, F.M. *et al.* (1989b). Dosing dimensions of light therapy: Duration and time of day. In Silverstone, T. and Thompson, C., eds., *Seasonal Affective Disorder*. London: Clinical Neuroscience Publishers, 187–204.

Terman, M., Terman, J.S., Quitkin, F.M. *et al.* (1989c). Light therapy for seasonal affective disorder: A review of efficacy. *Neuropsychopharmacology*, 2, 1–22.

Terman, M., Rifkin, J.B., Jacobs, J. *et al.* (2001). *Morningness-Eveningness Questionnaire (revised)* [online]. New York: New York State Psychiatric Institute. Available: http://www.cet.org (accessed April 15, 2012).

Voderholzer, U., Valerius, G., Schaerer, L. *et al.* (2003). Is the antidepressive effect of sleep deprivation stabilized by a three day phase advance of the sleep period? A pilot study. *European Archives of Psychiatry and Clinical Neuroscience*, 253, 68–72.

Williams, J.B.W. and Terman, M. (2003). *Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS)* [online]. New York: New York State Psychiatric Institute. Available: http://www.cet.org (accessed April 15, 2012).

Williams, J.B.W., Link, M.J., Rosenthal, N.E. *et al.* (2002). *Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorder Version (SIGH-SAD)*. Also, SIGH-SAD-SR (self-rating version) [online]. New York: New York State Psychiatric Institute. Available: http://www.cet.org (accessed April 15, 2012).

Wirz-Justice, A. (1998). Beginning to see the light. *Archives of General Psychiatry*, 55, 861–862.

Wirz-Justice, A. and Armstrong, S.M. (1996). Melatonin: Nature's soporific? *Journal of Sleep Research*, 5, 137–141.

Wirz-Justice, A. and van den Hoofdakker, R.H. (1999). Sleep deprivation in depression: What do we know, where do we go? *Biological Psychiatry*, 46, 445–453.

Wirz-Justice, A., Bromundt, V., and Cajochen, C. (2009a). Circadian disruption and psychiatric disorders: The importance of entrainment. *Sleep Med Clinics*, 4, 273–284.

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

Wirz-Justice, A., Remé, C., Prune, A. *et al.* (1997). Lithium decreases retinal sensitivity, but this is not cumulative with years of treatment. *Biological Psychiatry*, 41, 743–746.

Wirz-Justice, A., Terman, M., Oren, D.A. *et al.* (2004). Brightening depression. *Science*, 303, 467–469.

Wu, J.C., Kelsoe, J.R., Schachat, C. *et al.* (2009). Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. *Biological Psychiatry*, 66, 298–301.

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Contents

PART 5. CHRONOTHERAPY IN YOUR LIFE

Title Page:

Adjunctive Triple Chronotherapy (Combined Total Sleep Deprivation, Sleep Phase Advance, and Bright Light Therapy) Rapidly Improves Mood and Suicidality in Suicidal Depressed Inpatients: An Open Label Pilot Study

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Short title: Chronotherapy for Depression and Suicidality

Abstract:

Previous studies have demonstrated that combined total sleep deprivation, sleep phase advance, and bright light therapy (Triple Chronotherapy) produce a rapid and sustained antidepressant effect in acutely depressed individuals. To date no studies have explored the impact of the intervention on unipolar depressed individuals with acute concurrent suicidality. Participants were suicidal inpatients (N=10, Mean age=44, 6F) with unipolar depression. In addition to standard of care, they received open label Triple Chronotherapy. Participants underwent one night of total sleep deprivation (33-36 hours), followed by a three-night sleep phase advance along with four 30-minute sessions of bright light therapy (10,000 lux) each morning. Primary outcome measures included the 17 item Hamilton depression scale (HAM17), and the Columbia Suicide Severity Rating Scale (CSSRS), which were recorded at baseline prior to total sleep deprivation, and at protocol completion on day five. Both HAM17, and CSSRS scores were greatly reduced at the conclusion of the protocol. HAM17 scores dropped from a mean of 24.7 at baseline to a mean of 9.4 on day five ($p=.002$) with six of the ten individuals meeting criteria for remission. CSSRS scores dropped from a mean of 19.5 at baseline to a mean of 7.2 on day five ($p=.01$). The results of this small pilot trial demonstrate that adjunctive Triple Chronotherapy is feasible and tolerable in acutely suicidal and depressed inpatients. Limitations include a small number of participants, an open label design, and the lack of a comparison group. Randomized controlled studies are needed.

Keywords: Sleep deprivation; Suicidal Ideation, Chronotherapy; Depression; phototherapy; Inpatients.

1. Introduction:

Currently there are few rapid and dependable treatments for depression, other than electroconvulsive therapy (ECT), which involves risk of anesthesia and potential cognitive side effects. This lack of rapid treatments is problematic as suicide is the 10th leading cause of death in the United States, and is even higher among younger individuals between the ages of 10-24, where it is the second leading cause(Heron, 2013). Untreated depression is known to be associated with suicide risk with estimates that 60% of all suicides are associated with inadequately treated depression (Mann et al. , 2005). There is an apparent stratified risk of suicide in those who have been admitted to the inpatient unit for depression, with those who have suicidal thoughts, or suicide attempts, posing the highest lifetime risk of committing suicide (Bostwick, 2000). Depression is a major medical issue both domestically and abroad. Depression is the 4th leading cause of disability in the world and has an approximate lifetime prevalence of 16.5% in the United States(Kessler et al. , 2003, Murray and Lopez, 1996). Pharmacotherapy, and psychotherapy are the most commonly used treatments but only approximately 67% of non treatment resistant depressed individuals achieve remission with medications or psychotherapy, taking an average of 5-7 weeks to achieve remission in those who find an effective regimen(Rush et al. , 2006). Even electroconvulsive therapy (ECT), which is our most dependable, and effective treatment, still takes 2-3 weeks for therapeutic benefit, and has limited availability and cognitive side effects(Sackeim et al. , 2007). Although there are promising newer treatments such as repetitive transcranial magnetic stimulation (rTMS) (George et al. , 2014) and ketamine(Caddy, 2014), there are at this time no commonly used treatments that rapidly treat depression.

Studies have consistently reported a rapid antidepressant response to total sleep deprivation in both unipolar and bipolar depression, first studied by Pflug et al(Pflug and Tolle, 1971), and reviewed extensively by Wu et al(Wu and Bunney, 1990), Wirz-Justice et al(Wirz-Justice et al. , 2005), and Benedetti et al(Benedetti et al. , 2007). The clinical utility of this technique is limited however, because responders typically relapse rapidly following recovery sleep. The addition of pharmacotherapy (Benedetti et al. , 2001, Colombo et al. , 2000, Enrico Smeraldi, 1999, Martiny et al. , 2012, Shelton and Loosen, 1993, Szuba et al. , 1994, Wu et al. , 2009), sleep phase advance (Berger, 1999, Echizenya et al. , 2013), and bright light therapy(Echizenya, Suda, 2013, Martiny, Refsgaard, 2012, Neumeister et al. , 1996, Wu, Kelsoe, 2009) to sleep deprivation have each demonstrated efficacy in preventing some individuals from relapsing into depression. Some early studies have reported that combined total sleep deprivation, sleep phase advance, and bright light therapy, dubbed Triple Chronotherapy, along with concomitant pharmacotherapy, produces a rapid improvement in depressive symptoms which endures for as long as 9 weeks (Echizenya, Suda, 2013, Martiny, Refsgaard, 2012, Wu, Kelsoe, 2009). If the early, encouraging results of Triple Chronotherapy hold up to further study, the technique represents a near ideal inpatient treatment, as it is inexpensive, relatively easy to carry out, and has minimal side effects.

Despite encouraging early results, only one published report has attempted to use triple chronotherapy in suicidal patients, and in that trial only bipolar depressed patients were included. That study used a slightly different variation of chronotherapy that included

three nights of sleep deprivation every other night with three light therapy sessions, combined with lithium(Benedetti et al. , 2013). The lack of data utilizing Triple Chronotherapy in acutely suicidal patients significantly limits its utility in the United States, where few non-suicidal patients are admitted to the inpatient unit. Furthermore, published trials to this point have excluded those with comorbid illness, which also limits the clinical usefulness of this intervention to a minority of patients. We subsequently sought to determine if adjunctive triple chronotherapy was safe and feasible in acutely depressed and suicidal inpatients.

2. Materials and Methods:

2.1 Participants:

We included participants with non-psychotic unipolar, or bipolar depression (who were on a therapeutic dose of a mood stabilizer), age 18-75. We excluded patients who were in a mixed state, had active psychosis, had active panic disorder, were actively withdrawing from substance, had a history of seizures, or had active unstable medical or neurologic illness.

We recruited participants from inpatient units at the Medical University of South Carolina (MUSC) Institute of Psychiatry (IOP) during the months of October 2013-March 2014 after referral from the treating inpatient team. Inpatient teams referred a total of 21 participants, of those three were not interested in the study, and four met exclusion criteria. Of the remaining referrals, 14 signed written informed consent, one of which later failed initial screening. The remaining sample of 13 enrolled in the below described

protocol which was approved by the MUSC intuitional review board (IRB). Of the included participants one participant withdrew from the study prior to the first sleep deprivation and stated they were no longer wanting to participate, and two others were excluded from data analysis due to protocol deviations related to the investigative team, leaving a final sample of 10. Of the two that were withdrawn, our team missed awakening the first following the first recovery sleep night, and our team placed the second in an excessively noisy room during the first recovery night of sleep, and they were unable to sleep (They have a diagnoses of bipolar type I, and following two sleepless nights we thought the risk of manic switch outweighed any possible therapeutic benefit of continuing the protocol) (Figure 1). The mean age of participants was 44, 6 of which were women, and none of which had bipolar depression (Table 1). All but one participant carried comorbid Axis I, or Axis II diagnosis, which consisted of the following: Five participants met criteria for generalized anxiety disorder, four participants met criteria for dysthymia, three participants met criteria for borderline personality disorder, three participants met criteria for post traumatic stress disorder, three met criteria for alcohol dependence in early remission, two met criteria for social anxiety disorder, and one met criteria for opiate dependence in early remission. Only three participants were initially admitted for a suicide attempt, while all patients were admitted for suicidal ideation.

This was an adjunctive procedure, and with the exception of holding hypnotics on the night of sleep deprivation, all standard of care pharmacotherapy was allowed. In addition to pharmacotherapy, all patients on the unit received milieu therapy, group therapy, and social work interventions. The group was heterogeneous as far as treatment resistance.

The group had an average of 5.5±5.7 medications that were either failed or were not tolerated. One participant previously failed ECT. All participants were on antidepressants during the study; five were on serotonin selective reuptake inhibitors (SSRI)'s, two were on serotonin non-selective reuptake inhibitors (SNRI)'s, four were on trazodone, three were on mirtazapine, one was on vilazodone, one was on phenelzine, two were on cytomel, three were on benzodiazepines, one was on quetiapine, one was on gabapentin, one was on belladonna, and one was on melatonin. Prior to, or during the weeklong protocol, the following medications were started, or titrated: One had an SNRI titrated, one had phenelzine started, three had mirtazapine started or titrated, two had titrations of an SSRI, one had cytomel started, one had quetiapine started, one had prazosin started, one had a benzodiazepine started, and one had gabapentin started.

2.2 Triple Chronotherapy procedure:

Recruited participants filled out the Morningness-Eveningness questionnaire (MEQ) (Horne and Ostberg, 1976), which has been shown to predict optimal light therapy timing. Participants then underwent one night of total sleep deprivation (Day 0), followed by a three day sleep phase advance (Sleep occurred between 6pm, and 1am on day 1, 8pm and 3am on day 2, and 10pm and 5am on day 3). In addition they received bright light therapy on the mornings of days 1, 2, 3, and 4, for 30 minutes at 10,000lux, with the timing set by MEQ. The start time of light exposure varied between 6am and 8am. (Figure 2)

2.3 Data collection:

On the day proceeding total sleep deprivation (Day 0), after participants signed informed consent, we performed a chart review as well as reviewed pertinent laboratory testing. We then performed a MINI neuropsychiatric examination to confirm diagnoses, administered a 17-Item Hamilton depression rating scale (HAMD17), Columbia Suicide Severity Rating Scale (CSSRS), and a Young Mania Rating scale (YMRS), inquiring about the previous 7 days. In addition, we collected self report measures at baseline, including the Inventory of Depressive Symptoms Self Report (IDS-SR), the Patient Health Questionaire-9 (PHQ9), the Epworth Sleepiness scale (ESS), the Pittsburgh Sleep Quality Index (PSQI), and the Scale for Suicidal Ideation (SSI). On the day following total sleep deprivation, and the days following the first two nights of sleep phase advance (Days 1-3), we administered the 6-item version of the Hamilton Depression Rating Scale (HAMD6), the CSSRS, the YMRS, the IDS-SR, the ESS, and the SSI all asking about the previous day only. On the day following the third sleep phase advance night (Day4), we administered the HAM17, CSSRS, and YMRS, and collected the IDS-SR, ESS, SSI, PHQ9, and PSQI asking about the previous day only.

2.4 Data analysis:

We used Wilcoxon's rank sum test to evaluate the change in outcome measures throughout the four-day study follow-up. For the HAMD-17, we compared day 4 to baseline. For other measures collected on each day, we made pairwise comparisons of the change since baseline for each day of follow-up. We used SAS Enterprise version 4.3 for all analyses (SAS Institute, Inc., Cary NC).

3. Results:

As compared to baseline there was a statistically and clinically significant decrease in both clinician, and self rated scales of depression and suicidal ideation. The 17-Item Hamilton depression scale went from an average of 24.7 at day 0, to a final score of 9.4 on day 4. Six out of ten participants met criteria for remission on the Ham17 (60%), as defined by a score of 7 or below. Sixty-percent met criteria for response as defined by a drop in score of greater than 50%(Figures 3, 4). The Columbia Suicide Severity Index went from an average of 19.5 on day 0 to a final score of 7.2 on day 4. Sixty percent of participants had a 50% or more reduction in CSSRS scores (Figure 5). Self report measures were also collected each day, having been filled out while receiving light therapy, and can be found in table 2.

4. Discussion:

This small, open label pilot study suggests that adjunctive Triple Chronotherapy is safe and tolerable in acutely suicidal, unipolar depressed inpatients. These results complement and extend the recently published study demonstrating safety of another variant of Chronotherapy in suicidal Bipolar Depressed inpatients (Benedetti, Riccaboni, 2013). This conclusion, along with any conclusion regarding treatment efficacy, must however be made in the context of significant experimental limitations, with special attention made to the small sample size, significant medication changes, time in the structured hospital environment, and the lack of a control group.

It is possible that this small cohort of participants would have improved even more rapidly and robustly with treatment as usual, or that the response observed was directly the result

of treatment as usual, a placebo response, or some combination of the two. This is particularly true considering all patients were on concurrent pharmacotherapy, and receiving group therapy on the unit. However, typically neither pharmacotherapy, nor group psychotherapy has an onset of action that is as rapid as was observed in our cohort. Furthermore, comparison trials of Chronotherapy in the setting of medication use demonstrate that groups receiving both Chronotherapy and medications have a more rapid, and robust improvement as compared to groups receiving either alone, and response and remission rates have been consistent with our results (Benedetti, Barbini, 2001, Colombo, Lucca, 2000, Shelton and Loosen, 1993, Szuba, Baxter, 1994).

It is of note that Chronotherapy was well tolerated by all participants who agreed to the procedure. Most participants reported only transient sleepiness, which was most prominent between the hours of 3am and 6am on the night of total sleep deprivation, and following the first night of recovery sleep. Only three participants were withdrawn from the study, one of which withdrew before beginning total sleep deprivation, and the other two of which had to be withdrawn due to easily correctible study team errors (One we did not correctly wake up, and the other we placed in a room that was too close to unit activity).

A further limitation of this study that is particularly noteworthy is the lack of follow-up of our cohort after hospital discharge (Due to loss to follow-up). Historic data would suggest the possibility of rapid relapse (Wu and Bunney, 1990), however recent trials have demonstrated durability of the antidepressant effect of combined chronotherapeutic

interventions with medications (Benedetti et al. , 2005, Echizenya, Suda, 2013, Martiny, Refsgaard, 2012, Wu, Kelsoe, 2009).

After consideration of the above significant limitations, the results found in this pilot study still expand the potential clinical group that can undergo this intervention. Given the large effect size, ease of administration, mild side effects, and inexpensive nature of this intervention, further study is warranted. The two areas of study that are most lacking are data comparing active chronotherapy to an adequate active sham condition, and further durability data. Controlled trials would ideally include both an active sham group, and a treatment as usual group. An active sham could include partial sleep deprivation (Depriving the first part of the nights sleep), a three-day sleep phase delay, and placebo light therapy. All such sham interventions have been utilized previously and have been demonstrated to be safe. Such a sham group could control for placebo effects related to undergoing a procedure, and the added staff attention included in sleep deprivation, and a rigid sleep wake schedule. Including a treatment as usual group would control for improvement based upon pharmacotherapy, psychotherapy, and the structured hospital environment.

4.1 Conclusion:

Based upon the results of our small open label pilot study, Triple Chronotherapy is safe and feasible to administer in acutely depressed and suicidal inpatients. Further work is needed to determine treatment effects in a placebo-controlled trial.

References:

Benedetti F, Barbini B, Campori E, Fulgosi MC, Pontiggia A, Colombo C. Sleep phase advance and lithium to sustain the antidepressant effect of total sleep deprivation in bipolar depression: new findings supporting the internal coincidence model? Journal of psychiatric research. 2001;35:323-9.

Benedetti F, Barbini B, Colombo C, Smeraldi E. Chronotherapeutics in a psychiatric ward. Sleep Med Rev. 2007;11:509-22.

Benedetti F, Barbini B, Fulgosi MC, Colombo C, Dallaspezia S, Pontiggia A, et al. Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: acute response and long-term remission rates. The Journal of clinical psychiatry. 2005;66:1535-40.

Benedetti F, Riccaboni R, Locatelli C, Poletti S, Dallaspezia S, Colombo C. Rapid treatment response of suicidal symptoms to lithium, sleep deprivation, and light therapy (chronotherapeutics) in drug-resistant bipolar depression. The Journal of clinical psychiatry. 2013.

Berger D. How to preserve the antidepressive effect of sleep deprivation: A comparison of sleep phase advance and sleep phase delay. European archives of psychiatry and clinical neuroscience. 1999;249:231-7.

Bostwick MP, VS;. Affective Disorders and Suicide Risk: A Reexamination. The American journal of psychiatry. 2000:1925-32.

Caddy CG, G; White, TP; Shergill, SS; Tracy, D. Ketamine as the prototype glutamatergic antidepressant: pharmacodynamic actions, and a systematic review and meta-analysis of efficacy. Therapeutic Advances in Psychopharmacology. 2014;4:75-99.

Colombo C, Lucca A, Benedetti F, Barbini B, Campori E, Smeraldi E. Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. Psychiatry research. 2000;95:43-53.

Echizenya M, Suda H, Takeshima M, Inomata Y, Shimizu T. Total sleep deprivation followed by sleep phase advance and bright light therapy in drug-resistant mood disorders. Journal of affective disorders. 2013;144:28-33.
Enrico Smeraldi MD, Francesco Benedetti, M.D., Barbara Barbini, M.D., Euridice Campori, M.D., and Cristina Colombo, M.D. Sustained Antidepressant Effect of Sleep Deprivation Combined with Pindolol in Bipolar Depression A Placebo-Controlled Trial. NEUROPSYCHOPHARMACOLOGY. 1999;20.

George MS, Raman R, Benedek DM, Pelic CG, Grammer GG, Stokes KT, et al. A Two-site Pilot Randomized 3 Day Trial of High Dose Left Prefrontal Repetitive Transcranial Magnetic Stimulation (rTMS) for Suicidal Inpatients. Brain Stimul. 2014.

Heron M. Deaths: Leading Causes for 2010. National Vital Statistics Reports:. 2013;62.

Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. International journal of chronobiology. 1976;4:97-110.

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA : the journal of the American Medical Association. 2003;289:3095-105.

Mann JJ, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, et al. Suicide prevention strategies: a systematic review. JAMA : the journal of the American Medical Association. 2005;294:2064-74.

Martiny K, Refsgaard E, Lund V, Lunde M, Sorensen L, Thougaard B, et al. A 9-week randomized trial comparing a chronotherapeutic intervention (wake and light therapy) to exercise in major depressive disorder patients treated with duloxetine. The Journal of clinical psychiatry. 2012;73:1234-42.

Murray CJ, Lopez AD. Evidence-based health policy--lessons from the Global Burden of Disease Study. Science. 1996;274:740-3.

Neumeister A, Goessler R, Lucht M, Kapitany T, Bamas C, Kasper S. Bright light therapy stabilizes the antidepressant effect of partial sleep deprivation. Biological psychiatry. 1996;39:16-21.

Pflug B, Tolle R. Disturbance of the 24-hour rhythm in endogenous depression and the treatment of endogenous depression by sleep deprivation. International pharmacopsychiatry. 1971;6:187-96.

Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. The American journal of psychiatry. 2006;163:1905-17.

Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW, Olfson M. The cognitive effects of electroconvulsive therapy in community settings. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2007;32:244-54.
Shelton RC, Loosen PT. Sleep deprivation accelerates the response to nortriptyline. Progress in neuro-psychopharmacology & biological psychiatry. 1993;17:113-23.

Szuba MP, Baxter LR, Jr., Altshuler LL, Allen EM, Guze BH, Schwartz JM, et al. Lithium sustains the acute antidepressant effects of sleep deprivation: preliminary findings from a controlled study. Psychiatry research. 1994;51:283-95.

Wirz-Justice A, Benedetti F, Berger M, Lam RW, Martiny K, Terman M, et al. Chronotherapeutics (light and wake therapy) in affective disorders. Psychol Med. 2005;35:939-44.

Wu JC, Bunney WE. The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. The American journal of psychiatry. 1990;147:14-21.

Wu JC, Kelsoe JR, Schachat C, Bunney BG, DeModena A, Golshan S, et al. Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. Biological psychiatry. 2009;66:298-301.

Tables:

Table 1: Demographics

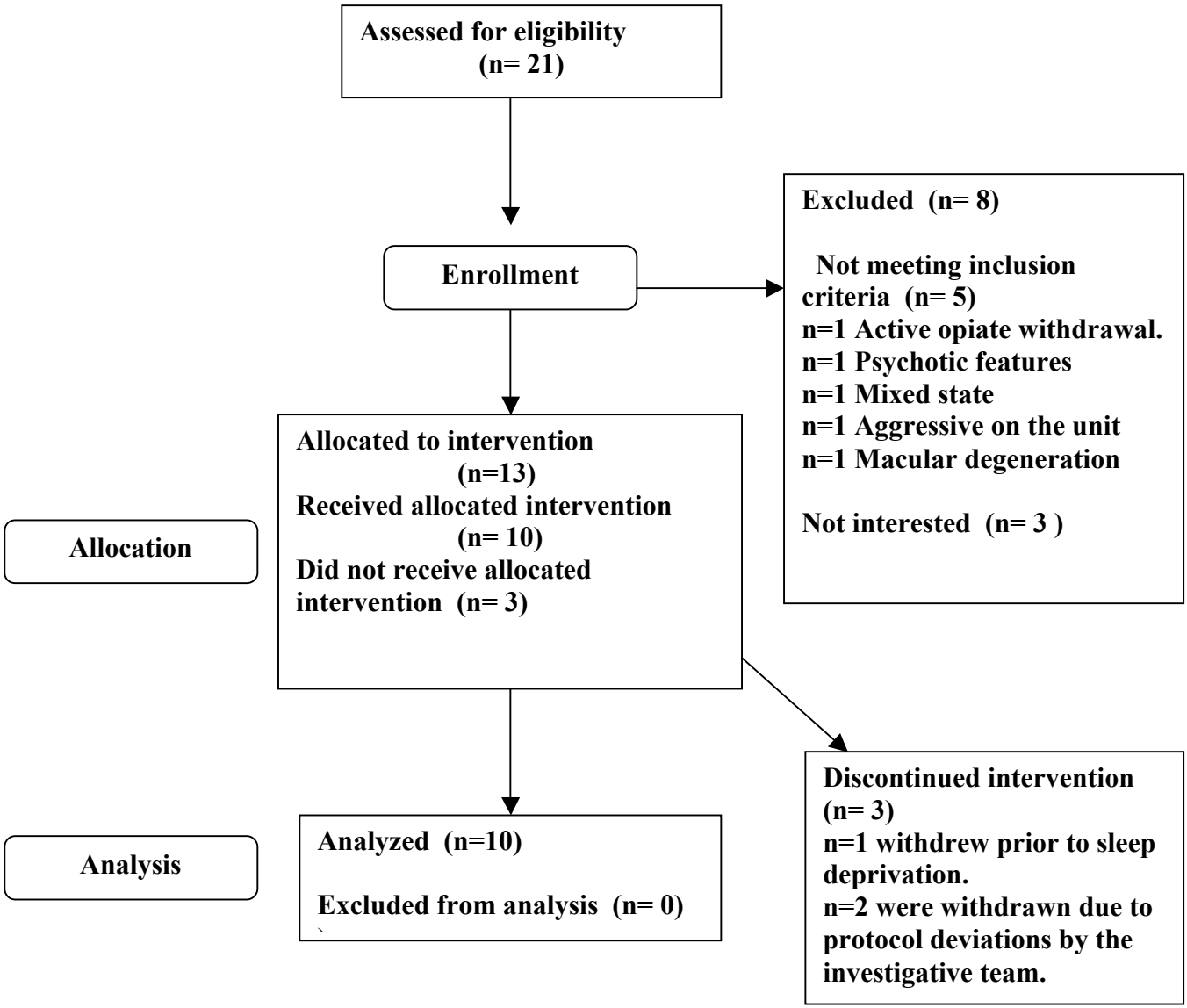
N=10	
Age	**Mean=44**
Gender	**4 Male, 6 Female**
Race/ethnicity	**9 Caucasian** **1 African American**

Table 2: Measures

Measure	Baseline	CAT Day 1	CAT Day 2	CAT Day 3	CAT Day 4
HAM-D [17]	**24.7(±4.2)**				**9.4(±7.3)** *p=.002*
HAM-D [6]	**12.3(± 1.8)**	**7.9(±3.9)** *p<.004*	**6(± 4.3)** *p=.002*	**4.5(± 4.5)** *p=.002*	**4.1(± 3.9)** *p<.004*
CSSRS	**19.5(±8.5)**	**6.5(±4.3)** *p<.004*	**8.1(± 7.4)** *p<.01*	**6.2(± 6.3)** *p<.004*	**7.2(± 5.5)** ***p<.01***
IDS	**52.1(±6.7)**	**45.4 (±11.5)** *p=.07*	**39.1(±16.8)** *p=.06*	**25.9(±13.5)** *p<.004*	**22.3(±14)** *p<.004*
SSI	**17.2(±9.4)**	**15(±9.8)**	**12.2(±10.5)** *p<.02*	**8.5(±8)** *p<.004*	**7.4(±7.9)** *p<.004*

HAM-D, 17-Item and 6-Item Hamilton Rating Scale for Depression; CSSRS, Columbia-Suicide Severity Rating Scale; IDS, Inventory of Depressive Symptomatology; SSI, Scale of Suicidal Ideation

Figure 1. Screening and Enrollment Flowchart

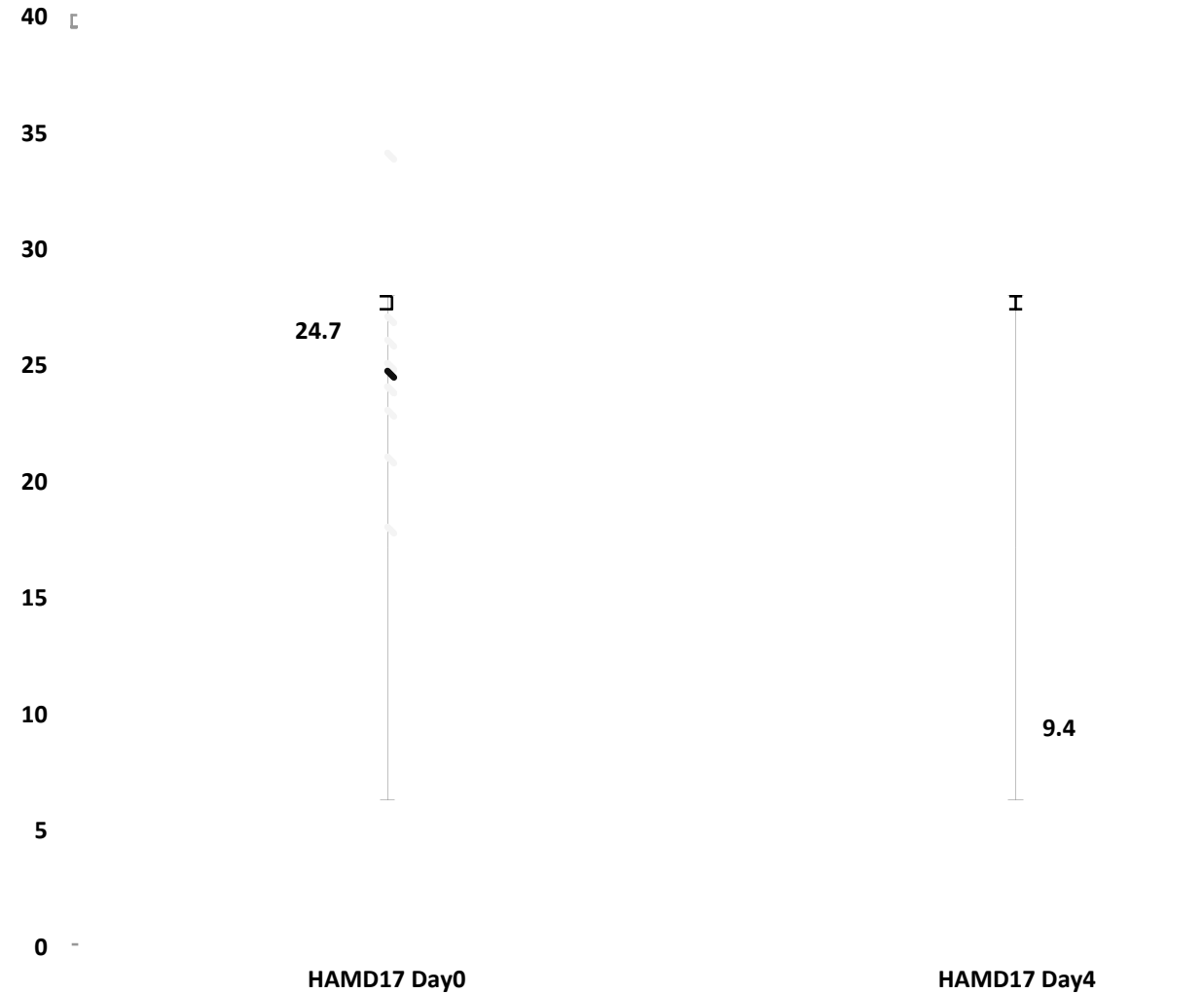


Day	1p	2p	3p	4p	5p	6p	7p	8p	9p	10p	11p	12a	1a	2a	3a	4a	5a	6a	7a	8a	9a	10a	11a	12p
Pre																								
0																							X	
1																							X	
2																							X	
3																							X	
4																							X	
Post																								

Wake	Sleep	Light	Assessment
			X

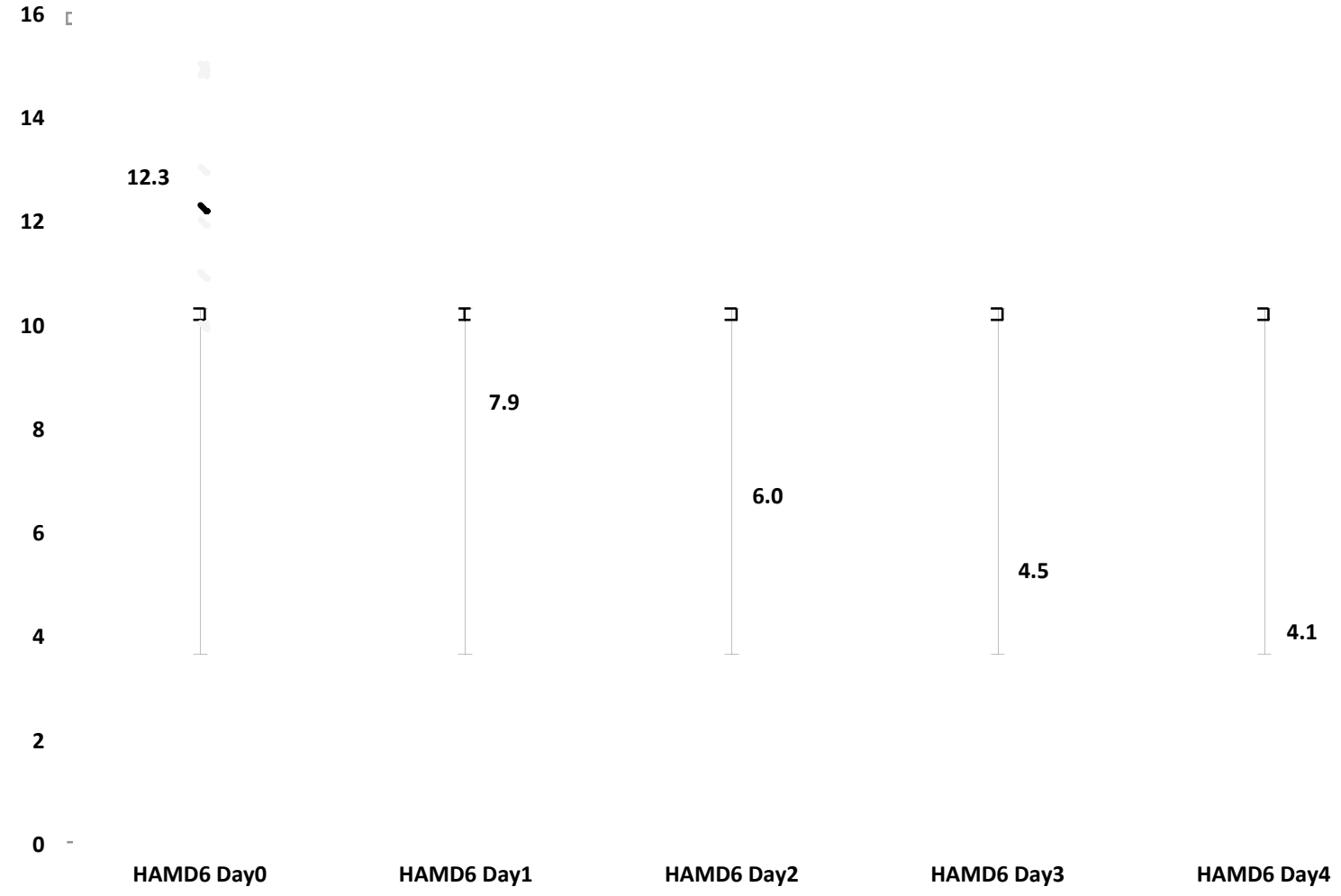
Figure(s)

Figure 3: Hamilton Depression Rating Scale 17-Item



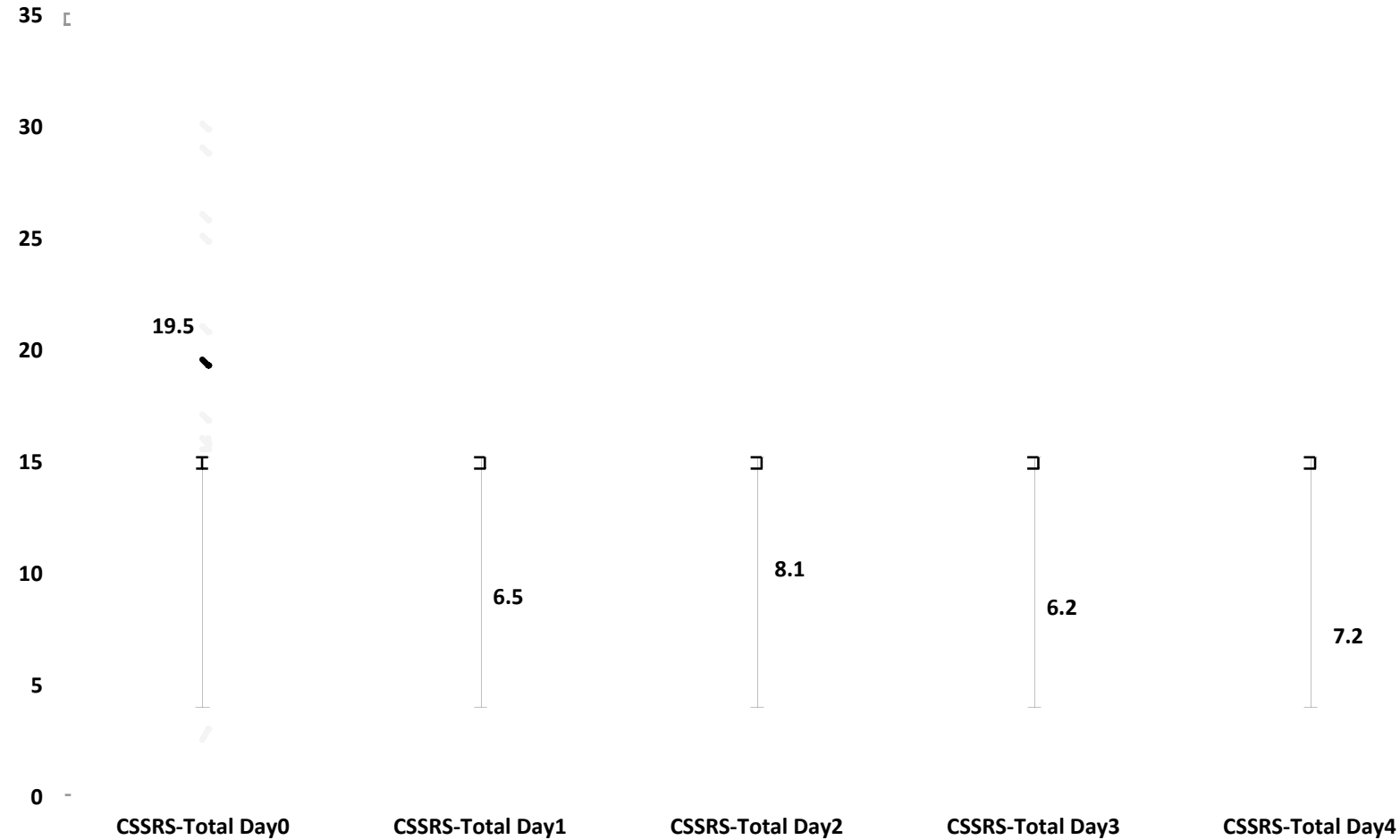
Figure(s)

Figure 4: Hamilton Depression Rating Scale 6-Item



Figure(s)

Figure 5: Columbia Suicide Severity Rating Scale Total



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QUESTIONNAIRE FOR PROSPECTIVE CHRONOTHERAPY OUTPATIENTS

Please answer all the questions on this 6-page form, make a copy for your records, and return the questionnaire by fax or email/scan for our promptest attention. (U.S. Mail may entail delays.) Please write with a dark pen. All information is confidential. Thank you for your interest.

Dear Doctors,
I am interested in your clinic services. I learned about you from:

_____

HOW MAY WE CONTACT YOU? (Please print.)

Name _____ Date __ __ / __ __ / __ __

Address _____ Birth __ __ / __ __ / __ __

City, State, ZIP _____ Sex M / F

Daytime phone _____ Evening phone _____

☐ Messages OK.
☐ No messages, please.
☐ OK to identify ourselves to others who may answer.
☐ Please do not identify.

☐ Messages OK.
☐ No messages, please.
☐ OK to identify ourselves to others who may answer.
☐ Please do not identify.

Personal e-mail _____ Personal fax _____

PLEASE CHECK APPLICABLE BOXES:

☐ I have read your clinic brochure or visited your website www.columbia-chronotherapy.org.
☐ I am currently under treatment with a mental health professional.
Please check: ☐ psychiatrist, ☐ psychologist, ☐ therapist.
☐ I am *not* currently under treatment.
☐ I am currently feeling symptoms of depression.
☐ I am currently experiencing sleep difficulty.
☐ I am filling out this questionnaire myself (I am the patient).
☐ Someone else is filling out this questionnaire for me. (Please identify.)

_____

QUESTIONS ABOUT YOUR MEDICAL HEALTH AND MEDICATIONS

At present, and over the past year, have you had any of the following medical conditions? (Please check appropriate boxes, and indicate drugs and doses if current.)

YES	CONDITION	CURRENT MEDICATIONS / DOSES
☐	Diabetes	
☐	Diabetes-related eye problems	
☐	Cancer (type: _____)	
☐	Cardiovascular disease	
☐	High blood pressure	
☐	Migraines	
☐	Thyroid: *high / low*	
☐	Retinal detachment	
☐	Retinitis pigmentosa	
☐	Macular degeneration	
☐	Cataracts: *current / lens replacement*	
☐	Chronic infections	
☐	HIV	
☐	Parkinson's disease	
☐	Chronic fatigue syndrome (CFS)	
☐	Menstrual irregularity of PMS	
☐	Perimenopausal symptoms	
☐	Drug allergies	
☐	Other allergies (specify):	
☐	Other (specify):	
☐	Other (specify):	

Do you use any medications or supplements not listed above? If so, please indicate with doses and frequency.

You may add an additional page if necessary.

When did you have your last physical examination (month/year)? __ __ / __ __

When did you have your last routine blood tests (month/year)? __ __ / __ __

When did you have your last eye examination (month/year)? __ __ / __ __

QUESTIONS ABOUT YOUR PSYCHIATRIC HISTORY AND MEDICATIONS

Have you been diagnosed by a doctor as having any of the following conditions in the past 5 years? (Please check appropriate boxes, and indicate drugs and doses if current.)

YES	CONDITION	CURRENT TREATMENT (medication, therapy, etc.)
☐	Major depressive disorder	
☐	Seasonal affective disorder (SAD)	
☐	Dysthymic disorder	
☐	Bipolar I disorder	
☐	Bipolar II disorder	
☐	Cyclothymic disorder	
☐	Anxiety disorder	
☐	Panic disorder	
☐	Obsessive compulsive disorder	
☐	Specific phobia	
☐	Posttraumatic stress disorder	
☐	Bulimia or anorexia nervosa, or binge eating disorder	
☐	Psychotic disorder, schizophrenia or schizoaffective disorder	
☐	Attention deficit disorder	
☐	Memory disorder, dementia or Alzheimer's disease	
☐	Substance addiction or dependency	
☐	Personality disorder	
☐	Sleep disorder	

Have you ever been hospitalized during an episode of a psychiatric disorder? If so, please describe circumstances, with dates and treatments, to the best of your recollection:

You may add an additional page if necessary.

If you are currently in treatment for any of the problems listed above:

1. Have you discussed with your doctor joining our program? ***Yes*** ***No***
2. Would you plan to consult with your doctor before joining the program? ***Yes*** ***No***
3. Would you permit direct consultation between your doctor and us? ***Yes*** ***No***

Please describe your current use of alcohol and any "recreational" drugs (amounts, frequency).

You may add an additional page if necessary.

Please indicate the extent to which each of the problems listed below, for which you indicate "yes", has created a problem for you in your life.

1. Were you ever afraid of going out of the house alone, being in crowds, standing in a line, or traveling on buses or trains? ***Yes*** ***No***

   ☐ minimal ☐ mild ☐ moderate ☐ moderate-severe ☐ severe

2. Have you ever been afraid to speak, eat, or write in front of other people? ***Yes*** ***No***

   ☐ minimal ☐ mild ☐ moderate ☐ moderate-severe ☐ severe

3. Have you ever been bothered by upsetting thoughts that didn't make any sense and kept coming back to you even when you tried to get them out of your mind? (Some examples are hurting someone you love, being contaminated by germs or dirt, or fearing that a bomb was going to go off.) ***Yes*** ***No***

   ☐ minimal ☐ mild ☐ moderate ☐ moderate-severe ☐ severe

4. Have there been certain things you have had to do over and over again and couldn't resist doing, like washing your hands repeatedly, or checking something repeatedly to make sure you'd done it right? ***Yes*** ***No***

   ☐ minimal ☐ mild ☐ moderate ☐ moderate-severe ☐ severe

5a. Have you worried much about your *physical* health? ***Yes*** ***No***
5b. Does your doctor say you worry too much? ***Yes*** ***No***

   ☐ minimal ☐ mild ☐ moderate ☐ moderate-severe ☐ severe

6. Have you ever had a time when you weighed much less than other people thought you ought to weigh, but you thought you looked fine? ***Yes*** ***No***

   ☐ minimal ☐ mild ☐ moderate ☐ moderate-severe ☐ severe

7. Have you ever had eating binges during which you ate a lot of food in a short period of time? ***Yes*** ***No***

   ☐ minimal ☐ mild ☐ moderate ☐ moderate-severe ☐ severe

   If you answered "yes" to question 7, please also indicate whether you have done anything specific to counteract the effects of such binges (like making yourself vomit, taking laxatives, strict dieting, fasting, or exercising a lot):

QUESTIONS ABOUT YOUR DAILY SCHEDULE AND SLEEP

1. For each day of the week, please list the hour you usually need to leave home for work or other engagements:

Mon	Tue	Wed	Thu	Fri	Sat	Sun
_____	_____	_____	_____	_____	_____	_____

2. Please list your usual work hours (if you are working away from home):

Mon	Tue	Wed	Thu	Fri	Sat	Sun
_	_	_	_	_	_	_

3. On workdays, about what time do you fall asleep? _____ … wake up? _____
4. On days off, about what time do you fall asleep? _____ … wake up? _____
5. Do you usually have difficulty falling asleep? ***Yes*** ***No*** … waking up? ***Yes*** ***No***
6. Do you usually have a sound or restless sleep? ***Sound*** ***Restless***
7. Do you use sleeping pills or sleep aids? ***Yes*** ***No***
   If yes, please be sure these are listed on page 2.

Have you used light therapy before? If so, please describe how you used it, what apparatus you used (manufacturer/model), and how you responded:

You may add an additional page if necessary.

In a sentence or two, please tell us what problem(s) you are seeking to address with us:

You may add an additional page if necessary.

PERMISSION TO CONSULT WITH YOUR DOCTORS

We appreciate your responses, and we'll contact you promptly after reviewing this questionnaire. In planning your participation in our program, it may be important for us to consult with your primary care doctor or mental health specialist before we schedule an appointment. We would make such contact only after talking with you beforehand and explaining the need. In order for us to take next steps, you need to complete the permission form on page 6 and return it with this questionnaire. Many thanks.

COMPREHENSIVE CHRONOTHERAPY GROUP

Mailing address: 377 West 20th Street, Suite 4M, New York, NY 10011
email: **nychronotherapy@gmail.com / *messages* 646 837 7337 / *fax* 347 287 6825**

CONFIDENTIAL MEMORANDUM

PATIENT'S PERMISSION TO RELEASE INFORMATION

Patient's name (printed) _____

Patient's signature _____

Date __ __ / __ __ / __ __

Dear Doctors,

In considering this patient's treatment at our outpatient clinic, we may need to discuss with you, or receive records, concerning the patient's history, diagnoses and treatment. We may also need to discuss with you coordination of adjunctive therapy with the patient's current treatment under your continued care as primary provider. Please do not hesitate to contact us with any questions or concerns.

We will contact you only after discussing the need for specific information with the patient.

All information will be protected under HIPPA regulatory standards.

The patient has agreed for us to request information of the following providers:

M.D. PRIMARY CARE PROVIDER *G.P., internist, etc.*	**PRIMARY MENTAL HEALTH PROVIDER** *Specify degree: M.D., Ph.D., L.C.S.W., etc.*
Name _____	Name _____ DEGREE
Address _____	Address _____
City, State, ZIP _____	City, State, ZIP _____
Telephone _____	Telephone _____
Fax _____	Fax _____

Sincerely yours,

Michael Terman, Ph.D. Program Director, Chronotherapy	Niles Drake, M.D. Program Psychiatrist	Margaret Mandel, Ed.D. Program Psychologist

DAILY SLEEP/MOOD/ENERGY LOG

INTRUCTIONS

1. Enter your name and the start date for this sheet.
2. After you wake up for the day, fill in 15-minute sleep intervals. If awake at night for 15 minutes or more, leave box blank. *Use your best recollection:* you should *not* be checking the clock while you are trying to sleep. Also mark daytime naps.
3. Enter the letter "L" (for light) in each box for the time of your light therapy session (if you are using lights).
4. Enter a symbol at appropriate times for medications and melatonin ("M" for melatonin). Define symbols on the list to the right.
5. For multiple medications taken at the same time, enter a "1", "2" or "3" at appropriate times, as shown on the list to the right.
6. In the morning, when you record your sleep, enter your average mood and energy ratings for *yesterday*.
7. Enter notes to explain unusual situations (for example, "out late," "stomach ache").
8. *Women:* if you are menstruating, add a note for each day.

IDENTIFY MEDICATIONS/DOSES TAKEN ONE OR MORE TIMES OF DAY, OR PRN ("AS NEEDED"). SPECIFY A SYMBOL FOR EACH DRUG.

1 - Morning: ______________________

2 - Midday: ______________________

3 - Evening: ______________________

4 - PRN: ______________________

NAME: ______________________

DAILY RATINGS
0 - worst ever
5 - feeling OK, fine
10 - highest ever

DAY OF WEEK: ________ **DATE:** ___/___/___ **NEXT DAY ➡**

12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11

noon **midnight** *Continue this day on the next timeline.*

Yesterday's mood ***energy***

NOTES (place at time): ______________________

DAY OF WEEK: ________ **DATE:** ___/___/___ **NEXT DAY ➡**

12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11

noon **midnight** *Continue this day on the next timeline.*

Yesterday's mood ***energy***

NOTES: ______________________

DAY OF WEEK: ________ **DATE:** ___/___/___ **NEXT DAY ➡**

12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11

noon **midnight** *Continue this day on the next timeline.*

Yesterday's mood ***energy***

NOTES: ______________________

DAY OF WEEK: ________ **DATE:** ___/___/___ **NEXT DAY ➡**

12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11

noon **midnight** *Continue this day on the next timeline.*

Yesterday's mood ***energy***

NOTES: ______________________

DAY OF WEEK: ________ **DATE:** ___/___/___ **NEXT DAY ➡**

12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11

noon **midnight** *Continue this day on the next timeline.*

Yesterday's mood ***energy***

NOTES: ______________________

DAY OF WEEK: ________ **DATE:** ___/___/___ **NEXT DAY ➡**

12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11

noon **midnight** *Continue this day on the next timeline.*

Yesterday's mood ***energy***

NOTES: ______________________

DAY OF WEEK: ________ **DATE:** ___/___/___ **NEXT DAY ➡**

12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11

noon **midnight** *Continue this day on the next page.*

Yesterday's mood ***energy***

NOTES: ______________________

PLEASE KEEP EXTRA COPIES OF THE BLANK FORM TO CONTINUE THE LOG.

Start a new page for the next week.

Personal Inventory for Depression and SAD (PIDS)

Michael Terman, Ph.D., and Janet B.W. Williams, D.S.W.
New York State Psychiatric Institute and
Department of Psychiatry Columbia University

SCORING INSTRUCTIONS

Tabulate ratings in the boxed space below each set of questions.

Part 1: Total the number, separately, of "yes", "no", and "?" responses.

Part 2: Total the circled ratings for the six questions. (*SPAQ* Global Seasonality Score; see Notes, below.)

Part 3: For Column A and B, separately, total the number of times each month (or "none") was circled.

Part 4: Total the number, separately, of "yes", "no", and "?" responses.

INTERPRETATION GUIDE

The following text is reprinted from the self-assessment version of this instrument *(PIDS-SA)*, and is thus written in a way that directly advises the respondent. For additional information about diagnosis and treatment of SAD and related syndromes, see: Terman, M., Williams, J.B.W., & Terman, J.S. (1991) Light therapy for winter depression: A clinician's guide. In *Innovations in Clinical Practice*, vol. 10, P.A. Keller & S.R. Heyman, eds. Sarasota, FL: Professional Resource Exchange. Pp. 179-221. (Reprints available by request on letterhead to: Winter Depression Program, New York State Psychiatric Institute, 722 West 168th Street, Unit 50, New York, NY 10032.)

PART 1. If you circled 5 or more problems, it is possible that you have had a major depressive disorder for which you should consider seeking help. Even if you circled only one or two problems you may want to consult with a psychiatrist, psychologist, social worker or other mental health professional if the problems worry you or interfere with your daily activities. You may have experienced some of these problems for <u>less</u> than two weeks — if so, your problem is probably not a classic 'major' depressive disorder, but still may be serious enough to merit consultation with a therapist and possibly treatment. To determine whether the problem might be seasonal, consider Parts 2 and 3 below.

PART 2. If your total score on Part 2 is less than 6, you fall within the 'nonseasonal' range. You probably do not have seasonal affective disorder (SAD). It is still possible, however, that you have experienced a chronic or intermittent depression that merits clinical attention.

If your score falls between 7 and 11, you may have a mild version of SAD for which seasonal changes are noticeable — and possibly even quite bothersome — but are probably not overwhelmingly difficult. If your score is 12 or more, SAD that is clinically significant is increasingly likely. But you still need to consider which months pose most problems, as shown in Part 3.

PART 3. People with <u>fall or winter</u> depression tend to score 4 or more per month in a series of 3-5 months beginning anywhere from September to January, as would be noted in Column A. For months outside that grouping the score tends to be zero, or nearly zero. In Column B, the same people will usually score 4 or more points per month over a series of 3-5 months beginning anywhere from March to June.

Some people show a different pattern, with scores <u>split</u> between Columns A and B during both winter and summer months. For example, they may feel worst and socialize least during the summer, especially July and August; during the same time period, they may eat least, lose most weight, and sleep least. In winter, they may feel best and socialize most, yet still tend to eat most, gain most weight, and sleep most. Such people may experience seasonal depression of the <u>summer</u> type, and treatment recommendations may well differ from those for winter depression.

Some people show <u>relatively</u> high scores in the fall and winter months in Column A (winter depression), but there is still a remaining scatter of good and bad months <u>throughout</u> the year. Such a pattern may indicate a 'winter worsening' of symptoms, rather than clear-cut SAD. Recommendations for winter treatment might be similar to those for winter-SAD, although there may be a need for multiple treatment approaches.

Some people experience depression in the winter as well as in the summer, but they feel fine in the spring and the fall. Their summer depression is usually not accompanied by oversleeping and overeating, in contrast with the winter. This is a special case of SAD, for which different treatments might be appropriate in the opposite seasons. Even people who experience only winter depression sometimes feel summertime slumps in mood and energy when the weather is rainy or dark for several days. They often find relief by brief use of their winter treatment during these periods.

PART 4. If you reported any of these tendencies, you have experienced winter symptoms that may respond to light therapy and various medications, regardless of whether or not you have depressed mood. The higher your score in Part 4, the more likely you are to have 'classic' winter-SAD. It is possible, however, to be depressed in winter <u>without</u> these symptoms — or even with <u>opposite</u> symptoms such as reduced sleep and appetite — if so, a therapist might recommend a different treatment from that for 'classic' SAD.

NOTES — Part 1 was adapted from the *Prime-MD Clinician Evaluation Guide (CEG)*, developed by Robert L. Spitzer, M.D., and Janet B.W. Williams, D.S.W., New York State Psychiatric Institute and Department of Psychiatry, Columbia University. Parts 2 and 3 were adapted from the *Seasonal Pattern Assessment Questionnaire (SPAQ)* developed by Norman E. Rosenthal, M.D., Gary J. Bradt, and Thomas A. Wehr, M.D., National Institute of Mental Health. Preparation of the *PIDS* was sponsored in part by Grant MH42931 from the National Institute of Mental Health. This questionnaire is under development and is subject to further revision. May 1993 version.

Personal Inventory for Depression and SAD *(PIDS)*

Name_____ **Date** _____

This questionnaire is designed to help determine the scope and timing of certain problems that many people have, and to help your clinician advise you about possible treatments, depending on your responses. This is not a method for self-diagnosis, but it does provide a quick way to identify personal problem areas that may deserve special attention. Circle your responses to the right of each question. Circle a "yes" or "no" response only if you are quite sure about it; if you are unsure, circle a question mark if it is given as an alternative. All information you provide is confidential.

PART 1. SOME QUESTIONS ABOUT DEPRESSION.

In the last year, have you had any single period of time — <u>lasting at least two weeks</u> — in which any of the following problems was present nearly every day? (Of course, you may also have had several such periods.)

Were there two weeks or more . . .

- when you had trouble falling asleep or staying asleep, or sleeping too much? ***YES NO ?***
- when you were feeling tired or had little energy? ***YES NO ?***
- when you experienced poor appetite or overeating? Or significant weight gain or loss, although you were not dieting? ***YES NO ?***
- when you found little interest or little pleasure in doing things? ***YES NO ?***
- when you were feeling down, depressed, or hopeless? ***YES NO ?***
- when you were feeling bad about yourself — or that you were a failure — or that you were letting yourself or your family down? ***YES NO ?***
- when you had trouble concentrating on things, like reading the newspaper or watching television? ***YES NO ?***
- when you were so fidgety or restless that you were moving around a lot more than usual? Or the opposite — moving or speaking so slowly that other people could have noticed? ***YES NO ?***
- when you found yourself thinking a lot about death or that you would be better off dead, or even of hurting yourself? ***YES NO ?***

Leave this box blank.
y__ n__ ?__

PART 2. HOW 'SEASONAL' A PERSON ARE YOU?

Circle <u>one</u> number on each line to indicate how much each of the following behaviors or feelings <u>changes with the seasons</u>. (For instance, you may find you sleep different hours in the winter than in the summer.)
(0 = no change, 1 = slight change, 2 = moderate change, 3 = marked change, 4 = extreme change.)

Change in your total sleep length (including nighttime sleep and naps)	***0 1 2 3 4***
Change in your level of social activity (including friends, family and co-workers)	***0 1 2 3 4***
Change in your general mood, or overall feeling of well-being	***0 1 2 3 4***
Change in your weight	***0 1 2 3 4***
Change in your appetite (both food cravings and the amount you eat)	***0 1 2 3 4***
Change in your energy level	***0 1 2 3 4***

Leave this box blank.
tot___

PART 3. WHICH MONTHS STAND OUT AS 'EXTREME' FOR YOU?

For each of the following behaviors or feelings, draw a circle around all applicable months. If no particular month stands out for any item, circle "<u>none</u>". You should circle a month <u>only if you recollect a distinct change</u> in comparison to other months, occurring for several years. You may circle several months for each item.

	COLUMN A													COLUMN B											
I tend to feel worst in	*Jan*	*Feb*	*Mar*	*Apr*	*May*	*Jun*	*Jul*	*Aug*	*Sep*	*Oct*	*Nov*	*Dec*	***none***	I tend to feel best in	*Jan*	*Feb*	*Mar*	*Apr*	*May*	*Jun*	*Jul*	*Aug*	*Sep*	*Oct*	*Nov*	*Dec*	***none***
I tend to eat most in	*Jan*	*Feb*	*Mar*	*Apr*	*May*	*Jun*	*Jul*	*Aug*	*Sep*	*Oct*	*Nov*	*Dec*	***none***	I tend to eat least in	*Jan*	*Feb*	*Mar*	*Apr*	*May*	*Jun*	*Jul*	*Aug*	*Sep*	*Oct*	*Nov*	*Dec*	***none***
I tend to gain most weight in	*Jan*	*Feb*	*Mar*	*Apr*	*May*	*Jun*	*Jul*	*Aug*	*Sep*	*Oct*	*Nov*	*Dec*	***none***	I tend to lose most weight in	*Jan*	*Feb*	*Mar*	*Apr*	*May*	*Jun*	*Jul*	*Aug*	*Sep*	*Oct*	*Nov*	*Dec*	***none***
I tend to sleep most in	*Jan*	*Feb*	*Mar*	*Apr*	*May*	*Jun*	*Jul*	*Aug*	*Sep*	*Oct*	*Nov*	*Dec*	***non***	I tend to sleep least in	*Jan*	*Feb*	*Mar*	*Apr*	*May*	*Jun*	*Jul*	*Aug*	*Sep*	*Oct*	*Nov*	*Dec*	***none***
I tend to have the least energy in	*Jan*	*Feb*	*Mar*	*Apr*	*May*	*Jun*	*Jul*	*Aug*	*Sep*	*Oct*	*Nov*	*Dec*	***none***	I tend to have the most energy in	*Jan*	*Feb*	*Mar*	*Apr*	*May*	*Jun*	*Jul*	*Aug*	*Sep*	*Oct*	*Nov*	*Dec*	***none***
I tend to have the lowest level of social activity in	*Jan*	*Feb*	*Mar*	*Apr*	*May*	*Jun*	*Jul*	*Aug*	*Sep*	*Oct*	*Nov*	*Dec*	***none***	I tend to have the highest level of social activity in	*Jan*	*Feb*	*Mar*	*Apr*	*May*	*Jun*	*Jul*	*Aug*	*Sep*	*Oct*	*Nov*	*Dec*	***none***

Leave this box blank.

	J	*F*	*M*	*A*	*M*	*J*	*J*	*A*	*S*	*O*	*N*	*D*	*none*
A	___	___	___	___	___	___	___	___	___	___	___	___	___
B	___	___	___	___	___	___	___	___	___	___	___	___	___

PART 4. MORE ABOUT POSSIBLE WINTER SYMPTOMS . . .

In comparison to other times of the year, during the winter months, which — if any — of the following symptoms tend to be present?

I tend to sleep longer hours (napping included).	***YES***	***NO***	***?***
I tend to have trouble waking up in the morning.	***YES***	***NO***	***?***
I tend to have low daytime energy, feeling tired most of the time.	***YES***	***NO***	***?***
I tend to feel worse, overall, in the late evening than in the morning.	***YES***	***NO***	***?***
I tend to have a distinct temporary slump in mood or energy in the afternoon.	***YES***	***NO***	***?***
I tend to crave more sweets and starches.	***YES***	***NO***	***?***
I tend to eat more sweets and starches, whether or not I crave them.	***YES***	***NO***	***?***
I tend to crave sweets, but mostly in the afternoon and evening.	***YES***	***NO***	***?***
I tend to gain more weight than in the summer.	***YES***	***NO***	***?***

Leave this box blank.
y__ n__ ?__

Personal Inventory for Depression and SAD (PIDS)

Michael Terman, Ph.D., and Janet B.W. Williams, D.S.W.
New York State Psychiatric Institute and
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PART 1. If you circled 5 or more problems, it is possible that you have had a major depressive disorder for which you should consider seeking help. Even if you circled only one or two problems you may want to consult with a psychiatrist, psychologist, social worker or other mental health professional if the problems worry you or interfere with your daily activities. You may have experienced some of these problems for <u>less</u> than two weeks — if so, your problem is probably not a classic 'major' depressive disorder, but still may be serious enough to merit consultation with a therapist and possibly treatment. To determine whether the problem might be seasonal, consider Parts 2 and 3 below.

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MORNINGNESS-EVENINGNES05S QUESTIONNAIRE
Self-Assessment Version (MEQ-SA)[1]

Name: _____ Date: _____

For each question, please select the answer that best describes you by circling the point value that best indicates how you have felt in recent weeks.

1. *Approximately* what time would you get up if you were entirely free to plan your day?

   [5] 5:00 AM–6:30 AM *(05:00–06:30 h)*
   [4] 6:30 AM–7:45 AM *(06:30–07:45 h)*
   [3] 7:45 AM–9:45 AM *(07:45–09:45 h)*
   [2] 9:45 AM–11:00 AM *(09:45–11:00 h)*
   [1] 11:00 AM–12 noon *(11:00–12:00 h)*

2. *Approximately* what time would you go to bed if you were entirely free to plan your evening?

   [5] 8:00 PM–9:00 PM *(20:00–21:00 h)*
   [4] 9:00 PM–10:15 PM *(21:00–22:15 h)*
   [3] 10:15 PM–12:30 AM *(22:15–00:30 h)*
   [2] 12:30 AM–1:45 AM *(00:30–01:45 h)*
   [1] 1:45 AM–3:00 AM *(01:45–03:00 h)*

3. If you usually have to get up at a specific time in the morning, how much do you depend on an alarm clock?

   [4] Not at all
   [3] Slightly
   [2] Somewhat
   [1] Very much

---

[1]Some stem questions and item choices have been rephrased from the original instrument (Horne and Östberg, 1976) to conform with spoken American English. Discrete item choices have been substituted for continuous graphic scales. Prepared by Terman M, Rifkin JB, Jacobs J, White TM (2001), New York State Psychiatric Institute, 1051 Riverside Drive, Unit 50, New York, NY, 10032. January 2008 version. Supported by National Institute of Health Grant MH42931. *See also:* automated English version (AutoMEQ) at www.cet.org.

Horne JA and Östberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. International Journal of Chronobiology, 1976: 4, 97-100.

4. How easy do you find it to get up in the morning (when you are not awakened unexpectedly)?

   [1] Very difficult
   [2] Somewhat difficult
   [3] Fairly easy
   [4] Very easy

5. How alert do you feel during the first half hour after you wake up in the morning?

   [1] Not at all alert
   [2] Slightly alert
   [3] Fairly alert
   [4] Very alert

6. How hungry do you feel during the first half hour after you wake up?

   [1] Not at all hungry
   [2] Slightly hungry
   [3] Fairly hungry
   [4] Very hungry

7. During the first half hour after you wake up in the morning, how do you feel?

   [1] Very tired
   [2] Fairly tired
   [3] Fairly refreshed
   [4] Very refreshed

8. If you had no commitments the next day, what time would you go to bed compared to your usual bedtime?

   [4] Seldom or never later
   [3] Less that 1 hour later
   [2] 1-2 hours later
   [1] More than 2 hours later

9. You have decided to do physical exercise. A friend suggests that you do this for one hour twice a week, and the best time for him is between 7-8 AM *(07-08 h)*. Bearing in mind nothing but your own internal "clock," how do you think you would perform?

   [4] Would be in good form
   [3] Would be in reasonable form
   [2] Would find it difficult
   [1] Would find it very difficult

10. At *approximately* what time in the evening do you feel tired, and, as a result, in need of sleep?

   [5] 8:00 PM–9:00 PM *(20:00–21:00 h)*
   [4] 9:00 PM–10:15 PM *(21:00–22:15 h)*
   [3] 10:15 PM–12:45 AM *(22:15–00:45 h)*
   [2] 12:45 AM–2:00 AM *(00:45–02:00 h)*
   [1] 2:00 AM–3:00 AM *(02:00–03:00 h)*

11. You want to be at your peak performance for a test that you know is going to be mentally exhausting and will last two hours. You are entirely free to plan your day. Considering only your "internal clock," which one of the four testing times would you choose?

   [6] 8 AM–10 AM *(08–10 h)*
   [4] 11 AM–1 PM *(11–13 h)*
   [2] 3 PM–5 PM *(15–17 h)*
   [0] 7 PM–9 PM *(19–21 h)*

12. If you got into bed at 11 PM *(23 h)*, how tired would you be?

   [0] Not at all tired
   [2] A little tired
   [3] Fairly tired
   [5] Very tired

13. For some reason you have gone to bed several hours later than usual, but there is no need to get up at any particular time the next morning. Which one of the following are you most likely to do?

    [4] Will wake up at usual time, but will not fall back asleep
    [3] Will wake up at usual time and will doze thereafter
    [2] Will wake up at usual time, but will fall asleep again
    [1] Will not wake up until later than usual

14. One night you have to remain awake between 4-6 AM *(04-06 h)* in order to carry out a night watch. You have no time commitments the next day. Which one of the alternatives would suit you best?

    [1] Would not go to bed until the watch is over
    [2] Would take a nap before and sleep after
    [3] Would take a good sleep before and nap after
    [4] Would sleep only before the watch

15. You have two hours of hard physical work. You are entirely free to plan your day. Considering only your internal "clock," which of the following times would you choose?

    [4] 8 AM–10 AM *(08–10 h)*
    [3] 11 AM–1 PM *(11–13 h)*
    [2] 3 PM–5 PM *(15–17 h)*
    [1] 7 PM–9 PM *(19–21 h)*

16. You have decided to do physical exercise. A friend suggests that you do this for one hour twice a week. The best time for her is between 10-11 PM *(22-23 h)*. Bearing in mind only your internal "clock," how well do you think you would perform?

    [1] Would be in good form
    [2] Would be in reasonable form
    [3] Would find it difficult
    [4] Would find it very difficult

17. Suppose you can choose your own work hours. Assume that you work a five-hour day (including breaks), your job is interesting, and you are paid based on your performance. At *approximately* what time would you choose to begin?

    [5] 5 hours starting between 4–8 AM *(04–08 h)*
    [4] 5 hours starting between 8–9 AM *(08–09 h)*
    [3] 5 hours starting between 9 AM–2 PM *(09–14 h)*
    [2] 5 hours starting between 2–5 PM *(14–17 h)*
    [1] 5 hours starting between 5 PM–4 AM *(17–04 h)*

18. At *approximately* what time of day do you usually feel your best?

    [5] 5–8 AM *(05–08 h)*
    [4] 8–10 AM *(08–10 h)*
    [3] 10 AM–5 PM *(10–17 h)*
    [2] 5–10 PM *(17–22 h)*
    [1] 10 PM–5 AM *(22–05 h)*

19. One hears about "morning types" and "evening types." Which one of these types do you consider yourself to be?

    [6] Definitely a morning type
    [4] Rather more a morning type than an evening type
    [2] Rather more an evening type than a morning type
    [1] Definitely an evening type

____ Total points for all 19 questions

INTERPRETING AND USING YOUR MORNINGNESS-EVENINGNESS SCORE

This questionnaire has 19 questions, each with a number of points. First, add up the points you circled and enter your total morningness-eveningness score here:

Scores can range from 16-86. Scores of 41 and below indicate "evening types." Scores of 59 and above indicate "morning types." Scores between 42-58 indicate "intermediate types."

16-30	31-41	42-58	59-69	70-86
definite evening	moderate evening	intermediate	moderate morning	definite morning

Occasionally a person has trouble with the questionnaire. For example, some of the questions are difficult to answer if you have been on a shift work schedule, if you don't work, or if your bedtime is unusually late. Your answers may be influenced by an illness or medications you may be taking. *If you are not confident about your answers, you should also not be confident about the advice that follows.*

One way to check this is to ask whether your morningness-eveningness score approximately matches the sleep onset and wake-up times listed below:

Score	16-30	31-41	42-58	59-69	70-86
Sleep onset	2:00-3:00 AM *(02:00-03:00 h)*	12:45-2:00 AM *(00:45-02:00 h)*	10:45 PM-12:45 AM *(22:45-00:45 h)*	9:30-10:45 PM *(21:30-22:45 h)*	9:00-9:30 PM *(21:00-21:30 h)*
Wake-up	10:00-11:30 AM *(10:00-11:30 h)*	8:30-10:00 AM *(08:30-10:00 h)*	6:30-8:30 AM *(06:30-08:30 h)*	5:00-6:30 AM *(05:00-06:30 h)*	4:00-5:00 AM *(04:00-05:00 h)*

If your usual sleep onset is earlier than 9:00 PM *(21:00 h)* or later than 3:00 AM *(03:00 h),* or your wake-up is earlier than 4:00 AM *(04:00 h)* or later than 11:30 AM *(11:30 h),* you should seek the advice of a light therapy clinician in order to proceed effectively with treatment.

We use the morningness-eveningness score to improve the antidepressant effect of light therapy. Although most people experience good antidepressant response to light therapy when they take a regular morning session using a 10,000 lux white light device *(see www.cet.org for recommendations)* for 30 minutes, often this will not give the best possible response. If your internal clock is shifted relative to external time (as indirectly measured by your morningness-eveningness score), the timing of light therapy needs to be adjusted.

The table at the top of the next page shows the recommended start time for light therapy for a wide range of morningness-eveningness scores. If your score falls beyond this range (either very low or very high), you should seek the advice of a light therapy clinician in order to proceed effectively with treatment.
.

Morningness-Eveningness Score	Start time for light therapy
23-26	8:15 AM
27-30	8:00 AM
31-34	7:45 AM
35-38	7:30 AM
39-41	7:15 AM
42-45	7:00 AM
46-49	6:45 AM
50-53	6:30 AM
54-57	6:15 AM
58-61	6:00 AM
62-65	5:45 AM
66-68	5:30 AM
69-72	5:15 AM
73-76	5:00 AM

If you usually sleep longer than 7 hours per night, you will need to wake up somewhat earlier than normal to achieve the effect – but you should feel better for doing that. Some people compensate by going to bed earlier, while others feel fine with shorter sleep. If you usually sleep less than 7 hours per night you will be able to maintain your current wake-up time. If you find yourself automatically waking up more than 30 minutes before your session start time, you should try moving the session later. Avoid taking sessions earlier than recommended, but if you happen to oversleep your alarm clock, it is better to take the session late than to skip it.

Our recommended light schedule for evening types – say, 8:00 AM (08:00 h) for a morningness-eveningness score of 30 – may make it difficult to get to work on time, yet taking the light earlier may not be helpful. Once you have noted improvement at the recommended hour, however, you can begin inching the light therapy session earlier by 15 minutes per day, enabling your internal clock to synchronize with your desired sleep-wake cycle and work schedule.

The personalized advice we give you here is based on a large clinical trial of patients with seasonal affective disorder (SAD) at Columbia University Medical Center in New York. Patients who took the light too late in the morning experienced only half the improvement of those who took it approximately at the times indicated. These guidelines are not only for SAD, but are also helpful in treatment of nonseasonal depression, for reducing insomnia at bedtime, and for reducing the urge to oversleep in the morning.

Our advice serves only as a *general guideline* for new users of light therapy. There are many individual factors that might call for a different schedule or dose (intensity, duration) of light. *Any person with clinical depression should proceed with light therapy only under clinical guidance.*

Reference: Terman M, Terman JS. Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. CNS Spectrums, 2005;10:647-663. (Downloadable at www.cet.org)

THE COLUMBIA EYE EXAM FOR USERS OF LIGHT TREATMENT

PATIENT	_____	EXAMINED BY	_____
ADDRESS	_____	ADDRESS	_____
	_____		_____
	_____		_____
PHONE	_____	PHONE	_____
REFERRED BY	_____	DATE OF EXAM	_____

CHECKLIST

RETINA		
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	+	–
Posttraumatic retinopathy	+	–
EYE COMPLAINTS		
Photophobia	+	–
Glare	+	–
Dry eyes	+	–
Blurred vision	+	–
Metamorphopsia	+	–
Color vision *(poor / good)*	+	–
Night vision *(poor / good)*	+	–
Other complaints:		

OTHER		
Inflammatory diseases of anterior segment/uveal tract	+	–
Glaucoma	+	–
Cataracts	+	–
Optic nerve affections	+	–
Keratoconjunctivitis sicca	+	–
Hypothyroidism	+	–
hormone supplement (yes / no)	+	–
stable (yes / no)	+	–
CURRENT MEDICATIONS		
Antidepressants (tricyclic)	+	–
Neuroleptics (phenothiazine)	+	–
Lithium	+	–
Tryptophan or melatonin	+	–
St. John's Wort (hypericum)	+	–
Psoralens	+	–
Antimalarial/antirheumatics	+	–
Diuretics (hydrocholorthiazide)	+	–
Porphyrins	+	–
Tetracycline	+	–
Sulfonamides	+	–
Other photosensitizers:		

EXAMINATION

Best corrected visual acuity

	R	L	
V_{SC}	_____	_____	
V_{CC}	_____	_____	Wearing _____
			_____

Ocular motility (9 cardinal directions of gaze)

R L

Intraocular pressure *(applanation), noting time of day:* _____

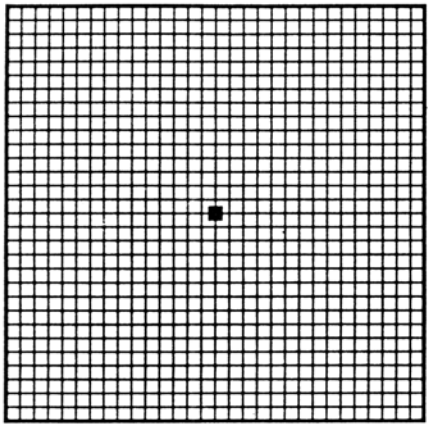
R L

Notes: Examining doctor should include a summary note indicating any problematic ocular conditions. This set of tests was specified for patients in the Clinical Chronobiology Program, New York Psychiatric Institute, Columbia-Presbyterian Medical Center, New York, NY 10032. The development team included: Pamela F. Gallin, M.D., Brian Rafferty, A.B., and Michael Terman, Ph.D., of Columbia University; Ronald M. Burde, M.D., of the Albert Einstein College of Medicine; and Charlotte E. Remé, M.D., of the University of Zürich, Switzerland. November 2000 version.

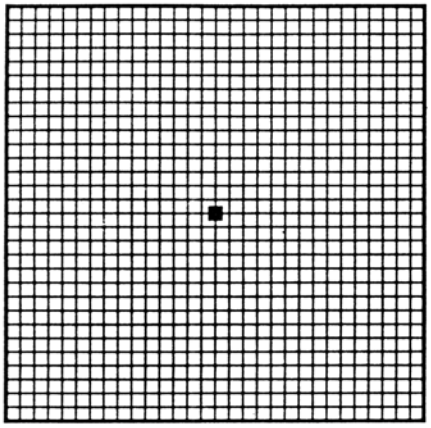
References: (1) Terman M, Remé CE, Rafferty B, Gallin PF, Terman JS. (1990) Bright light therapy for winter depression: potential ocular effects and theoretical implications. *Photochemistry and Photobiology* 51: 781-793. (2) Gallin PF, Terman M, Remé CE, Rafferty B, Terman JS, Burde RM. (1995) Ophthalmologic examination of patients with seasonal affective disorder, before and after bright light therapy. *American Journal of Ophthalmology* 119:202-210. (3) Remé CE, Rol P, Kaase H, Terman M. (1996) Bright light therapy in focus: lamp emission spectra and ocular safety. *Technology and Health Care* 4:403-413.

EYE EXAM, cont.

Amsler grid



R normal, abnormal (specify)

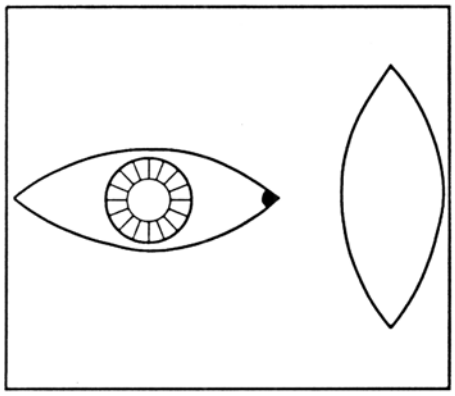


L normal, abnormal (specify)

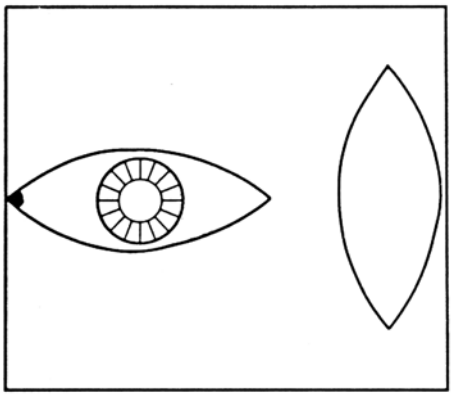
Pupillary reactions

R			L		
direct	+	–	direct	+	–
indirect	+	–	indirect	+	–

Slit lamp examination

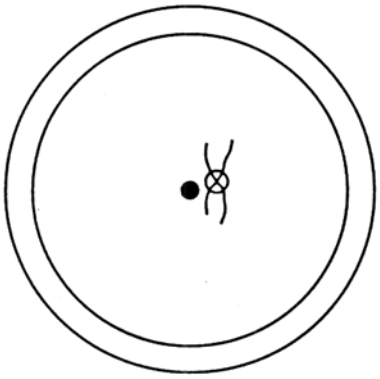


R

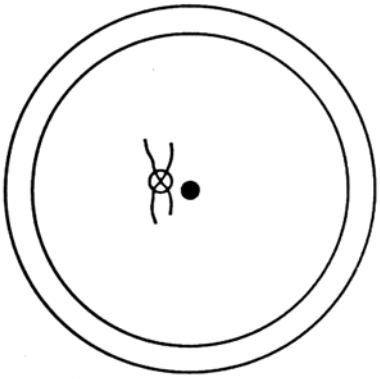


L

Ocular fundus *(check which:* __direct / __indirect / __mydriasis)



R c/d = _____



L c/d = _____

Bright Light Exposure Risks

Cautionary Notes About Bright Light Exposure

Light energy can interact with and damage skin and eye tissues, especially when a photosensitizing molecule—whether from a drug or produced by the body—is bound within those tissues. The highest risk (for damage to the skin, and cornea and lens of the eyes) is from invisible, short-wavelength ultraviolet (UV) light, which has been filtered out of CET's recommended light therapy system.

Long-term exposure to intense visible light in the blue range adjacent to the UV range may also pose a hazard to retinal photoreceptors and the pigment epithelium, which takes part in the photoreceptor renewal process. Above age 50, there is concern about blue-light exacerbation of age-related macular degeneration. Although some blue is an important component of white light exposure, lamps with relatively less blue (for example, soft-white fluorescents with color temperatures in the range of 3000-4000 Kelvin) should be favored over cool-white, daylight, or "full spectrum" lamps (5000 Kelvin and higher).

Pre-Existing Medical Conditions May Enhance Exposure Risks

There are certain pre-existing medical conditions of eyes and skin (retinal dystrophies, age-related macular degeneration, porphyria, lupus erythematodes, chronic actinic dermatitis and solar urticaria) that also can show photosensitized reactions to intense visible light. In such cases, bright light therapy should be administered only under guidance of an ophthalmologist or dermatologist, as indicated. Ophthalmologists should keep in mind that in some genetic retinal diseases the eyes are especially light sensitive.

Medications & Enhanced Exposure Risks

Certain medications are known to photosensitize skin and/or retinal tissues. Examples in the visible range of light include psychiatric neuroleptic drugs (e.g., phenothiazine), psoralen drugs, antiarrhythmic drugs (e.g., amiodarone), antimalarial and antirheumatic drugs, porphyrin drugs used in photodynamic treatment of skin diseases, and St. John's Wort (hypericum). Bright light therapy should not be used concurrently with these drugs. Melatonin can be used in conjunction with light therapy at opposite times of day (usually, evening and morning, respectively), but if used concurrently, it can cause photosensitization.

Drugs that photosensitize primarily in the invisible UVA range (just below the blue range) may also have a "tail" of light absorption that extends into the lower visible blue light range, which could cause photosensitization. Examples are tetracycline, diuretic drugs (e.g., hydrochlorothiazide), sulfonamide drugs and tricyclic antidepressants (e.g., imipramine, nortriptyline, desipramine, amitriptyline). If such a reaction is experienced or suspected, bright light therapy should be discontinued unless substitute medication is available, or it can be administered with protective measures under medical supervision.

In Conclusion

For the practice of bright light therapy, we must therefore consider the wavelength range of the light (and with that, its energy range) and the absorbing tissues in the eye. For normal healthy eyes, the exposure to bright white light is a physiological situation and does not inflict any overt damage to the skin, visual cells and pigment epithelium. There are, however, certain important caveats:

- Medications that can enter the skin or retina and that absorb light in the visible range. This might cause photosensitization with subsequent absorption of "too many photons," leading to damage. If you want to use bright light therapy but are questioning your medication, consult an ophthalmologist or dermatologist.
- Certain inherited dystrophies of the retina that alter the visual pigments and can render the retina especially sensitive to visible light. If you suffer from an inherited retinal dystrophy and want to use bright light therapy, consult an ophthalmologist.
- Age–related or other macular degenerations. For age–related macular degeneration, genetic factors increase the risk of disease by about 50%. Patients with such risk factors, or those with several family members suffering macular degeneration, should consult an ophthalmologist before using bright light therapy.
- Young eyes up to an age of about 30–40 years transmit much more light to the retina than older eyes. Thus, young eyes receive generally higher light doses than older ones.

Sources

Vincent DeLeo, M.D., St. Luke's-Roosevelt Medical Center, New York; Charlotte Remé, M.D., University of Zurich, Switzerland.

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INSTRUCTIONS TO PATIENTS FOR CONDUCTING LIGHT THERAPY SESSIONS

Sit under the lights daily beginning at _____ and ending at _____. (This schedule may change after we observe your initial response.)

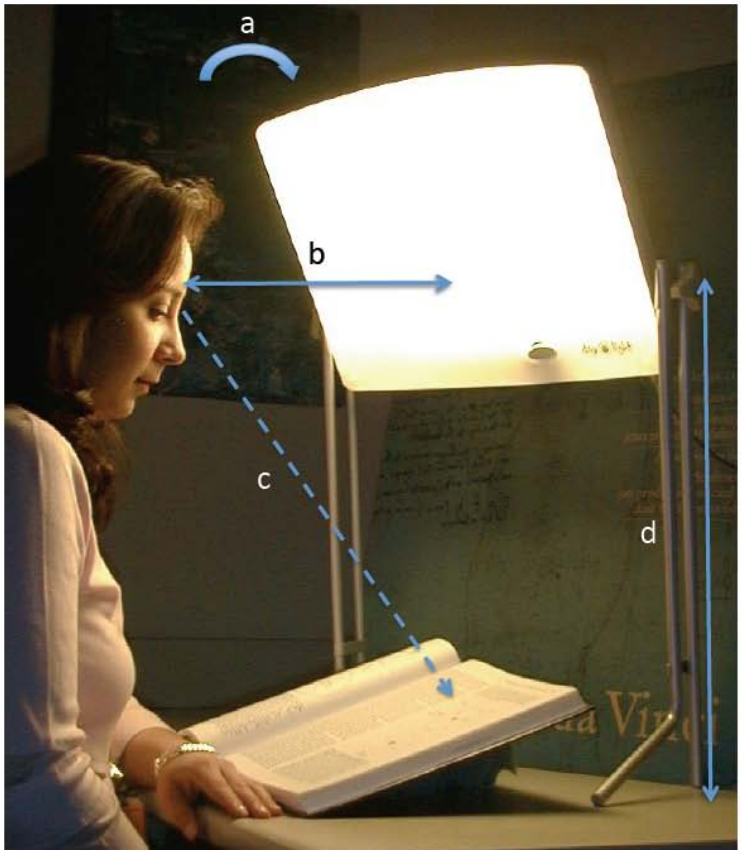
Tilt the light box downward by about 30 degrees, so the light shines down toward your head. The light box screen should be 12-13 inches from your eyes. When you look forward at the screen, your eye level should be about 1/3 to 1/2 from the bottom of the screen. Adjust your table or chair height as needed. During treatment, do not look directly into the screen. Rather, concentrate on the illuminated table surface while sitting erect. Do not bend forward or tilt your head down: the goal is to maximize light to your eyes while you maintain a downward gaze.

During the session, you can have breakfast, read, write, listen to music, use your cell phone, etc. Keep a large set of reading material on the table, so you can choose either easy or challenging things to read depending how you feel at the moment.

If you wake up before the session is scheduled, begin morning activities under regular room light, and wait to begin the session. (Do not start the session earlier.) If you oversleep, begin the session as soon as possible after you wake up. If you oversleep for more than 2 days in a row, let us know.

If you begin to feel any disturbing symptoms (like agitation or mild nausea) during a session, turn off the lights immediately and phone or email a report to Dr. Terman. We will get back to you to specify corrective steps.

If there is a psychiatric emergency, immediately contact your primary provider. If he or she is not available, you should go to the nearest emergency room. Be sure also to inform us by phone or email.



cet

HOW TO POSITION YOUR LIGHT BOX

a – Tilt the screen forward to an angle of about 30° from the vertical.

b – When looking straight forward with your head erect, the distance of the eyes should be about 12 inches (30 cm) from the screen, for 10,000 lux light on the 'high' switch setting. Do not sit closer or bend in toward the screen.

c – Focus downward toward the table surface during the session. Do not look into the lights.

d – Adjust the height of the device, or your seat or table, so your eye level is ⅓ to ½ up the screen when looking straight forward with your head erect.

DAILY SLEEP/MOOD/ENERGY LOG

INTRUCTIONS

1. Enter your name and the start date for this sheet.
2. After you wake up for the day, fill in 15-minute sleep intervals. If awake at night for 15 minutes or more, leave box blank. *Use your best recollection:* you should *not* be checking the clock while you are trying to sleep. Also mark daytime naps.
3. Enter the letter "L" (for light) in each box for the time of your light therapy session (if you are using lights).
4. Enter a symbol at appropriate times for medications and melatonin ("M" for melatonin). Define symbols on the list to the right.
5. For multiple medications taken at the same time, enter a "1", "2" or "3" at appropriate times, as shown on the list to the right.
6. In the morning, when you record your sleep, enter your average mood and energy ratings for *yesterday*.
7. Enter notes to explain unusual situations (for example, "out late," "stomach ache").
8. *Women:* if you are menstruating, add a note for each day.

IDENTIFY MEDICATIONS/DOSES TAKEN ONE OR MORE TIMES OF DAY, OR PRN ("AS NEEDED"). SPECIFY A SYMBOL FOR EACH DRUG.

1 - Morning: ____________________

2 - Midday: ____________________

3 - Evening: ____________________

4 - PRN: ____________________

NAME: ____________________

DAILY RATINGS
0 - worst ever
5 - feeling OK, fine
10 - highest ever

DAY OF WEEK: ________ **DATE:** ___/___/___ **NEXT DAY ➞**

12 1 2 3 4 5 6 7 8 9 10 11 | 12 1 2 3 4 5 6 7 8 9 10 11

noon | **midnight** *Continue this day on the next timeline.*

Yesterday's mood ☐ ***energy*** ☐

NOTES (place at time): ____________________

DAY OF WEEK: ________ **DATE:** ___/___/___ **NEXT DAY ➞**

12 1 2 3 4 5 6 7 8 9 10 11 | 12 1 2 3 4 5 6 7 8 9 10 11

noon | **midnight** *Continue this day on the next timeline.*

Yesterday's mood ☐ ***energy*** ☐

NOTES: ____________________

DAY OF WEEK: ________ **DATE:** ___/___/___ **NEXT DAY ➞**

12 1 2 3 4 5 6 7 8 9 10 11 | 12 1 2 3 4 5 6 7 8 9 10 11

noon | **midnight** *Continue this day on the next timeline.*

Yesterday's mood ☐ ***energy*** ☐

NOTES: ____________________

DAY OF WEEK: ________ **DATE:** ___/___/___ **NEXT DAY ➞**

12 1 2 3 4 5 6 7 8 9 10 11 | 12 1 2 3 4 5 6 7 8 9 10 11

noon | **midnight** *Continue this day on the next timeline.*

Yesterday's mood ☐ ***energy*** ☐

NOTES: ____________________

DAY OF WEEK: ________ **DATE:** ___/___/___ **NEXT DAY ➞**

12 1 2 3 4 5 6 7 8 9 10 11 | 12 1 2 3 4 5 6 7 8 9 10 11

noon | **midnight** *Continue this day on the next timeline.*

Yesterday's mood ☐ ***energy*** ☐

NOTES: ____________________

DAY OF WEEK: ________ **DATE:** ___/___/___ **NEXT DAY ➞**

12 1 2 3 4 5 6 7 8 9 10 11 | 12 1 2 3 4 5 6 7 8 9 10 11

noon | **midnight** *Continue this day on the next timeline.*

Yesterday's mood ☐ ***energy*** ☐

NOTES: ____________________

DAY OF WEEK: ________ **DATE:** ___/___/___ **NEXT DAY ➞**

12 1 2 3 4 5 6 7 8 9 10 11 | 12 1 2 3 4 5 6 7 8 9 10 11

noon | **midnight** *Continue this day on the next page.*

Yesterday's mood ☐ ***energy*** ☐

NOTES: ____________________

PLEASE KEEP EXTRA COPIES OF THE BLANK FORM TO CONTINUE THE LOG.

Start a new page for the next week.

Name ______________________________

COMPREHENSIVE CHRONOTHERAPY GROUP

Daily Log of Sleep Time, Light Therapy, Mood and Energy

Instructions: Complete the entries for each day after your final morning awakening. For mood and energy ratings, choose a number between 0 and 10, where 0 = the lowest in your life, 5 = normal, OK, or "no complaints", and 10 = the highest in your life.

Date	Day of Week *(circle)*	*Yesterday, I took melatonin at* (PM/AM)…	*Last night, I went to bed at about* (PM/AM)…	*Last night, I fell asleep at about* (PM/AM)…	*This morning, my final wake-up time was* (AM/PM)…	*Today, I started the lights at* (AM/PM)…	*Today, I finished the lights at* (AM/PM)…	*Yesterday, my overall mood level was* (0-10)…	*Yesterday, my overall energy level was* (0-10)…
__ / __ / __	M-Tu-W-Th-F-Sa-Su								
__ / __ / __	M-Tu-W-Th-F-Sa-Su								
__ / __ / __	M-Tu-W-Th-F-Sa-Su								
__ / __ / __	M-Tu-W-Th-F-Sa-Su								
__ / __ / __	M-Tu-W-Th-F-Sa-Su								
__ / __ / __	M-Tu-W-Th-F-Sa-Su								
__ / __ / __	M-Tu-W-Th-F-Sa-Su								
__ / __ / __	M-Tu-W-Th-F-Sa-Su								
__ / __ / __	M-Tu-W-Th-F-Sa-Su								
__ / __ / __	M-Tu-W-Th-F-Sa-Su								
__ / __ / __	M-Tu-W-Th-F-Sa-Su								
__ / __ / __	M-Tu-W-Th-F-Sa-Su								
__ / __ / __	M-Tu-W-Th-F-Sa-Su								
__ / __ / __	M-Tu-W-Th-F-Sa-Su								
__ / __ / __	M-Tu-W-Th-F-Sa-Su								

Send logs to fax 1-347-287-6825, or email nychronotherapy@gmail.com

Saliva Melatonin
Home Collection Procedure

Study ID Number _____ **Sampling Date _____**
mo/day/yr

Plan to stay home all evening and to stay under dim light conditions for 5 hours. You will be taking saliva samples every 30 minutes for about 4 ½ hrs in the evening, ending when you go to bed.

1. **Light Conditions**. Remove contact lenses. Wear the dark goggles (provided) starting 30 minutes before the first sample. While wearing the goggles, keep the light in the room sufficient to watch TV and to move from room to room.
2. **Restrict eating, drinking and medications.** Alcohol is not permitted during the clinical trial. On the day of saliva sampling, you are allowed a cup of coffee or tea only at breakfast; thereafter you must not drink any caffeinated drinks (including cola soft drinks). In addition, the following drinks, food and drugs are prohibited all day: beverages with artificial colorants, bananas, chocolate, aspirin (or aspirin containing products) and ibuprofen (Advil, Motrin, etc.) Dinner must be finished at least 30 minutes before the first saliva sample. No food or drinks other than water are allowed during the collection period. You may take a small sip of water immediately after depositing a saliva sample, but you must not drink water for 20 minutes before each sample.
3. **Tooth brushing.** After dinner, carefully but gently brush your teeth without using toothpaste and actively swish with water to expel any food particles. Do not brush your teeth again until after collecting all 9 samples.
4. **How to take a sample.** At the times indicated in the chart below, select the Salivette tube (marked with your subject identifier number – please don't write your name on tubes) and labeled for the appropriate sample (#1-#9), starting with the tube marked #1. Remove the cap without touching the absorbent swab. Pop the swab into your mouth and soak up saliva for 5 minutes by slowly moving the swab around your mouth. Then, directly deposit the swab into the small plastic container that sits inside the larger tube (don't touch the swab with your fingers) and close the cap tightly until it snaps shut to avoid any evaporation or leakage. Place each sample in your refrigerator as soon as it is completed.
5. **When all 9 samples have been collected**, store them in the clear labeled Zip-Loc bag in your freezer until you are ready to return them. Also, fold this instruction sheet and place it with the samples inside the Zip-Loc bag.
6. **Place the plastic gel pack** in your freezer at least one day before returning the samples.
7. **Returning the samples to the clinic.** Place the frozen gel pack and the Zip-Loc bag with samples from your freezer in the insulated transport bag. Remember to return the goggles and this instruction sheet with your samples please.

Finish dinner and put on the dark goggles at _____ P.M. **Bedtime will be at _____ P.M.**

Sample #	Begins at:	Make a check mark when completed:
1	_____ P.M.	_____
2	_____ P.M.	_____
3	_____ P.M.	_____
4	_____ P.M.	_____
5	_____ P.M.	_____
6	_____ P.M.	_____
7	_____ P.M.	_____
8	_____ P.M.	_____
9	_____ P.M.	_____

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EQUIPMENT AND SUPPLIES SOURCES

RECOMMENDED	ITEM	APPROX. PRICE	SOURCE
☐	DayLight Model DL930 (10,000 lux light box)	$153.79	Amazon.com http://ow.ly/rLqk2 (September 2014 price)
☐	FreshAIR high density ionizer with wrist strap	$165.00	CET online store, http://www.cet.org
☐	Per2 dawn simulator	$79.00	CET online store, http://www.cet.org
☐	HoMedics SS-2000F Sound Spa Relaxation Machine	$19.99	Amazon.com http://ow.ly/rLqxF (December 2013 price)
☐	f.lux software	free	http://stereopsis.com/flux/ set nighttime: 2700 Kelvin set daytime: 4500 Kelvin
☐	Photonic Developments LBL short-wavelength protective glasses (fitover or nonfitover)	$68.00 to $80.00	CET online store, http://www.cet.org
☐	*Reset Your Inner Clock* by Dr. Terman	$11.72 paperback $7.99 Kindle	Amazon.com http://ow.ly/rLqeH (September 2014 prices)
☐	Smartphone scanner apps (PDF-to-email)	$5-$7	iPhone app store: Scanner Pro http://ow.ly/rLpT3 Android Marketplace: CamScanner http://ow.ly/rLpZD

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re: HCPCS E0203, Therapeutic light box

Patient SAMPLE

Address _____

_____

Insurance ID no. SAMPLE

Date of Purchase _____

Vendor _____ *(Attach receipt.)*

To Whom It May Concern:

The patient has purchased a bright light therapy system (UpLift Technologies Day-Light 10,000 lux) for supervised use in home treatment. Diagnosis of (underlined): Major Depressive Disorder, Chronic (296.2), Major Depressive Disorder, Recurrent (296.3), Bipolar I Disorder (296.4, 296.5), Bipolar Disorder NOS (296.80), Bipolar II Disorder (296.89), Circadian Rhythm Sleep Disorder (307.45, 327.31), Dyssomnia NOS (307.47), Depressive Disorder NOS (311), Sleep Disorder – Hypersomnia Type (780.52), or Attention Deficit/ Hyperactivity Disorder (314) provides medical indication for use of light monotherapy or in combination with medication. We endorse insurance reimbursement for the apparatus as durable medical equipment (cf. Blue Cross/Blue Shield policy statement E01.01.04, 1 August 2003).

Outpatient light therapy has professional consensus for both first-line and adjunctive treatment of seasonal and nonseasonal depression:

American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder. Am J Psychiatry 2000 Apr;157(4 Suppl):1-45.

Depression Guidelines Panel. Depression in Primary Care: Volume 2. Treatment of Major Depression. Washington, DC: Agency for Health Care Policy and Research. Dept of Health and Human Services; 1993. Publication 93-0551.

Even C, Schröder CM, Friedman S, Rouillon F. Efficacy of light therapy in nonseasonal depression: a systematic review. J Affect Disord. 2008;108:11-23.

Goel N, Terman M, Terman JS, et al. Controlled trial of bright light and negative air ions for chronic depression. Psychol Med. 2005;35:945-55.

Lam R, Levitt A. (eds): Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder. Vancouver, BC, Clinical and Academic Publishing, 1999.

Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry*. 2005;162:656-662.

Terman M, Terman JS. Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety and side effects. *CNS Spectrums.* 2005;10:647-663.

Terman M, Terman JS. Light therapy. In *Principles and Practice of Sleep Medicine,* 4th ed. Kryger M, Roth T, Dement W, Eds. Philadelphia, Elsevier. 2005;1258-1274.

Tuunainen A, Kripke DF, Endo T. Light therapy for non-seasonal depression. *Cochrane Database Sys Rev*. 2005;2:CD004050.

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

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Doctor's name (printed) SAMPLE

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Signature