New York State Psychiatric Institute

Institutional Review Board

November 30, 2016

To: Dr. Jonathan Stewart

From: Dr. Edward Nunes, Co-Chairman
Dr. Laurence Greenhill, Co-Chairman

Subject: Approval Notice

Your protocol # **7361**entitled: **ARE BRIGHT LIGHTS AND REGULATED SLEEP EFFECTIVE TREATMENT FOR DEPRESSION?** Protocol version date 11/30/2016 and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **November 30, 2016 to November 20, 2017.** (Reviewed at the Full Board meeting on November 21, 2016.)

Consent requirements:
☐ Not applicable:
☐ 45CFR46.116 (d) alteration of consent to obtain verbal consent for the telephone interview
√ Signature by the person(s) obtaining consent is required to document the consent process
☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: √ No ☐ Yes

Field Monitoring Requirements: √ Routine ☐Special: _____

✓ Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.
✓ A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.
✓ Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.
✓ All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.

Cc: RFMH Business Office (grant)

Encl: Independent Evaluator, CF, cover sheet, adherence, questionnaire, HIPAA

EN/LG/alw

Signed copy on file at IRB

Protocol Title:
Are bright lights and regulated sleep effective treatment for depression?

Version Date:
11/30/2016

Protocol Number:
7361

First Approval:
11/30/2016

Clinic:
Depression Evaluation Service

Expiration Date:
Not yet accepted

Contact Principal Investigator:
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Co-Investigator(s):
David Hellerstein, MD

Research Chief:
B. Timothy Walsh, MD

Cover Sheet

Choose from the following that is applicable to your study
I am submitting a new protocol

Division & Personnel

Division

What Division/Department does the PI belong to?
Therapeutics
Within the division/department, what Center or group are you affiliated with, if any?
Depression Evaluation Service

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
None

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Use of Placebo or Sham Treatment
✓ Medication-Free Period or Treatment Washout
✓ Somatic Treatment or Intervention
✓ Internet-based Data Collection or Transmission

Population

Indicate which of the following populations will be included in this research

✓ Adults
✓ Adults over 50
✓ Employees or Students
✓ Individuals with HIV/AIDS

Research Support/Funding

Will an existing internal account be used to support the project?
Yes
Describe internal account
Any DES account from which project expenses can be drawn (specifically, l**ight boxes, activity monitors, amber and clear goggles,** and melatonin collection/analysis costs)
Is the project externally funded or is external funding planned?
No

Study Location

Indicate if the research is/will be conducted at any of the following

✓ NYSPI
✓ Other Columbia University Medical Center Facilities

This protocol describes research conducted by the PI at other facilities/locations
Yes

✓ Other Facilities

Other Facilities

Type in location(s)

Lay Summary of Proposed Research

Lay Summary of Proposed Research

Research Question: Is Chronotherapy (i.e., missing a night of sleep, shifting sleep time and bright morning lights to adjust the biological clock) effective treatment for non-bipolar depression?

Antidepressant medications do not result in quick remissions and they produce side effects. "Jet lag" can be thought of as resulting from the internal clock being out of sync with external time; as the internal clock aligns with sun time, the symptoms of jet lag lessen. Preliminary data suggest some depressed patients act as if their internal biological clock is out of sync with the outside world and re-aligning their clock with the timing of sunlight lessens their depressed mood and accompanying depressive symptoms. This "chronotherapy" may produce remission during the first week of treatment while causing minimal problems. This study aims to demonstrate the efficacy of chronotherapy by comparing its efficacy to an alternative protocol we consider unlikely to produce the same effects. Whether a given patient will be instructed to use chronotherapy or the alternative protocol will be determined randomly (i.e., by chance, essentially a computerized flip of a coin). Prior to determination of which protocol a patient will follow, each patient will declare their desired sleep time (for example, 11 p.m. to 7 a.m.). All patients will be assigned specific times to sleep and sit in front of bight lights wearing clear (Chronotherapy) or amber (alternative protocol) goggles. Those assigned Chronotherapy will miss a night of sleep while those in the alternative protocol will not; assigned sleep times will also differ between groups using different strategies to shift the timing of their sleep from their ideal sleep time as determined by their MEQ score to their desired sleep time. All subjects will be rated daily by telephone for the first week after their Wake Night (those assigned Chronotherapy) or for the first week following randomization (those assigned the alternative protocol), and then weekly for an additional five weeks. Whenever possible, weekly visits will be in person, although telephone visits will be allowed. All subjects will be rated at baseline, 1 week and 6 weeks by an Independent Evaluator blind to treatment assignment. After the six week post-randomization evaluation, all subjects will be offered six months of continued treatment and be rated monthly. Treatment during this six month period may consist of Chronotherapy or conventional antidepressants as the patient and doctor determine. Standard ratings of depression, over-all illness and functioning will be obtained; melatonin, sleep logs and activity monitoring will measure the timing of the biological clock. Change in the symptom measures will determine whether chronotherapy is as effective as, less effective than or more effective than the alternative treatment. Chronotherapy will be judged effective if it is more effective than the alternative treatment. Secondary analyses will analyze timing of melatonin rise, timing of sleep and activity to determine whether the timing of the biological clock changes, and if so whether clock changes correlate with improvement. Measures of functioning will determine whether functioning improves coincident with**,** independent of or subsequent to mood improvement.

Background, Significance and Rationale

Background, Significance and Rationale
While chronotherapy (variously including some number of nights without sleep coupled with early morning bright lights and set times for sleep with or without an advance in the timing of allowed sleep) has some degree of acceptance as effective treatment for affective disorders, the majority of the literature addresses bipolar illness. We found three studies that address depressed patients who do not have bipolar disorder. One concluded that chronotherapy is more effective for and is more quickly effective in depressed patients with bipolar disorder than those without a bipolar history, but conclusions as to whether this treatment is effective for nonbipolar patients cannot be made as there was no comparison condition (Barbini, 1998). Two studies (Martiny, 2012; Sahlem, 2014) included nonbipolar depressed subjects but neither separately reported response by polarity, although one stated that the nonbipolar subjects' response "did not differ". Both, however, also gave patients standard antidepressant treatment; i.e., chronotherapy was used as an add-on or augmentation rather than as the only treatment. Thus, Chronotherapy for nonbipolar depression appears to us to be insufficiently studied to judge its efficacy in this population. Our preliminary work (IRB #5491 and #6938) suggest our version of chonotherapy may be effective alone for nonbipolar depression. To date, we have treated 18 such patients; 10 (56%) were remitted at 1 week and 10 (56%) were remitted at 6 weeks. These results compare favorably to antidepressant medications. Szegedi (see uploads), for example, compiled data from 41 randomized, controlled trials; no drug resulted in increased remissions at week one relative to placebo. Ra**p**idly titrated mirtazapine resulted in significantly more remissions than placebo at week 2 (13% vs 7%), while all other drugs including usual dose mirtazapine, venlafaxine, selective serotonin re-uptake inhibitors, tricyclic antidepressants, trazodone and matprotyline separated from placebo at week 3 or later. Even at week 6, the highest remission rate was TCA at 40%. So, even considering the 95% confidence limits of 10 out of 18 range from 31-78%, these two open pilot studies raise the possibility that some patients can improve quickly, even in days, rather than the weeks it takes antidepressant medications to produce remissions. Definitive studies demonstrating the ability of chronotherapy to produce rapid remissions have not been conducted. This study aims to fill that void.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

Research Question
Is Chronotherapy effective treatment for nonbipolar depression?

Specific Aim #1: Demonstrate that Chronotherapy is effective treatment for nonbipolar depressive illness after one week of treatment.

Specific Aim #2: Demonstrate that Chronotherapy is effective treatment for nonbipolar depressive illness after six weeks.

Specific Aim #3: Demonstrate that Chronotherapy shifts the biological clock.

Hypothesis #1: Patients assigned Chronotherapy will be more likely to be remitted at week 1 than those assigned alternative treatment.

Hypothesis #2: Patients assigned Chronotherapy will be more likely to be remitted at week 6 than those assigned alternative treatment.

Hypothesis #3: Shift (earlier) of the onset of night-time melatonin secretion levels will be greater in chonotherapy-treated patients than in those receiving alternative treatment.

Description of Subject Population

Sample #1

Specify subject population
nonbipolar depression
Number of completers required to accomplish study aims
60
Projected number of subjects who will be enrolled to obtain required number of completers
75
Age range of subject population
18-65

Gender, Racial and Ethnic Breakdown

We anticipate our study population will consist of roughly:

Females 60%

Hispanics 15%

Race
Caucasian 65%
African-American/Black 15%
Asian 15%
Other/Mixed/Unstated 5%

Description of subject population
As above

Recruitment Procedures

Describe settings where recruitment will occur

Depression Evaluation Service: 3rd Floor New York State Psychiatric Institute, 1051 Riverside Dr., New York, New York

3 Columbus Circle: 14th floor, Suite 140**8**, 3 Columbus Circle, New York, New York

How and by whom will subjects be approached and/or recruited?

We anticipate that most patients will be approached and recruited by the clinician interviewing patients in IRB Protocol #6669R once it has been presumptively determined that all inclusion and no exclusion criteria have been met.

Additional patients initially recruited for another DES study may be suggested for this study once they complete any treatment portion of the other study (patients in the post-treatment follow-up phase of the other study will be eligible for recruitment into this protocol assuming they meet all inclusion and no exclusion criteria, agree to and sign consent for this protocol). Such patients from other protocols will either be recruited by their clinician in the other study (if that clinician is authorized to obtain consent for this protocol) or referred by the other study's clinician to a DES clinician authorized to obtain informed consent for this protocol.

Patients referred from other NYSPI clinicians and from CUMC will be interviewed and recruited through Protocol #6669R.

How will the study be advertised/publicized?
We do not envision advertising this study at this time. However, should we decide to advertise, any text and/or pictures will be submitted to the IRB for approval prior to their use, which will occur only after IRB approval. Non-advertising publicity may occur from time to time in the form of publicized interviews such as appearances on talk shows or news reports and print media articles based on interviews.
Do you have ads/recruitment material requiring review at this time?
No
Does this study involve a clinical trial?
Yes
YOU MUST REGISTER AT ClinicalTrials.gov IMMEDIATELY UPON RECEIPT OF IRB APPROVAL AND PRIOR TO ENROLLMENT OF THE FIRST SUBJECT. YOU WILL BE PROVIDED WITH A NCT REGISTRATION NUMBER ON REGISTRATION. PLEASE REVISE THIS SECTION OF THE PROTOCOL SUMMARY FORM TO INCLUDE THE NCT NUMBER AND RE-SUBMIT AS AN AMENDMENT TO THE IRB.

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement

Protocol #7088 involves a single blood draw to analyze for epigenetic markers; this blood draw may occur while patients participate in this protocol

Protocol #6669R is the DES Screening Protocol which most patients entering this study will complete prior to entry to this protocol

Protocol #5768 is a study of Cognitive Behavior Therapy; patients who do not remit upon completion of that protocol may be offered participation in this protocol, while non-remitters in this protocol may be offered treatment in #5768

We are still following some participants in Study #6457 (which compared desvenlafaxine to placebo) and #6263 (AKA #7160R) (which compared sertraline to placebo, non-responders crossed to bupropion or sertraline, respectively). While unlikely, should any such patients be eligible for this study, we would approach them. We would not endeavor to make them eligible, for example, by stopping current treatment in order to produce eligibility.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
nonbiopolar depression
Create or insert table to describe the inclusion criteria and methods to ascertain them

1. Age 18-65	1. Ask patient and compare stated age to reported DOB
2. Currently depressed	2. Has an affective disorder diagnosis per SCID interview (i.e., major depression, persistent depressive disorder, unspecified depressive disorder)
3. In reasonably good physical health	3. No active medical problem not under good control (e.g., someone with hypertension whose current blood pressure is in the normal range, someone with diabetes having a hemoglobin A1C < 7; abnormal thyroid tests [low TSH in someone taking thyroid medication is OK); so, medical history (from patient), labs, and when indicated discussion with primary care physician

Create or insert table to describe the exclusion criteria and methods to ascertain them

1. Bipolar disorder (I, II or unspecified)	1. SCID interview

2. History of psychosis	2. SCID interview
3. Unstable medical condition	3. medical history, labs, physical examination
4. Current (past six months) drug or alcohol use disorder	4. SCID interview; urine toxicology
5. Need for hospitalization	5. Clinician's judgment based on depression severity, suicidality or any other reason
6. Treating clinician determination not to include patient in this protocol	6. Clinician's judgment
7. Currently taking medication approved for the treatment of depression	7. Patient report
8. Un- or poorly controlled hypertension	8. BP on repeated readings of >= 150 systolic or >= 100 diastolic
9. Pregnancy	9. Patient report; lab test

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
6669R
Describe Study Consent Procedures
The consenting clinician after determining the patient is presumptively eligible (e.g., prior to lab results

returning) will explain the study procedures as well as alternatives, risks and possible benefits, answer any questions and offer the IRB approved study consent, watch the patient read the consent, answer any further queries and then watch while the patients signs the consent.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form
✓ Information Sheet

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Hellerstein, David, MD
Stewart, Jonathan, MD
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Potential participants will be interviewed under Protocol #6669R. Those meeting all Inclusion Criteria and no Exclusion Criteria will be offered participation in the study. For clarification purposes, no otherwise eligible subject will be offered participation in this study who is currently taking approved antidepressant medication and the DES will not suggest or recommend discontinuation of such medication in order to create an eligible subject. Informed consent will be obtained prior to any procedures specific to this protocol. If labs and physical have been done within three months, these will be obtained and reviewed; potentially exclusionary labs will either exclude the subject or be repeated to determine eligibility vs. exclusion; such recent labs and physical examinations will not be repeated unless the consenting physician deems a repeat appropriate; urine for pregnancy and drug testing will be obtained from all potential subjects whether recent such tests exist or not. All other patients who sign consent will have blood drawn, urine collected, EKG obtained and physical examination performed. Blood analyses will include SMA-25 (which assesses kidney and liver function, several electrolytes such as calcium, sodium and potassium and some other bodily functions), TSH (assessing thyroid function); urinalysis measures kidney and bladder function; other analyses of urine will test for commonly abused substances and pregnancy (if appropriate). Electrocardiogram assesses heart function. The Mini-Mental Status Examination (given to those over 60 years of age) assesses cognitive function (such as memory). Patients and doctors will complete a variety of ratings to assess mood, over-all symptoms, the timing of their biological clock and psychosocial functioning (see Table in "Uploads" for schedule of when ratings are done and by whom, and "Assessment Instruments" below for names, acronyms and descriptions of the assessment scales). Patients will be given an activity monitor to wear and sleep/activity/mood logs to complete daily. They will return in 1-2 weeks (although at patient's discretion, this time will be allowed to last up to 30 days) at which time mood symptoms will be reassessed. Those who do not remain depressed will not receive further treatment through the protocol although they will be offered three months of "open treatment" (i.e, they can consult with a DES psychiatrist who will prescribe whatever treatment the patient and doctor agree upon and available to the DES psychiatrist to use). Those still depressed will be randomly assigned to treatment with Chronotherapy or

alternative treatment (see below for descriptions). Prior to randomization, all patients will declare what time they desire to end up sleeping ("desired sleep time").

Chronotherapy

Patients assigned chronotherapy will determine which night during the ensuing week they will be able to miss a night of sleep ("Wake Night"); their chronotherapy protocol will begin that night. Followign their Wake Night, they will be instructed to sleep 8 hours at specific times; their first allowed sleep will be on the evening following their Wake Night starting at six hours prior to their desired sleep onset time. Their second allowed 8 hours of sleep time will be the following night starting three hours prior to their desired sleep onset time. Those whose desired sleep time is within two hours of the times determined by their responses to the Morningness-Eveningness Questionnaire (MEQ) will thereafter be instructed to sleep only at their desired sleep time. Subjects whose desired sleep time is more than two hours earlier than their MEQ derived ideal sleep time will be given instructions to sleep desired minus six and desired minus 3 hours the initial two allowed sleep nights; thereafter their allowed sleep will be later and later in maximal 3 hour increments until allowed sleep coincides with MEQ determined sleep times; thereafter, their allowed sleep will shift half an hour earlier every two-four days (depending on their ability to waken earlier) until their allowed sleep coincides with their desired sleep time. Whichever allowed sleep paradigm is followed, once sleep is at the desired time, their allowed sleep time will remain their desired sleep time thereafter. Patients whose desired sleep time is within two hours of their MEQ-determined ideal sleep time will sit in front of the bright lights wearing clear goggles throughout at their desired wake-up time beginning the morning following their Wake Night. Those whose MEQ-determined ideal sleep time is more than two hours different from their ideal sleep time will initially sit in front of the bright lights at their MEQ-determined ideal wake-up time, also beginning the morning following their Wake Night; as wake-up times shift earlier, time in front of the bright lights will shift with their allowed wake-up time. For the six weeks following randomization, whenever they sit in front of the light box, patients will be instructed to wear clear goggles.

To date, the longest time from wake-up prior to institution of a "Wake Night" until post-Wake Night allowed sleep has been 42 hours. Should time from prior wake-up to six hours earlier than desired sleep onset time project to more than 42 hours, first allowed sleep time will be shifted earlier so that first allowed sleep time is no more than 42 hours after their previous day's wake-up time. An additional day or days of shifting sleep will be added such that three hour per day increments (likely shorter on the last night) in allowed sleep time ends at their desired sleep time.

Should any patient have difficulty getting to sleep at the assigned time and/or waking at the prescribed time, they will enter a remedial protocol. This protocol will allow such patients to go to sleep when they feel tired and spontaneously waken for two nights, using the bright lights at the time they spontaneously waken (or at the previously assigned time if spontaneous wakening is earlier than the assigned time). The mean go to sleep and wake-up times of these two nights will determine their allowed sleep onset and wake-up times and the resulting wake-up time will be their new time to sit in front of the bright lights. They will then shift their allowed sleep and light use times half hour forward or back as appropriate until they are sleeping at their desired time and using the bright lights at their desired wake-up time. Should they have trouble shifting in half-hour decrements, shorter decrements will be used.

Alternative treatment

Patients randomized to alternative treatment will also be assigned specific allowed 8 hour sleep times and sit in front of the bright lights for half an hour each morning. Patients assigned alternative treatment will NOT miss a night of sleep; that is, they will not have a Wake Night. Their allowed sleep times will start at their MEQ-determined ideal sleep time. Subsequently, allowed sleep will shift in half hour increments or decrements as appropriate until allowed sleep coincides with desired sleep. They will sit in front of the bright lights each morning on waking up. Whenever they sit in front of the light box, they will be instructed to wear the amber goggles. The remedial protocol above will be followed with any patient unable to shift their sleep.

Ratings and timing of ratings will be identical for all patients. That is, all will complete the same rating scales throughout. In particular, all subjects will log in for 12 hours out of 24 during their initial 24 hours post-randomization, complete daily mood, sleep and energy logs, wear an activity monitor and have call-in interviews daily during the first post-randomization week. All will be interviewed by an independent evaluator blind to treatment assignment at baseline and Weeks 1 and 6, with ratings by their study clinician daily for the first week and weekly thereafter. At week 6, remitters will be recommended to continue bright light and allowed sleep times, although they will be asked to return their light boxes, goggles and activity monitors. Nonremitters will be offered alternative treatment, including Chronotherapy if assigned to the alternative treatment group and standard antidepressants whichever their assigned study treatment. All randomized subjects will continue to be seen at least monthly for six months with continued ratings each month.

Use of Light Boxes

All fecund women will be instructed to stop using the light box should they become pregnant. Also, regardless of group assignment, patients will be instructed to sit about 18 inches from the light box with eyes open but not looking directly at the light; instead they should read or use their computer or other sedentary activity. They should remain 18 inches from the light for 30 minutes. However, should side effects occur (e.g., overstimulation), the time may be decreased. Tolerance of the light box plus continuing depressed mood will trigger the doctor recommending longer light box use in weekly 15 minute increments up to 60 minutes total; first available increment would be at the week 2 visit, decrements can occur at any time.

Melatonin

All randomized subjects on the night they are randomized will collect saliva to later be analyzed for melatonin. They will be given tubes each of which contains a cotton swab with instructions to place a swab in their mouth every half hour (so, nine swabs = over a four hour period), write the date and time each swab was collected on the tube, refrigerate until they bring the vials in at their next visit. This is repeated over a three hour period at approximately one week (patients who have difficulty reaching their intended sleeping time will delay 2nd salvia collection until they reach their desired sleep time). In order to prevent ambient light from preventing melatonin secretion, all subjects will be issued blue-blocking amber goggles with instructions to wear them from an hour prior to start of saliva collection until the last saliva collection on each of the two nights during which saliva is collected.

Independent Evaluation

All study subjects who are randomized will be evaluated by someone who has no idea what their treatment has been, whether treatment has begun or how long treatment has been if currently being treated. These

Independent Evaluations will occur prior to institution of post-randomization procedures (typically on day of randomization), at the end of Week 1 and at the end of Week 6 post-randomization. If possible, this evaluation will be in person, but when in person interviewing is not possible these evaluations will be made by telephone. Independent Evaluators will be instructed not to ask any questions about treatment or where the interviewee is in the study. Participants will be instructed not to say anything to the Independent Evaluator about whether they are in treatment, or if in treatment what that treatment might be.

Independent Evaluators will be individuals trained in use of the Hamilton Rating Scale for Depression. They will not know what the study entails or be informed where the individual is in the study, that is, whether treatment has begun or what treatment the subject may be receiving. I have lined up Sudha Raman, M.A., as an Independent Evaluator. She has been trained in the obtaining the necessary information and scoring the Hamilton Rating Scale for Depression and has experience rating depressed patients using a structure version of the Hamilton Rating Scale for Depression (the SIGH-SAD) and has agreed to act as an Independent Evaluator in this study. I am searching for at least one (preferably two) additional individuals to also act as Independent Evaluators. Preferably such individuals will be already trained and have experience using the Hamilton Rating Scale for Depression; however, I will train candidates if necessary.

To assess whether Independent Evaluators are indeed "blind," following each evaluation, the Independent Evaluator will complete a form asking about whether they suspect the study subject is receiving treatment and if so what that treatment might be and why they think so.

Telephone Visits

Ratings on the six days following randomization will be by telephone. Other ratings will be in person whenever possible. However, we recognize that sometimes in person visits are not possible for patients; when this occurs, some evaluations and ratings are better both clinically and scientifically than are missed evaluations and ratings. Therefore, telephone ratings will be allowed at all visits after randomization. Once a patient is randomized to Chronotherapy, should he/she elect to remain awake some night other than the night they were randomized, a telephone visit the day they will later remain awake will reassess the ratings.

Protocol Violations

I was asked by the IRB Subcommittee to explicitly address what happens clinically and scientifically if patients do not adhere to their Wake Night. Falling asleep, for example, when the individual is assigned to remain awake, not logging in at the prescribed times and all other variances from the protocol will not automatically remove the patient from the protocol. To the extent that it is reasonable and possible, the protocol will be continued through Week 6 as if the violation had not occurred. It is difficult to enumerate each and every possible protocol violation with how each would be handled. The principle will be that from the point the violation is noted, the protocol will be resumed as if the violation had not occurred, though some violations might require new assigned sleep times. The only exception would be if the patient objected or it makes no clinical sense; an example of the latter would be if a patient was supposed to sleep from, say, 6 pm until 2 am, instead slept from noon to 8 pm, we would not insist he/she go back to bed til 2 am but would ask the patient to continue their 8 am bright lights and try not to sleep again til 9 pm the following night (assuming those had been the predetermined times for sleep and lights).

Scientifically, we will record protocol violations (see "Protocol Adherence Form) but all analyses will be "intent to treat". That is, once a patient is randomized, he/she is included in all efficacy analyses out to the

point at which there are no more data; missing intermediate data will be estimated by interpolation, missing end data will be estimated by last observation carried forward.

Treatment after six weeks

Following the six weeks post-randomization period, **for reasons best known to the IRB all fecund women not already known to be pregnant will provide a urine to be tested for pregnancy. While we will make the request of all fecund women, we will not deny post-study treatment to any who fail for any or no reason to supply a post-treatment urine sample. A**ll patients will be offered continued treatment at the DES as determined jointly by patient and DES physician. In general, those who did well with Chronotherapy would have the recommendation they continue a.m. bright lights and regular sleep times, though they could opt for alternative treatment or to discontinue these and see how they do having the back-up of returning to this or instituting different treatment should depressive symptoms return. Those who do well with the alternative protocol will be allowed to continue it, but with the explanation that we think they probably improved for reasons other than something specific about the Alternative Protocol; therefore, they might best see how things go without the a.m. lights, amber goggles and specific sleep times, reverting to these or other standard treatments should symptoms return. Alternative Treatment subjects who do not benefit, will be offered the alternative of Chronotherapy or standard antidepressant medications. Nonresponders to Chronotherapy will be offered standard antidepressant medications.

Prior to beginning treatment and again six weeks after randomization, all patients will be told that light boxes, goggles, and post-study (i.e., beginning six weeks post-randomization) medications are their responsibility and will not be paid for or supplied by the DES or the NYSPI. They will be informed that the light boxes we use in the study cost about $150. They will receive six months of clinical visits with a DES psychiatrist beginning six weeks after randomization.

You can upload charts or diagrams if any
Flow Chart.22Nov16.pdf

Criteria for Early Discontinuation

Criteria for Early Discontinuation

1) patient withdraws consent

2) clinician judgment that change in treatment should not wait until end of study (i.e., six week post-randomization evaluation)

3) need for hospitalization

4) overt suicidality or clinician judgment that overt suicidality is a significant risk prior to six week post-randomization evaluation.

After six weeks, patients receive "open treatment" (that is, patient and doctor negotiate what, if any, treatment will be) so following the six week randomized treatment period there is nothing to withdraw, although patients throughout can choose not to continue treatment or can choose to continue treatment without the ratings being done and circumstances may dictate a change in what the open treatment is.

A study doctor (right now that would be Drs. Hellerstein and Stewart, possibly later also Dr. Steinberg) will always be available to patients by telephone and patients will be so informed. In addition, for the first week post-randomization, a study doctor will telephone patients each day, obtaining the information needed to rate the SIGH-ADS, thereby learning about worsening or other reasons to consider removing the patient from the study and/or asking the patient to be seen earlier than next visit or other instruction, such as go to nearest Emergency Room.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
See Flow Chart, below (which should be identical to that uploaded under "Study Procedures"). I have included below ratings with which I suspected the IRB might not be familiar. Should the IRB desire additional documents, I will be pleased to provide them.
Please attach copies, unless standard instruments are used
Flow Chart.22Nov16.pdf
Independent Evaluator Treatment Guess.27Oct16.pdf
MEQ.8Apr11.pdf
PATIENT ADHERENCE FORM.pdf
MEQ-rev 11_01.pdf

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
Approximately 7 weeks, although delays in obtaining labs, waiting for a 'clean' urine, scheduling, patients desire to delay their Wake Night might in some cases delay randomization beyond a week. Study participation concludes after 6 weeks, and the 6 months after study participation is considered clinical treatment. **Nevertheless, pregnancy testing will be requested from fecund women prior to institution of post-study treatment.**
Maximum duration of delay to standard care or treatment of known efficacy
Same as above. As the purpose of this study is to demonstrate the efficacy of Chronotherapy, it cannot be considered to have "known efficacy." Hence, all subjects will be delayed in potentially receiving treatment of "known efficacy."
Treatment to be provided at the end of the study
This depends on the definition of "end of the study." If the end of formal randomizaed treatment, then the six months of "open" follow-up is the duration of post-study treatment. If "end of study" is considered the

end of rating scales, then there is no further commitment of the DES to treat the patient, as these continue through the six months of "open" treatment. "Open treatment" means the study does not determine what the treatment is; instead the treating doctor and the patient together determine what the treatment will be.

Clinical Treatment Alternatives

Clinical treatment alternatives
Standard treatments include about 30 marketed antidepressant medications, several FDA-approved devices, including electroconvulsive treatment, transcranial magnetic stimulation and vagal nerve stimulation, and several psychotherapies having some degree of evidence of efficacy, including cognitive behavior therapy, interpersonal psychotherapy and cognitive behavioral analysis system of psychotherapy. To our knowledge, none has been compared to chronotherapy, so comparative efficacy is unknown. And, as efficacy of chronotherapy is unknown, it cannot be considered to be an effective treatment; nor is it a generally accepted treatment.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

1. overstimulation - both remaining awake over night and bright lights can be stimulating. A worry is that such stimulation will result in hypomania or even mania. Most find the overstimulation uncomfortable and do not like it (as opposed to hypomania which is generally liked by those experiencing it). While we have occasionally had reports of overstimulation attributable to bright lights, we have not seen mania or hypomania. Benedetti (2012; see Uploads) estimates the risk of switching is 6% in patients with bipolar disorder, somewhat less than his estimate of a 15% switch rate during other forms of treatment. As patients with bipolar disorder carry an inherent risk to switch mood states, it is unclear that the 6% switch rate in bipolar illness ought to be attributed to the chronotherapy. And, if there is a risk in non-bipolar illness, it ought to be lower than in bipolar disorder, though we are unaware of literature suggesting a frequency of "switching" in nonbipolar patients.

2. fatigue - will likely occur following a night of missed sleep.

3. eye damage - while this has been listed as a risk, to our knowledge it has never been demonstrated. Indeed, the only prospective study of which we are aware (Gallin et al, 1995) found no eye/retinal changes after six weeks (N=50) or after 3-6 years (N=17). Indeed, sunlight is quite safe except for ultraviolet (UV) exposure and prolonged exposure to direct bright light; the light boxes we will use in this study do not emit significant UV light, nor is the 10,000 lux intensity of the light boxes we will use anywhere near the intensity of light known to produce retinal damage. To our knowledge, no ophthalmologist recommends that we avoid going outdoors between 9 a.m. and 4 p.m. when outdoor light is at or greater than 10,000 lux. See "Uploads" for the Gallin reference.

4. patient's depression may not improve - this, of course, is the risk of any treatment one might choose, or of not being treated. It is unclear, however, whether chronotherapy improves on not being treated or approximates/surpasses accepted treatments.

5. pregnancy - while it makes sense that simulated sunlight ought not to adversely affect a pregnancy, to our knowledge, this has not been studied so the affect of the bright lights we have patients use in this study must be considered of unknown risk to a pregnancy. We are also unaware of documentation of missed sleep or regulated sleep adversely affecting pregnancy, so also consider these to have unknown risk to pregnancy.

Describe procedures for minimizing risks

1. overstimulation - we have not seen overstimulation during Wake Nights, but have occasionally had patients report it at the end of a session using bright lights. Should it be reported during a Wake Night, the patient would be instructed to find a quiet dark place in which to sit or lie quietly, try to calm down and not worry should they fall asleep. In the more likely case that it occurs during or following light treatment, the patient would be instructed to decrease their light exposure by sitting further away from the lamp or sitting in front of the lamp for a shorter time. In the case of patients who experience overstimulation toward the end of their light exposure, they would be instructed to sit in front of the lights for the amount of time prior to their experience of overstimulation. Thus, if overstimulation began after 25 minutes, they would be instructed next time to sit in front of the lights for 20 minutes.

2. fatigue - reassurance that fatigue will decrease as they recover their sleep in nights subsequent to their Wake Night. Should uncharacteristic (i.e., not present prior to treatment) fatigue continue after apparent sleep recovery, this will be take as evidence that the new timing of their sleep is out of sync with their biological clock such that a significant portion of their assigned sleep time is occurring when their biological clock insists they ought to be awake. That is, the paradigm has not shifted their clock. This will trigger a new attempt to shift their clock as is outlined for patients whose MEQ-determined ideal sleep time is more than two hours different from their desired sleep time. All patients will be warned re driving and using heavy/dangerous equipment during and following missed sleep as well as if significant fatigue occurs at other times.

3. eye damage - as damage from light is mainly attributed to exposure to ultraviolet rays and very high intensity light, this risk will be minimized by limiting bright light use to devices certified to emit only visible light; that is, not to emit UV light. And at a much lower intensity than used, for example in laser surgery or emitted by the noonday sun (> 100,000 lux, or more than 100 times the intensity of the emission of the light boxes we use [lux is measured on a logarithmic scale, not a linear scale]) which would damage the retina if stared at for too long a time. That is, the intensity of light used in this study is one the eye often experiences and one no one is warned against.

4. depression may not improve - as noted, this is a risk whether one pursues accepted treatment or does nothing. The odds of either treatment approach relieving a patient's depression is unknown and the purpose of this protocol is to begin determining those odds. Attention, a listening (hopefully) ear, activating oneself to come to weekly meetings may be expected to produce more benefit than not being engaged in treatment. While the protocol will not automatically remove patients whose symptoms do not improve prior to six weeks post-randomization, patients and clinicians will always have the option of discontinuing the protocol

for any reason, including but not limited to the emergence of suicidal ideation/activity and worsening symptoms whether such worsening includes suicidal ideation/activity or not. We will leave it to patient preference and treater's clinical judgment, however, whether to continue or remove patients.

5. Pregnancy - all fecund women will be told at their consenting visit that risk of the study procedures to an unborn fetus is unknown; therefore, they must discontinue all study procedures if they think they might be pregnant until it becomes known they are not pregnant. And, immediately contact a study physician. **In addition, pregnancy testing will be performed at the patient's consenting visit and again following the six week experimental treatment immediately prior to "open" treatment, although failure to provide urine for pregnancy testing will not lead to denial of "open" treatment. Failure to provide a specimen for pregnancy testing or a positive pregnancy test prior to experimental treatment would lead to denial of experimental treatment.**

Methods to Protect Confidentiality

Describe methods to protect confidentiality
Confidentiality will be maintained by keeping physical data in locked file cabinets, while electronic data will be collected within the HIPAA compiant StudyTRAX system, which when downloaded will be kept behind the PI firewall in data files accessible only to authorized staff using a password. We do not anticipate sharing data with researchers outside PI, but if this were to occur, only data with identifying information (e.g., name, birth date) removed will be sent outside PI, and prior IRB approval would be obtained. Should it become necessary for the treating psychiatrist to contact the subject's primary physician to obtain copies of their medical records or release our records to other providers, explicit written agreement for such record transfers will be obtained from the patient.
Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects
Their depression may improve, either with initial treatment, or with subsequent treatment. If their depression improves without use of medication, they may be spared taking medication.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
No

Uploads

Upload copy(ies) of unbolded Consent Form(s)
Wake DB CF.unbolded.22Nov16.pdf
Upload copy(ies) of bolded Consent Form(s)
Wake DB CF.bolded.22Nov16.pdf
Upload copy(ies) of unbolded Information Sheet(s)
Cover Sheet for DB Wake.unbolded.15Sept16.pdf
Upload copy(ies) of bolded Information Sheet(s)
Cover Sheet for DB Wake.bolded.15Sept16.pdf
Upload copy(ies) of the HIPAA form
HIPAA.DB Wake.15Sept16.pdf
Upload any additional documents that may be related to this study
Szegedi.Early Onset.JCP2009.pdf
Bennedetti 2012.pdf
Barbini.UP_BP.PsychRes1998.pdf
Martiny.PLOS One.2013.pdf
Sahlem.JPsychRes2014.pdf
IRB Memo.11.07.16.pdf
Negative effect of BL on retina.Gallin 1995 Am J Ophthal.pdf

References

References

Szegedi et al: Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: A meta-analysis including 6562 patients. J Clin Psychiatry 2009;70(3):344-53.

Benedetti F: Antidepressant chronotherapeutics for bipolar depression. *Dialogues in Clinical Neuroscience 14*:401-11;2012.

Barbini et al: The unipolar-bipolar dichotomy and the response to sleep deprivation. *Psychiatry Research 79*:43-50;1998.

Gallin et al: Ophthalmoolgic examination of patients with seasonal affective disorder, before and after bright light therapy. *Am J Ophthalmology 119*:202-210;1995.

Martiny K 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. J Clin Psychiatry 73:1234-42;2012.

Sahlem et al: Adjunctive chronotherapy (combined total sleep deprivation, sleep phase adv ance, and bright light therapy) rapidly improves mood and suicidality in suicidal depressed inpatients: An open label pilot study. J Psychiatric Res 59:101-7;2014.

22 November 2016 IRB #7361

CONSENT FORM

Are Bright Lights and Regulated Sleep Times Effective Treatment for Depression?

Purpose and Overview

The purpose of this study is to find out whether sleeping only at regulated times and sitting in front of a bright light wearing different colored or clear goggles is effective treatment for depression. You are being asked to participate in this study because you are depressed and do not have mood swings (bipolar disorder).

Voluntary

Participation in this research study is voluntary. If you decide not to participate, or if you later decide to stop participating, or your doctor removes you from study participation for any reason, you will not lose any benefits to which you are otherwise entitled. A decision not to participate or withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute or Columbia University.

Alternatives to Participation

There are alternatives to your participating in this study. If you previously participated in another treatment study, you may be eligible for further treatment without taking part in this study. You can go to a private doctor or to a psychiatry clinic where you may receive any of the medications marketed for depression. Electroconvulsive treatment and focused psychotherapy are also accepted treatments for depression. Electrical stimulation of a nerve in the neck (called the vagus nerve) has also been approved by the FDA.

Study Procedures

In order to find out if you can be treated in this study, you will receive a complete psychiatric evaluation by a study psychiatrist. If the study psychiatrist decides you can participate, you will be given this consent form to read. If you then agree to participate and are satisfied that your questions have been answered, you will then sign the consent form. A member of the research team will then complete research rating forms, you will complete self-report ratings, about 15 cc (approximately a tablespoon) of blood will be drawn for routine laboratory testing (for example, to make sure your kidneys and liver are healthy), a doctor will perform a physical examination (for example, listen to your heart and lungs, look into your eyes) and you will provide a urine specimen (to be checked for kidney function, pregnancy if you are a woman of child-bearing age, and street drugs such as heroin and cocaine). These tests will determine if you have a medical disorder such as low thyroid function that might be the cause of your depression or that should be treated prior to your entry into this. If you have one of these medical problems, your doctor will discuss this with you at the first visit after it is found, or telephone you if it requires quicker attention.

You have been offered participation in this study because you are depressed. Once you have agreed and signed the study consent form, you will be asked to answer questions about your mood, prior treatment, the times of the day you like to do things, a variety of common psychiatric symptoms and your interest and functioning in several life circumstances, like work and family. You will wear an activity monitor (which looks like a wrist watch) and keep a log of your sleep, mood and energy for about seven weeks. After 1-2 weeks (you can choose to wait up to 30 days before re-evaluation), you will be re-evaluated. If you remain significantly depressed at this re-evaluation, and remain agreeable,

you will begin sleeping only at assigned times (regulated sleep therapy) plus sitting in front of bright lights wearing goggles. The timing of your allowed sleep and whether the goggles you wear will be clear or amber will be determined randomly (as if by a flip of a coin). Whatever timing and goggles you are assigned you will continue for the next six weeks, initially with daily telephone evaluations and from the end of week 1 through the end of week 6 weekly in person. At the time you are randomized and again at weeks 1 and 6 visits you will also be evaluated by a rater who does not know whether you have begun treatment or what treatment you may be receiving. It is important that you not let on whether you have begun treatment, or, if you have, what that treatment has been.

Light and Regulated Sleep Therapy

Treatment will be with bright lights and regulated sleep times. To help us determine whether this approach is effective treatment and which times for sleep and bright lights and how best to use the bright lights, by chance different patients will receive different instructions. All will be given specific times they are allowed to sleep and specific times to sit in front of the bright lights. Time sitting in front of the bright lights will begin at 30 minutes, but if you have trouble tolerating the light your doctor may tell you to decrease this time shorter (to as little as 10 minutes), and if you tolerate the light but remain depressed your doctor may tell you to increase the time (up to 60 minutes). For some the specific sleep times may include a 48 hour period during which they are not allow to sleep as long as 42 hours. You will be provided goggles both to wear in the evening during saliva collection for melatonin and when sitting in front of the bright lights. Some goggles will be clear and some will be amber. Prior to being told your specific times for allowed sleep and use of the bright lights, you will complete the Morningness-Eveningness Questionnaire; your answers will suggest where your biologic clock is currently set and partially determine the times you will be allowed to sleep and instructed to use the bright lights. You will also report the time you want to be sleeping which will also determine the sleep instructions and timing of your bright light use.

Risks and Inconveniences

General. A general risk is that you may remain depressed. It has not been determined whether the combination of wake therapy, light therapy and regular allowed sleep is effective for your disorder. Second, suicide is a risk in patients who are depressed. Patients with bipolar disorder may become manic. These risks will be minimized by: (a) exclusion of patients known to have bipolar disorder; (b) not participating in the study if you or your doctor consider you to be at significant risk to harm yourself or in need of hospitalization; (c) discontinuing study participation should you become significantly worse or significantly suicidal; (d) offer of hospitalization in the case of significant worsening/suicidal thoughts/behavior; (e) weekly visits and 24 hour phone availability of an experienced research psychiatrist.

Remaining awake for long periods. The major risk of remaining awake for long periods is mania. This possibility will be minimized by only including patients without a history of mania or hypomania (a period of being “high” without being manic), constant availability of access to a research psychiatrist by telephone. An additional risk is being drowsy at times alertness is required, such as driving or operating heavy machinery. Therefore, if assigned extended periods of wakefulness or if you feel sleepy, you should not drive or operate heavy machinery.

Light Therapy. Patients may become over-stimulated, and those with bipolar disorder may become manic. As this study will not include patients known to have bipolar disorder, this risk seems minimal, but likely not zero, especially since not all patients with bipolar disorder are known to have it. More commonly, over-stimulation is described as “like too much coffee” and can be eliminated by decreasing

bright light exposure, either by decreasing the time in front of the light or increasing the distance from the light, or both. Occasionally, light exposure may also cause headache, nausea or eye irritation. Again, these will be counteracted by increasing the distance for the light, decreasing the time you sit at the light or both. Long-term research studies have found that light therapy is safe for the retina of the eye. Nevertheless, **as a precaution, we will examine your retina to see whether there are already signs of damage, and you will not receive light therapy if you have retinal conditions such as retinitis pigmentosa or macular degeneration**. As the lights used are similar to early morning light in intensity but without any ultraviolet radiation, they may be considered safer than going outside on a sunny day.

Additional Risks

Participation in this study may involve risks that we currently do not know. Some discomfort may be associated with the drawing of blood samples. A maximum of 1 tablespoon of blood will be taken unless there is a medical reason to obtain extra blood. There is a minor risk of bleeding, bruising, or infection at the site of the needle insertion. With any treatment there is the risk that the treatment may not help and the depression might become worse. Also, if a treatment is effective or partially effective there is the risk of worsening of symptoms if the treatment is stopped or the dose is reduced.

Benefits

Your depression may improve.

You will be informed if significant new information becomes known about treatment of depression or about the treatments used in this study, especially if such information might affect the willingness of some subjects to continue their participation.

Confidentiality

All study information is kept in locked cabinets at the Depression Evaluation service at the New York State Psychiatric Institute or in a secure HIPAA compliant computer accessable only by study staff. Records will be kept confidential to the extent permitted by law. Your name and other personal identifying information will be stored in an electronically secure database at New York Psychiatric Institute. Any publications will present only group data and not include information that could identify you. Records will be available to research staff, and to Federal, State and Institutional regulatory personnel (who may review records as part of routine audits). Also, you should be aware that there are legal advocacy organizations that have the authority under New York State law to access otherwise confidential subject records, though they cannot re-disclose this information without the subject's consent. Electronically stored/transmitted data will be password protected with access only to study personnel.

There are limits to confidentiality. For example:

If your answers indicate a serious problem that may jeopardize your safety or health, then the researchers will contact your physician or emergency personnel as seems appropriate to your well-being. Also, suspected or known neglect or sexual or physical abuse of a child, or threatened violence to self or others will be reported to the appropriate authorities.

Study Compensation

Tests that are part of the research study are provided free of charge, and neither

you nor your insurance company or other third party payer will be billed for these, including hospitalization, if at the New York State Psychiatric Institute. Any tests not required by the research will be paid for by you or your insurance company. In addition, following 6 weeks, regardless of initial treatment assignment, all participants will continue to be followed and complete monthly ratings for an additional six months; during this post-6 week six months, the cost of any prescription, whether for medication or light box will be your responsibility. After this six month post-12 week treatment period, should you and your doctor determine that further psychiatric treatment is indicated, your doctor will help you find an appropriate treater.

In Case of Injury

Federal regulations require that we inform participants about our institution's policy with regard to compensation and payment for treatment of research-related injuries. In case of injury, New York State Psychiatric Institute will provide short term emergency medical treatment, which has been determined to be necessary by New York State Psychiatric Institute's doctors. In addition, we will provide assistance in arranging follow up care in such instances. New York State Psychiatric Institute and Research Foundation for Mental Hygiene do not provide compensation or payment for treatment of research related injuries. However, you should be aware that you do not give up your legal right to seek such compensation through the court by participating in this research.

Questions

Your study doctor will answer any questions you may have now or in the future to the best of his/her ability. If you should have additional questions, you can contact the Principal Investigator, Jonathan W. Stewart, M.D., (646-774-8070).

If you have any questions about your rights as a research participant, want to provide feedback, or have a complaint, you may call the NYSPI Institutional Review Board (IRB). (An IRB is a committee that protects the rights of participants in research studies). You may call the IRB Main Office at (646)774-7155 during regular office hours. You will be notified of significant new findings that may relate to your willingness to continue to participate.

Women of Child-bearing Age

While these treatments are considered to be fairly safe during pregnancy, the study excludes women who are pregnant. Therefore, a pregnancy test will be performed and if it is positive, you cannot participate. Also, we ask that you use reasonable precautions not to become pregnant while participating and if you choose to be treated with medication after the initial six weeks of treatment. Because the safety of missing a night of sleep, keeping specific sleep schedules or bright lights are unknown in pregnancy, you should not be pregnant or become pregnant while using these treatments. Should you become pregnant, you should immediately contact a study psychiatrist and discontinue any treatment until informed otherwise by a study psychiatrist. **After the six weeks research treatment, you will again be asked to produce a urine specimen which will be tested for pregnancy. If do not produce a urine at the six week time point, continuing treatment will not be denied.**

By signing this form, you are indicating that you have discussed this research study and consent form with an investigator, and he/she has answered all of your questions about the study to the best of his/her ability. Your study doctor will answer to the best of his/her ability any questions you may have about the study, your psychiatric condition or your reaction to the study procedures. If you have any further questions, you may call Jonathan W. Stewart, M.D., the Principal Investigator of this study, at 646-774-8070.

You will receive a copy of this consent form to keep.

Documentation of Consent

I voluntarily agree to participate in the research study described above.

Print name: _____

Signed: _____

Date: _____

I have discussed the proposed research with this participant including the risks, benefits, and alternatives to participation (including the alternative of not participating in the research). The participant has had an opportunity to ask questions and in my opinion is capable of freely consenting to participate in this research.

Print name: _____

Person Designated to Obtain Consent

Signed: _____

Date: _____

Table - Flow Chart																				
	00	RZ	D1	D2	D3	D4	D5	D6	D7	W2	W3	W4	W5	W6	M1	M2	M3	M4	M5	M6
Clinician-Rated Measures																				
- SCID	X																			
- HIGH-C	X	X							X	X	X	X	X	X	X	X	X	X	X	X
- SIGH-ADS	X	X							X	X	X	X	X	X	X	X	X	X	X	X
- CGI	X	X							X	X	X	X	X	X	X	X	X	X	X	X
- m-HIGH-C		X	X	X	X	X	X	X	X											
- m-SIGH-ADS		X	X	X	X	X	X	X	X											
- m-CGI		X	X	X	X	X	X	X	X											
- MMSE*	X																			
Independent Evaluator																				
- SIGH-ADS		**X**							X					X						
- CGI		**X**							X					X						
- **IE Treatment Guess**		**X**							**X**					**X**						
Patient-Rated Measures																				
- QIDS	X	X							X	X	X	X	X	X	X	X	X	X	X	X
- Expectation Form	**X**																			
- PGI	X	X							X	X	X	X	X	X	X	X	X	X	X	X
- MEQ	X	X												X						X
- SCL-90	X	X							X					X			X			X
- sleep log	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
- m-QIDS		X	X	X	X	X	X	X	X											
- m-PGI		X	X	X	X	X	X	X	X											
Laboratory and other																				

- PE	X																			
- labs	X																			
- saliva for melatonin		X							X											
- urine for pregnancy**	**X**							**X**												

* used only for those aged 60 and above

**** only for fecund women not already known to be pregnant**

KEY TO ABBREVIATIONS

CGI (Clinical Global Impression) - this is a clinician rated global measure of the patient's over-all psychopathology and improvement over the past week, improvement compared to pre-treatment

HIGH-C (Hypomania Interview Guide including Hyperthymia, Current Assessment Version) - this is a clinician-rated measure of manic/hypomanic symptoms rated over the past week

labs (laboratory examinations) - these include **EKG,** blood and urine; blood is examined for hematology (e.g., whether the patient is anemic) and routine blood chemistry (e.g., whether the patient has problems with their liver, kidney or thyroid); analysis of the urine determines whether there is a kidney

m-CGI - this is identical to the CGI except it measures the past 24 hours

m-HIGH-C - this is identical to the HIGH-C except modified to measure the past 24 hours

m-PGI - this is identical to the PGI except it is rated for the past 24 hours

m-QIDS - this is identical to the QIDS except it omits sleep and weight items and is rated for the past 24 hours

m-SIGH-ADS - this is identical to the SIGH-ADS except sleep and weight items are removed and ratings are for the past 24 hours

MEQ (Morningness-Eveningness Questionnaire) - this is a 19-item patient-rated questionnaire asking the times of the day respondents prefer to eat, sleep and perform various functions, like exercise, test-taking and working; answers indicate the timing of the individual's biological clock

MMSE (Mini-Mental Status Examination) – this is a standard method for evaluating whether someone is cognitively intact or demented

PE - physical examination

PGI (Patient Global Impression)- this is identical to the CGI except patient-rated, asking patients to rate their over-all symptoms over the past week and improvement relative to pre-treatment

QIDS-SR (Quick Inventory of Depressive Symptoms, Self-Rated) - this is a patient-rated 16-item measure of depressive symptoms which has been shown to correlate highly with the clinician-rated 30-item Inventory of Depressive Symptoms

SCID (Structured Clinical Interview for DSM Diagnoses) - this is a standard semi-structured interview enabling assignment of the major clinical diagnoses according to the DSM diagnostic system, both current and life-time

SCL-90 (90 item Symptom Check List) - this instrument includes 90 common psychiatric symptoms covering 9 areas of psychopathology, including depression, anxiety, psychosis

SIGH-ADS (Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Supplement) - this is a clinician-rated measure of depressive symptoms which generates scores for the 17, 21 and 25 item Hamilton Rating Scale for Depression as well as a score summarizing the 8 items intended to measure symptoms of atypical depression

Sleep Log - The patient completes this daily, 7 days to a page, indicating when sleep occurred, mood and energy each day, timing of light exposure and any medications

NYSPI IRB Approved
7361
11/30/2016 -> 11/20/2017

Independent Evaluator Treatment Guess

IE Name: _____

Patient Study ID _____

Date _____

Do you think the subject is currently being treated?

____ Yes

____ No

What treatment has this patient been receiving? (Even if you have no idea, please make a wild guess; if you think treatment has not begun, this answer would be “none”)

How long has the patient been receiving this treatment? (If you think treatment has not begun, the answer would be “0")

_____ Days Weeks Months Years (insert # and circle the time period

Why did you guess the patient was not being treated, or, if treated, what that treatment might be?

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: _____

Table - Flow Chart																				
	00	RZ	D1	D2	D3	D4	D5	D6	D7	W2	W3	W4	W5	W6	M1	M2	M3	M4	M5	M6
Clinician-Rated Measures																				
- SCID	X																			
- HIGH-C	X	X							X	X	X	X	X	X	X	X	X	X	X	X
- SIGH-ADS	X	X							X	X	X	X	X	X	X	X	X	X	X	X
- CGI	X	X							X	X	X	X	X	X	X	X	X	X	X	X
- m-HIGH-C		X	X	X	X	X	X	X	X											
- m-SIGH-ADS		X	X	X	X	X	X	X	X											
- m-CGI		X	X	X	X	X	X	X	X											
- MMSE*	X																			
Independent Evaluator																				
- SIGH-ADS		**X**							X					X						
- CGI		**X**							X					X						
- **IE Treatment Guess**		**X**							**X**					**X**						
Patient-Rated Measures																				
- QIDS	X	X							X	X	X	X	X	X	X	X	X	X	X	X
- Expectation Form	**X**																			
- PGI	X	X							X	X	X	X	X	X	X	X	X	X	X	X
- MEQ	X	X												X						X
- SCL-90	X	X							X					X			X			X
- sleep log	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
- m-QIDS		X	X	X	X	X	X	X	X											
- m-PGI		X	X	X	X	X	X	X	X											
Laboratory and other																				

- PE	X																			
- labs	X																			
- saliva for melatonin		X							X											
- urine for pregnancy**	**X**							**X**												

* used only for those aged 60 and above

**** only for fecund women not already known to be pregnant**

KEY TO ABBREVIATIONS

CGI (Clinical Global Impression) - this is a clinician rated global measure of the patient's over-all psychopathology and improvement over the past week, improvement compared to pre-treatment

HIGH-C (Hypomania Interview Guide including Hyperthymia, Current Assessment Version) - this is a clinician-rated measure of manic/hypomanic symptoms rated over the past week

labs (laboratory examinations) - these include **EKG,** blood and urine; blood is examined for hematology (e.g., whether the patient is anemic) and routine blood chemistry (e.g., whether the patient has problems with their liver, kidney or thyroid); analysis of the urine determines whether there is a kidney

m-CGI - this is identical to the CGI except it measures the past 24 hours

m-HIGH-C - this is identical to the HIGH-C except modified to measure the past 24 hours

m-PGI - this is identical to the PGI except it is rated for the past 24 hours

m-QIDS - this is identical to the QIDS except it omits sleep and weight items and is rated for the past 24 hours

m-SIGH-ADS - this is identical to the SIGH-ADS except sleep and weight items are removed and ratings are for the past 24 hours

MEQ (Morningness-Eveningness Questionnaire) - this is a 19-item patient-rated questionnaire asking the times of the day respondents prefer to eat, sleep and perform various functions, like exercise, test-taking and working; answers indicate the timing of the individual's biological clock

MMSE (Mini-Mental Status Examination) – this is a standard method for evaluating whether someone is cognitively intact or demented

PE - physical examination

PGI (Patient Global Impression)- this is identical to the CGI except patient-rated, asking patients to rate their over-all symptoms over the past week and improvement relative to pre-treatment

QIDS-SR (Quick Inventory of Depressive Symptoms, Self-Rated) - this is a patient-rated 16-item measure of depressive symptoms which has been shown to correlate highly with the clinician-rated 30-item Inventory of Depressive Symptoms

SCID (Structured Clinical Interview for DSM Diagnoses) - this is a standard semi-structured interview enabling assignment of the major clinical diagnoses according to the DSM diagnostic system, both current and life-time

SCL-90 (90 item Symptom Check List) - this instrument includes 90 common psychiatric symptoms covering 9 areas of psychopathology, including depression, anxiety, psychosis

SIGH-ADS (Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Supplement) - this is a clinician-rated measure of depressive symptoms which generates scores for the 17, 21 and 25 item Hamilton Rating Scale for Depression as well as a score summarizing the 8 items intended to measure symptoms of atypical depression

Sleep Log - The patient completes this daily, 7 days to a page, indicating when sleep occurred, mood and energy each day, timing of light exposure and any medications

Early Improvement in the First 2 Weeks as a Predictor of Treatment Outcome in Patients With Major Depressive Disorder: A Meta-Analysis Including 6562 Patients

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Objective: New evidence indicates that treatment response can be predicted with high sensitivity after 2 weeks of treatment. Here, we assess whether early improvement with antidepressant treatment predicts treatment outcome in patients with major depressive disorder (MDD).

Data Sources: Forty-one clinical trials comparing mirtazapine with active comparators or placebo in inpatients and outpatients (all-treated population, N = 6907; intent-to-treat population, N = 6562) with MDD (DSM-III-R or DSM-IV Criteria) were examined for early improvement (≥ 20% score reduction from baseline on the 17-item Hamilton Rating Scale for Depression [HAM-D-17] within 2 weeks of treatment) and its relationship to treatment outcome.

Study Selection: Data were obtained from a systematic search of single- or double-blind clinical trials (clinical trials database, Organon, a part of Schering-Plough Corporation, Oss, The Netherlands). All included trials (a total of 41) employed antidepressant treatment for more than 4 weeks and a maximum of 8 weeks. The studies ranged from March 1982 to December 2003. Trials were excluded if there were no HAM-D-17 ratings available, no diagnosis of MDD, or if the study was not blinded. Trials were also excluded if HAM-D-17 assessments were not available at week 2, week 4, and at least once beyond week 4.

Data Synthesis: Early improvement predicted stable response and stable remission with high sensitivity (≥ 81% and ≥ 87%, respectively). Studies utilizing rapid titration vs. slow titration of mirtazapine demonstrated improved sensitivity for stable responders (98%, [95% CI = 93% to 100%] vs. 91% [95% CI = 89% to 93%]) and stable remitters (100%, [95% CI = 92% to 100%] vs. 93% [95% CI = 91% to 95%]). Negative predictive values for stable responders and stable remitters were much higher (range = 82%–100%) than positive predictive values (range = 19%–60%).

Conclusions: These results indicate that early improvement with antidepressant medication can predict subsequent treatment outcome with high sensitivity in patients with major depressive disorder. The high negative predictive values indicate little chance of stable response or stable remission in the absence of improvement within 2 weeks. A lack of improvement during the first 2 weeks of therapy may indicate that changes in depression management should be considered earlier than conventionally thought.

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When a patient with major depressive disorder (MDD) starts antidepressant drug treatment, the ability to identify as early as possible those people who will not benefit from a particular type of treatment could minimize unnecessary drug exposure, lessen suffering, and limit resource use. This ability in turn allows for earlier initiation of a treatment adaptation such as alternative or adjunctive treatment. The early identification of nonresponders is also important because selection of an antidepressant agent is still primarily guided by trial and error.

Although the current expert consensus indicates that antidepressants may have a rapid onset of action in some individuals,[1–4] most current treatment guidelines do not contain recommendations for adapting an individual's treatment during the early course of therapy (e.g., within the first 2 weeks of treatment). Rather, treatment guidelines reflect the outdated belief that antidepressant response usually appears with a delay of several weeks[5]

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and suggest that treatment should be changed if a partial response has not occurred after 4 to 6 weeks.[6–10] This advice was reinforced by the perception that placebo-controlled trials do not usually show a significant effect of treatment before treatment week 3. This perception reflected the assumption that early improvement was indicative of a placebo response associated with an irregular time course of recovery.[11–13] To a large extent, these beliefs are no longer held by experts in the treatment community.[14] However, physicians who follow the most current treatment guidelines may not consider a medication change within the first 2 weeks of treatment to be a useful strategy for improving the management of depression.

Because most antidepressant treatment guidelines continue to suggest 4 to 6 weeks of treatment until nonresponse can be assumed, substantial patience and adherence is required from depressed patients, particularly when pessimism and hopelessness dominate the outlook of these patients. Ineffective treatment is especially problematic in depression because it can increase the risk that patients lose confidence in and detach from their treating physicians, stop taking their prescribed treatment, or lose hope that their symptoms can be effectively treated. As a result, the risk of serious complications, such as suicide, is increased. Clearly, early identification of patients who subsequently will not benefit from a longer course of antidepressant therapy has immense clinical significance.

The hypothesis that antidepressants have a delayed onset of action gained support from the way data from clinical trials are analyzed. Most trials, including pivotal trials used to demonstrate efficacy for regulatory authorities, use group comparisons to detect significant mean differences between the antidepressant and placebo. Using this analytic approach, statistically significant differences between effective antidepressants and placebo are usually detected after 3 to 4 weeks of treatment. This approach assumes that mean differences adequately reflect changes observed in the individual patient. However, an examination of data from individuals participating in antidepressant clinical trials reveals a high degree of variability between patients. This broad range of responses suggests that individual responsiveness may not be adequately represented by the assumption of the "average" patient.

The delayed-onset hypothesis for antidepressant action is now being challenged. Many studies have not only reported onset of antidepressant action within the first 2 weeks of treatment,[1–3,14–20] but have also substantiated a close relationship between improvement of depression symptoms within the first 2 weeks of treatment and the final treatment response.[16–20] For example, Stassen and colleagues[16–19] analyzed the time course of intraindividual treatment outcomes in patients with depression by means of survival analyses. In these studies, patients who improved during the first 2 weeks of antidepressant treatment, as indexed by a ≥ 20% reduction in score on the 17-item Hamilton Rating Scale for Depression (HAM-D-17), showed substantial response at the study endpoint, as indexed by a ≥ 50% reduction in HAM-D-17 score. Stassen and colleagues argued not only that early improvement predicted response at study endpoint but also that lack of improvement was associated with little chance of response if the treatment strategy remained unchanged. It is important to note that the criterion of a 20% score reduction has been chosen as an early indicator of improvement because it can be reliably measured in clinical trials and translates into a clinically relevant change in the severity of depressive symptoms in patients (e.g., for a moderately depressed patient with an initial HAM-D-17 score of 20 points, it means a decrease of 4 points). However, a change of 20% is not a sensible target for therapeutic intervention and should not be understood as such.

As early as 1987, Katz et al.[21] reported that the onset of improvement occurred within the first 10 days of treatment across several domains in hospitalized patients with MDD who were being treated with a tricyclic antidepressant (TCA). This study did not include a placebo control group; thus, it could be questioned whether the early clinical treatment effects observed were due to drug effects or placebo effects. This issue was addressed in a subsequent randomized, parallel-group, placebo-controlled study in which patients were treated with the selective serotonin reuptake inhibitor (SSRI) paroxetine or the norepinephrine reuptake inhibitor desipramine.[4] In this study, early treatment-specific behavioral changes were demonstrated that were not observed in the placebo-treated group, and these early changes were highly predictive of ultimate clinical responses to antidepressant therapy. It was argued that these results could eventually be directly applied to clinical practice. Nierenberg and colleagues[15] have also reported that more than 50% of patients who eventually responded to fluoxetine treatment started to improve during the first 2 weeks of treatment. This same group has also reported that early nonresponse to fluoxetine treatment predicted poor 8-week outcomes.[22] Clearly, evidence continues to accumulate that indicates early individual improvement is a key predictor of treatment response.

In 2003, Szegedi et al.[20] examined early improvement with antidepressant treatment in a randomized controlled trial comparing mirtazapine and paroxetine in patients with a *Diagnostic and Statistical Manual of Mental Disorders* (DSM) diagnosis of major depression. Improvement occurred in a majority of patients within 2 weeks of initiating treatment, and this improvement was a highly sensitive predictor of later stable response or stable remission for both drugs. Furthermore, negative predictive value approached maximal values as early as week 2 for

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mirtazapine and week 3 for paroxetine. Less than 10% of patients who had not improved after 2 weeks of treatment became stable responders or remitters over the course of the study. These results indicate that response or nonresponse to antidepressant treatment can be predicted with high sensitivity after 2 weeks of therapy. Clearly, such findings could have significant clinical relevance if applied in clinical practice. The capacity to predict outcome during the early stages of treatment could not only shorten the length of ineffective treatments but could also decrease morbidity, mortality, and resource use associated with prolonged depression.

In the report by Szegedi et al.,[20] several caveats were considered in regard to interpretation of their data. First, the sample consisted primarily of moderately depressed outpatients. Although it was noted that this population was representative of the patients typically encountered in primary care settings and that their conclusions were fully appropriate for that patient population, it was unclear if the conclusions could be generalized to more severely depressed patients. Second, the results were confined to mirtazapine and paroxetine, so it was unclear if the results could be generalized to other antidepressants. Third, the lack of a placebo group in this study limited the ability to generalize these observations.[16]

The objective of the present study was to confirm the findings of Szegedi et al.[20] in a large patient population with MDD. Data from 6562 patients with MDD who participated in randomized, single- or double-blind clinical trials comparing mirtazapine with active comparators or placebo from March 1982 to December 2003 were retrospectively examined to determine the time course of improvement, response, and remission in individual patients, as well as the predictive capacity of early improvement for later treatment outcome.

METHOD

Inclusion of Studies

Analyses were carried out using data obtained from a systematic search of single- or double-blind clinical trials (clinical trials database; Organon, a part of Schering-Plough Corporation, Roseland, N.J.) comparing mirtazapine with active comparators or placebo in patients with MDD. The studies ranged from March 1982 to December 2003. The algorithm for trial selection is provided in Figure 1. Trials were excluded if there were no HAM-D-17 ratings available, no diagnosis of MDD, or if the study was not blinded. Trials were also excluded if HAM-D-17 assessments were not available at week 2, week 4, and at least once beyond week 4.

Patient Population

All patients met DSM-III-R or DSM-IV criteria for the diagnosis of at least 1 major depressive episode. The HAM-D-17 total score was used to assess the baseline severity of depressive symptoms (mild = < 22; moderate = 22–25; severe = > 25). Each study was approved by the institutional review board for the participating site. Written informed consent was obtained from all participants prior to participation in the original clinical trials and all studies were conducted in compliance with the current revision of the Declaration of Helsinki.

Outcome Measures

For the purpose of this analysis, the following patient groups were defined:

1. Early improvers: patients having a reduction in HAM-D-17 score of ≥ 20% compared with baseline within the first 2 weeks of treatment. This threshold represents a clinically meaningful change in the patient's state and can be reliably assessed.
2. Treatment responders: patients having a reduction in HAM-D-17 score of ≥ 50% from baseline.
3. Stable responders: patients having a reduction in HAM-D-17 score of ≥ 50% from baseline at 4 weeks of treatment and at all subsequent assessments.
4. Symptom remitters: patients having a reduction in HAM-D-17 score to ≤ 7 points.
5. Stable remitters: patients having a reduction in HAM-D-17 score to ≤ 7 points at week 4 of treatment and at all subsequent assessments.

Statistical Analyses

Analyses of the predictive value of early response for stable response and remission at 4 weeks were performed on the intent-to-treat (ITT) population. The method of last observation carried forward (LOCF) was used for missing values. The number of early improvers, responders, stable responders, remitters, and stable remitters was entered into a contingency table. The following indices, as well as their respective 95% Fisher exact CIs, were then calculated:

1. Sensitivity: [Early improvers who became stable responders or stable remitters/(Early improvers who became stable responders or stable remitters + Early nonimprovers who became stable responders or stable remitters)] × 100.
2. Specificity: [Early nonimprovers who did not become stable responders or stable remitters/(Early nonimprovers who did not become stable responders or stable remitters + Early improvers who did not become stable responders or stable remitters)] × 100.
3. Positive predictive value: (Early improvers who became stable responders or stable remitters/All improvers) × 100.

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4. Negative predictive value (Early nonimprovers who did not become stable responders or stable remitters/All nonimprovers) × 100.
5. False positives: 100% – Specificity.
6. False negatives: 100% – Sensitivity.

All statistical analyses were performed using SAS analytic software (SAS Institute Inc., Cary, N.C.).

RESULTS

Studies Included

A total of 145 trials were identified (Figure 1). Trials were excluded from the analysis if there were no HAM-D-17 ratings (N = 71), no MDD diagnosis (N = 3), or if the study was not blinded (N = 19). An additional 11 trials were excluded because a valid HAM-D-17 assessment was not available at week 2, week 4, and at least once beyond week 4.

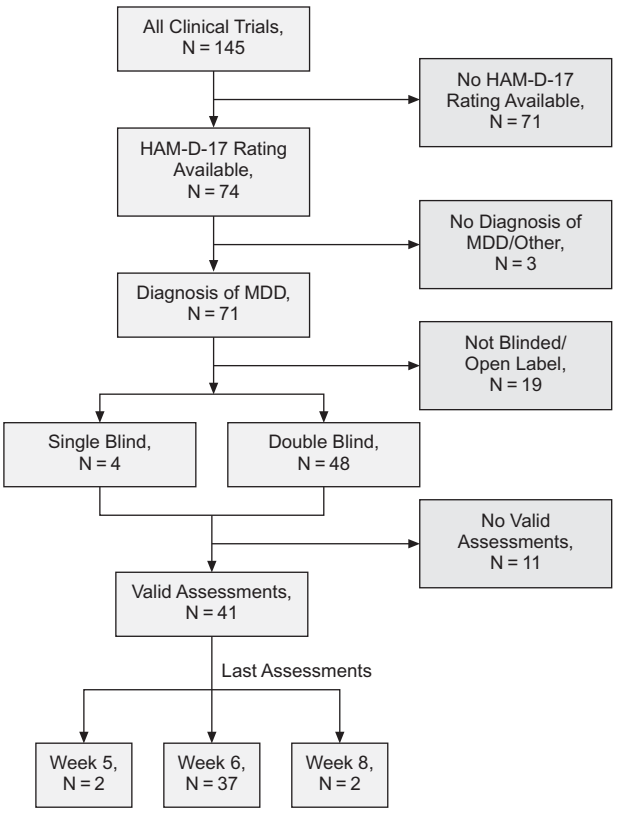
A total of 41 single- or double-blind clinical trials in patients with MDD were included in the analyses. The majority consisted of a 6-week antidepressant treatment period (N = 37). The remaining trials consisted of 5-week (N = 2) or 8-week (N = 2) antidepressant treatment periods. All studies used common inclusion/exclusion criteria, but varied in the criterion for depression severity required for enrollment.

Demographic Characteristics

The all-treated and ITT populations consisted of 6907 and 6562 patients, respectively. Demographic characteristics for the ITT population are presented in Table 1. As indexed by mean HAM-D-17 scores, a majority of patients (68%) met criteria for moderate or severe depression at baseline. In 20 studies, data on previous episodes of depression were available; the majority of patients (63%) in these studies had a history of previous episodes of depression. In 27 studies, data on the duration of current MDD were available. In these studies, the duration of the current MDD exceeded 1 month in more than 90% of patients (< 1 month, 9%; 1–6 months, 44%; 6 months to 1 year, 20%; > 1 year, 27%).

The noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine was used in all studies. The classes of antidepressants that were active comparators included the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine; the SSRIs (paroxetine, fluoxetine, citalopram, sertraline, and fluvoxamine); the TCAs (amitriptyline, doxepin, and clomipramine); the tetracyclic antidepressant maprotiline, and trazodone (chemically unrelated to other antidepressants). Fifty-two percent of patients were taking mirtazapine. The percentages of patients taking other antidepressants or placebo were SSRI = 21%; TCA = 11%; placebo = 10%; trazodone or maprotiline = 4%; and venlafaxine = 3%. In 2 trials that focused on rapid dose titration, mirtazapine and venlafaxine were studied head to head. The results from these 2 trials for mirtazapine patients (3% of the all-treated population) are also discussed.

Figure 1. Systematic Review of Clinical Trials[a]



[a]A total of 145 clinical trials from March 1982 to December 2003 were reviewed for inclusion in the analyses. Trials were systematically excluded from the analysis if there were no HAM-D-17 ratings, no diagnosis of MDD, if the study was not blinded, and if the study did not have a HAM-D-17 assessment at week 2, week 4, and at least once beyond week 4.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MDD = major depressive disorder.

Treatment Response

The majority of patients had at least a 20% reduction in HAM-D-17 total score by week 2 of treatment (Table 2). Of these, the highest proportion of improvers was observed across all weeks for patients who had rapid titration with mirtazapine.

The numbers of responders, stable responders, remitters, and stable remitters across treatment weeks demonstrate that responses to treatment follow a similar time course (Table 3). More than one half of patients taking active treatment became stable responders, and more than one third of patients taking active treatment became stable remitters at the end of treatment.

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Table 1. Demographic Characteristics at Baseline for the Intent-to-Treat Population[a]

Characteristic	Placebo	Mirtazapine	Venlafaxine	SSRI	TCA	Other[b]	Total
Sex							
Male	394 (62)	2084 (61)	118 (62)	844 (61)	487 (69)	160 (68)	4087 (62)
Female	244 (38)	1318 (39)	72 (38)	535 (39)	217 (31)	77 (33)	2463 (38)
Data unavailable	3 (1)	4 (< 1)	0 (0)	0 (0)	5 (1)	0 (0)	12 (< 1)
Race							
Asian	4 (1)	178 (5)	0 (0)	167 (12)	3 (< 1)	1 (< 1)	353 (5)
Black	30 (5)	71 (2)	0 (0)	27 (2)	5 (1)	0 (0)	133 (2)
White	509 (79)	1790 (53)	116 (61)	845 (61)	268 (38)	45 (19)	3573 (54)
Other	22 (3)	55 (2)	0 (0)	26 (2)	4 (1)	1 (< 1)	108 (2)
Data unavailable	76 (12)	1312 (39)	74 (39)	314 (23)	429 (61)	190 (80)	2395 (37)
Age, y							
< 18	85 (13)	165 (5)	0 (0)	0 (0)	0 (0)	0 (0)	250 (4)
18–24	39 (6)	156 (5)	10 (5)	105 (8)	28 (4)	3 (1)	341 (5)
25–44	284 (44)	1393 (41)	79 (42)	595 (43)	295 (42)	67 (28)	2713 (41)
45–59	158 (25)	1129 (33)	81 (43)	442 (32)	248 (35)	111 (47)	2169 (33)
≥ 60	72 (11)	559 (16)	20 (11)	237 (17)	133 (19)	56 (24)	1077 (16)
Data unavailable	3 (1)	4 (< 1)	0 (0)	0 (0)	5 (1)	0 (0)	12 (< 1)
Mean (SD), y	38.9 (15.8)	44.3 (15.1)	44.5 (11.6)	45.3 (14.5)	47.3 (13.6)	50.4 (12.0)	44.5 (14.9)
HAM-D-17 total score, Mean (SD)	22.8 (4.3)	24.0 (4.7)	26.5 (3.5)	24.0 (4.3)	24.4 (4.7)	26.0 (4.9)	24.1 (4.6)
HAM-D-17 severity score							
Mild[c]	261 (41)	1145 (34)	10 (5)	429 (31)	208 (29)	45 (19)	2098 (32)
Moderate[d]	221 (35)	1085 (32)	71 (37)	482 (35)	236 (33)	66 (28)	2161 (33)
Severe[e]	158 (25)	1167 (34)	108 (56)	464 (34)	265 (37)	126 (53)	2288 (35)
Data unavailable	1 (< 1)	9 (< 1)	1 (1)	4 (< 1)	0 (0)	0 (0.0)	15 (< 1)

[a]All data presented as N (%) unless otherwise noted.
[b]Other = trazodone or maprotiline.
[c]Baseline HAM-D-17 total score < 22.
[d]Baseline HAM-D-17 total score ≥ 22 and ≤ 25.
[e]Baseline HAM-D-17 total score > 25.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Predictive Value of Early Improvement

The predictive values of early improvement for treatment outcome (stable response and stable remission) are presented in Table 4. Across all treatments, early improvement was a highly sensitive predictor of stable response (range = 81%–98%) and stable remission (range = 87%–100%). However, early improvement was not a highly *specific* predictor for stable response (range = 43%–60%) or stable remission (range = 30%–53%). Furthermore, negative predictive values for stable response (range = 82%–96%) and stable remission (range = 95%–100%) were higher than positive predictive values for these groups (ranges = 43%–60% and 19%–28%, respectively).

In the 2 head-to-head trials that focused on rapid dose titration, the predictive value of early improvement was enhanced (Table 4). In these studies, rapid dose titration of mirtazapine was associated with the highest sensitivity for predicting later stable responders (98%, 95% CI = 93% to 100%) and stable remitters (100%, 95% CI = 92% to 100%). These 2 studies also had the highest positive and negative predictive values for stable responders (60%, 95% CI = 52% to 68% and 96%, 95% CI = 86% to 100%, respectively) and stable remitters (28%, 95% CI = 21% to 36% and 100%, 95% CI = 93% to 100%), as well as the lowest false-negative rates (stable responder: 2%, 95% CI = 0.3% to 8%; stable remitter: 0%, 95% CI = 0% to 8%). A direct comparison of slow versus rapid dose titration for venlafaxine was not possible. However, rapid titration of venlafaxine was associated with high sensitivity for predicting later stable responders (96%, 95% CI = 89% to 99%) and stable remitters (100%, 95% CI = 89% to 100%), high positive and negative predictive values for stable responders (56%, 95% CI = 47% to 64% and 94%, 95% CI = 84% to 99%, respectively) and stable remitters (23%, 95% CI = 17% to 31% and 100%, 95% CI = 93% to 100%), and low false-negative rates (stable responder: 4%, 95% CI = 1% to 11%; stable remitter: 0%, 95% CI = 0% to 11%).

Outcomes of Early Improvement

We examined the percentage of early improvers and those without early improvement who later became stable responders (Figure 2) and stable remitters (Figure 3). By the end of treatment, 2285 (53%) early improvers were stable responders and 1084 (25%) were stable remitters. As such, early improvers constituted 90% (2285 of 2544) and 92% (1084 of 1177) of all stable responders and stable remitters, respectively. These results clearly show that patients who improve within the first 2 weeks of antidepressant therapy are highly likely to achieve stable response and stable remission after 4 weeks or longer of

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Table 2. HAMD-17 Improvers[a] by Treatment Week for the Intent-to-Treat Population

Treatment, N (%)[b]	Week 1	Week 2	Week 3[c]	Week 4	Beyond Week 4
Placebo (N = 641)					
No	388 (69)	306 (48)	231 (41)	244 (38)	216 (34)
Yes	176 (31)	334 (52)	333 (59)	396 (62)	424 (66)
Mirtazapine (N = 3406)					
No	1415 (53)	1088 (32)	464 (25)	700 (21)	569 (17)
Yes	1240 (47)	2309 (68)	1414 (75)	2697 (79)	2828 (83)
Mirtazapine (rapid titration, N = 202)					
No	84 (42)	48 (24)	31 (25)	32 (16)	28 (14)
Yes	118 (58)	154 (76)	94 (75)	170 (84)	174 (86)
Venlafaxine (rapid titration, N = 190)					
No	100 (53)	52 (28)	28 (24)	43 (23)	37 (20)
Yes	89 (47)	137 (72)	87 (76)	146 (77)	152 (80)
SSRI (N = 1378)					
No	829 (63)	503 (37)	252 (31)	318 (23)	248 (18)
Yes	477 (37)	872 (63)	574 (69)	1057 (77)	1127 (82)
TCA (N = 709)					
No	251 (62)	219 (31)	66 (22)	137 (19)	103 (15)
Yes	153 (38)	490 (69)	240 (78)	572 (81)	606 (85)
Other[d] (N = 237)					
No	105 (64)	95 (40)	19 (29)	46 (19)	41 (17)
Yes	59 (36)	142 (60)	46 (71)	191 (81)	196 (83)

[a]Improvers were defined as having a ≥ 20% reduction in HAM-D-17 total score.
[b]Percentages are based on the total number of patients actually assessed at a given study week.
[c]Week 3 was not a scheduled assessment in all studies.
[d]Other = trazodone or maprotiline.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

continued treatment. In contrast, only 11% and 4.1% of patients, respectively, who did not improve within the first 2 weeks became stable responders or stable remitters. These results appear to be very robust. Similar analyses of early improvement predicting treatment response in data from a subset of patients for whom data from the Montgomery-Asberg Depression Rating Scale (MADRS) were available yielded similar results (data not presented).

DISCUSSION

The results of this analysis confirm that early improvement in depressive symptoms is frequently observed during the course of treatment with various antidepressant therapies, including mirtazapine, and that early improvement heralds a greater likelihood of stable response to medication and stable remission of symptoms. Importantly, the lack of early improvement is associated with low rates of medication response and symptom remission. These data thus provide further evidence against the delayed-onset hypothesis for antidepressant treatment response.[23–25] and further enforce the notion that an early improvement during treatment is expected with various antidepressant drugs. Thus a lack of early improvement may warrant the need for a change in treatment strategy. It should be noted that prospective and direct comparisons of response and remission rates in nonimprovers who continue treatment compared to those who changed treatment is needed to validate this recommendation. However, if found to be true, such an approach will have far-reaching implications for clinical practice.

The most immediate and practical consequence of this analysis is that a patient's individual early improvement may predict that individual's later stable response or remission with high sensitivity. Most prominently, a lack of early response to treatment at 2 weeks was highly predictive of a lack of stable response or stable remission. This is consistent with previous findings that indicated that the presence or absence of early improvement during mirtazapine or paroxetine treatment was highly predictive of therapeutic outcome.[20] In addition, in patients treated with *Hypericum* extracts, a reduction of depressive symptoms during the first 2 weeks of treatment was a sensitive predictor of sustained response.[26] The current analysis extends these findings to a variety of widely used antidepressants with different pharmacologic profiles. Furthermore, the finding that early individual improvement can predict sustained response is consistent with the finding that the response trajectory early during treatment is a useful predictor of response to antidepressants.[27] In fact, the criterion set forth in the current analysis (i.e., 20% improvement over 2 weeks) represents a favorable response trajectory.

It should be noted that there are important methodological differences between the approach of Quitkin and colleagues[13] and the strategy examined herein. Specifically, they measured outcome using the Clinical Global Impressions scale and required that patients be rated as "much improved" or "very much improved" to be counted as responders. In addition, they studied treatment with TCAs

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Table 3. Responders[a] and Remitters[b] by Treatment Week for the Intent-to-Treat Population

	Responders					Stable Responders				
Treatment, N (%)	Week 1	Week 2	Week 3[d]	Week 4	Beyond Week 4	Week 1	Week 2	Week 3[d]	Week 4	Beyond Week 4
Placebo (N = 641)										
No	530 (94)	532 (83)	429 (76)	447 (70)	370 (58)	550 (98)	567 (89)	479 (85)	477 (75)	397 (62)
Yes	34 (6)	108 (17)	135 (24)	193 (30)	270 (42)	14 (2)	73 (11)	85 (15)	163 (25)	243 (38)
Mirtazapine (N = 3406)										
No	2372 (89)	2522 (74)	1168 (62)	1806 (53)	1349 (40)	2476 (93)	2721 (80)	1315 (70)	1984 (58)	1422 (42)
Yes	283 (11)	875 (26)	710 (38)	1591 (47)	2048 (60)	179 (7)	676 (20)	563 (30)	1413 (42)	1975 (58)
Mirtazapine (rapid titration, N = 202)										
No	164 (81)	118 (58)	64 (51)	91 (45)	79 (39)	167 (83)	135 (67)	73 (58)	108 (53)	84 (42)
Yes	38 (19)	84 (42)	61 (49)	111 (55)	123 (61)	35 (17)	67 (33)	52 (42)	94 (47)	118 (58)
Venlafaxine (rapid titration, N = 190)										
No	177 (94)	135 (71)	77 (67)	100 (53)	91 (48)	179 (95)	148 (78)	80 (70)	110 (58)	93 (49)
Yes	12 (6)	54 (29)	38 (33)	89 (47)	98 (52)	10 (5)	41 (22)	35 (30)	79 (42)	96 (51)
SSRI (N = 1378)										
No	1215 (93)	1080 (79)	571 (69)	812 (59)	542 (39)	1246 (95)	1160 (84)	636 (77)	884 (64)	571 (42)
Yes	91 (7)	295 (21)	255 (31)	563 (41)	833 (61)	60 (5)	215 (16)	190 (23)	491 (36)	804 (58)
TCA (N = 709)										
No	378 (94)	542 (76)	204 (67)	369 (52)	247 (35)	387 (96)	582 (82)	227 (74)	401 (57)	265 (37)
Yes	26 (6)	167 (24)	102 (33)	340 (48)	462 (65)	17 (4)	127 (18)	79 (26)	308 (43)	444 (63)
Other[e] (N = 237)										
No	151 (92)	201 (85)	49 (75)	138 (58)	92 (39)	156 (95)	212 (89)	53 (82)	147 (62)	97 (41)
Yes	13 (8)	36 (15)	16 (25)	99 (42)	145 (61)	8 (5)	25 (11)	12 (18)	90 (38)	140 (59)
	Remitters					Stable Remitters				
Treatment, N (%)	Week 1	Week 2	Week 3[b]	Week 4	Beyond Week 4	Week 1	Week 2	Week 3[b]	Week 4	Beyond Week 4
Placebo (N = 641)										
No	547 (97)	597 (93)	501 (89)	533 (83)	460 (72)	561 (99)	621 (97)	529 (94)	562 (88)	490 (77)
Yes	17 (3)	43 (7)	63 (11)	107 (17)	180 (28)	3 (1)	19 (3)	35 (6)	78 (12)	150 (23)
Mirtazapine (N = 3406)										
No	2568 (97)	3048 (90)	1536 (82)	2572 (76)	2072 (61)	2609 (98)	3165 (93)	1649 (88)	2722 (80)	2141 (63)
Yes	87 (3)	349 (10)	342 (18)	825 (24)	1325 (39)	46 (2)	232 (7)	229 (12)	675 (20)	1256 (37)
Mirtazapine (rapid titration, N = 202)										
No	194 (96)	175 (87)	100 (80)	151 (75)	132 (65)	196 (97)	182 (90)	107 (86)	159 (79)	135 (67)
Yes	8 (4)	27 (13)	25 (20)	51 (25)	70 (35)	6 (3)	20 (10)	18 (14)	43 (21)	67 (33)
Venlafaxine (rapid titration, N = 190)										
No	186 (98)	177 (94)	102 (89)	150 (79)	133 (70)	188 (99)	182 (96)	104 (90)	157 (83)	135 (71)
Yes	3 (2)	12 (6)	13 (11)	39 (21)	56 (30)	1 (1)	7 (4)	11 (10)	32 (17)	54 (29)
SSRI (N = 1378)										
No	1285 (98)	1273 (93)	719 (87)	1110 (81)	845 (61)	1292 (99)	1307 (95)	755 (91)	1158 (84)	866 (63)
Yes	21 (2)	102 (7)	107 (13)	265 (19)	530 (39)	14 (1)	68 (5)	71 (9)	217 (16)	509 (37)
TCA (N = 709)										
No	396 (98)	650 (92)	261 (85)	541 (76)	428 (60)	401 (99)	667 (94)	278 (91)	565 (80)	437 (62)
Yes	8 (2)	59 (8)	45 (15)	168 (24)	281 (40)	3 (1)	42 (6)	28 (9)	144 (20)	272 (38)
Other[e] (N = 237)										
No	163 (99)	229 (97)	62 (95)	200 (84)	163 (69)	164 (100)	235 (99)	63 (97)	206 (87)	166 (70)
Yes	1 (1)	8 (3)	3 (5)	37 (16)	74 (31)	0 (0)	2 (1)	2 (3)	31 (13)	71 (30)

[a]Responders were defined as having a reduction in HAM-D-17 score of ≥ 50% from baseline. Stable responders were defined as having a reduction in HAM-D-17 score of ≥ 50% from baseline at 4 weeks of treatment and at study endpoint.
[b]Remitters were defined as having a reduction in HAM-D-17 score to ≤ 7 points. Stable remitters were defined as having a reduction in HAM-D-17 score to = 7 points at week 4 of treatment and at all subsequent assessments.
[c]Percentages are based on the total number of patients actually assessed at a given study week.
[d]Week 3 was not a scheduled assessment in all studies.
[e]Other = trazodone or maprotiline.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

(predominantly imipramine) and monoamine oxidase inhibitors (predominantly phenelzine). These agents must be started at subtherapeutic doses and titrated upwards during the first 2 weeks of treatment to improve tolerability. Thus, the association of early improvement with placebo response in their analyses could reflect both the requirement of a more substantial level of improvement and the fact that therapeutic doses of TCAs and monoamine oxidase inhibitors were generally not achieved until the end of the first 2 weeks of therapy.[13]

It is important to note that high sensitivity does not mean that the presence of early improvement invariably leads to stable response or remission, as indicated by the limited specificity of early improvement. In fact, the

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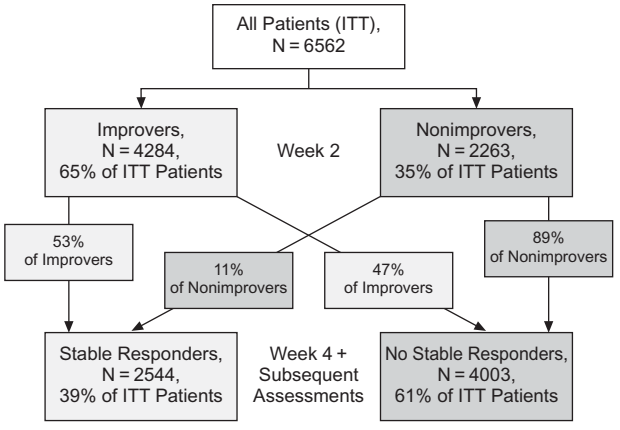
Table 4. Predictive Value of Early Improvement[a] for the Intent-to-Treat Population

Treatment	Sensitivity (95% CI)[b]	Specificity (95% CI)[b]	Positive Predictive Value (95% CI)[b]	Negative Predictive Value (95% CI)[b]	False-Positive Rate (95% CI)[b]	False-Negative Rate (95% CI)[b]
Stable Responder Rates						
Placebo (N = 640)	88 (82 to 93)	60 (56 to 93)	43 (38 to 49)	94 (91 to 96)	40 (35 to 44)	12 (7 to 18)
Mirtazapine (N = 3397)	91 (89 to 93)	48 (46 to 51)	56 (54 to 58)	88 (86 to 90)	52 (49 to 54)	9 (8 to 11)
Mirtazapine (rapid titration N = 202)	98 (93 to 100)	43 (33 to 53)	60 (52 to 68)	96 (86 to 100)	57 (48 to 67)	2 (0.3 to 8)
Venlafaxine (rapid titration, N = 189)	96 (89 to 99)	45 (35 to 54)	56 (47 to 64)	94 (84 to 99)	56 (46 to 65)	4 (1 to 11)
SSRI (N = 1375)	88 (85 to 91)	50 (47 to 54)	50 (46 to 53)	86 (85 to 91)	50 (46 to 53)	12 (9 to 15)
TCA (N = 709)	89 (85 to 92)	46 (41 to 51)	56 (51 to 60)	84 (79 to 89)	54 (49 to 59)	11 (8 to 15)
Other (N = 237)[c]	81 (72 to 89)	53 (45 to 61)	51 (43 to 60)	82 (73 to 89)	47 (39 to 55)	19 (11 to 29)
Stable Remitter Rates						
Placebo (N = 640)	91 (82 to 96)	53 (49 to 57)	21 (17 to 26)	98 (95 to 99)	47 (43 to 51)	9 (4 to 18)
Mirtazapine (N = 3397)	93 (91 to 95)	38 (36 to 40)	27 (25 to 29)	96 (94 to 97)	62 (60 to 64)	7 (5 to 10)
Mirtazapine (rapid titration N = 202)	100 (92 to 100)	30 (23 to 38)	28 (21 to 36)	100 (93 to 100)	70 (62 to 77)	0 (0 to 8)
Venlafaxine (rapid titration N = 189)	100 (89 to 100)	33 (26 to 41)	23 (17 to 31)	100 (93 to 100)	67 (59 to 74)	0 (0 to 11)
SSRI (N = 1375)	90 (86 to 94)	42 (39 to 45)	23 (20 to 25)	96 (94 to 97)	58 (56 to 61)	10 (6 to 14)
TCA (N = 709)	92 (86 to 96)	37 (33 to 41)	27 (23 to 31)	95 (91 to 97)	63 (59 to 67)	8 (4 to 14)
Other (N = 237)[c]	87 (70 to 96)	44 (37 to 51)	19 (13 to 26)	96 (90 to 99)	56 (49 to 63)	13 (4 to 30)

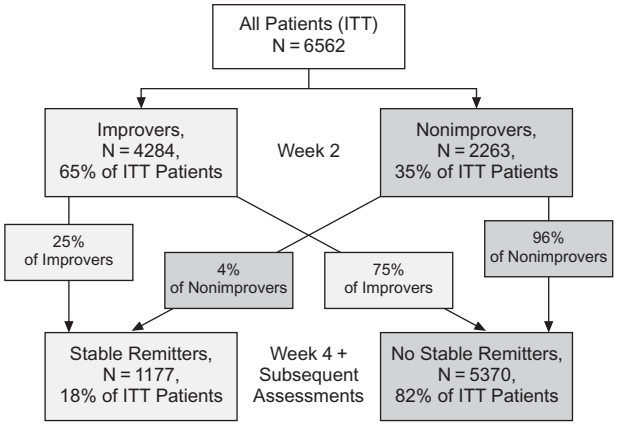
[a]Early improvement was defined as having a ≥ 20% reduction of HAM-D-17 total score within the first 2 weeks of antidepressant therapy.
[b]Fischer exact CI.
[c]Other = trazodone or maprotiline.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Figure 2. Patient Flow for Stable Responders[a]



[a]The number and percentage of patients who became stable responders were determined from patients who improved with treatment at week 2 and from those who initially did not improve but did so at week 4 and at the end of treatment. All treatments, including placebo, are represented.
Abbreviation: ITT = intent-to-treat.

Figure 3. Patient Flow for Stable Remitters[a]



[a]The number and percentage of patients who became stable remitters were determined from patients who improved with treatment at week 2 and from those who initially did not improve but did so at week 4 and at the end of treatment. All treatments, including placebo, are represented.
Abbreviation: ITT = intent-to-treat.

consistently higher negative predictive values in relation to the positive predictive values indicate that the absence of early improvement is more predictive of a later lack of stable response or stable remission with continued treatment. Early improvement was a clinical predictor of treatment success in roughly 50% of early improvers. However, unsuccessful treatment outcome was predicted for roughly 90% of those who did not experience early treatment improvement.

In further regard to the predictive value of a lack of early improvement, it should be noted that it is unclear whether these results would change if the treatment duration were extended. The possibility that some portion of week 2 nonimprovers may have demonstrated sustained response or remission if treatment was extended should be acknowledged. However, based on our analyses, we would argue that the number of patients doing so would be small. Furthermore, the overall response and remission rates reported in this analysis (51%–63% and 29%–37%, respectively) are comparable to those of other published reports, including the first step of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

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study,[28] which reported a 48.6% response rate at 5.5 weeks and a 36.8% remission rate at 6.3 weeks. This outcome suggests that any further additional improvement in the treatment groups would probably be minimal. It should also be noted that, because the current analysis primarily included patients with acute MDD, it is unclear how the predictive indices might change in patients with chronic depression or a complicated treatment course.

It is also important to note that our contention that early improvement is a critical factor that can be used to predict treatment response still implies that in a majority of patients, full treatment benefit will require continued treatment of several weeks. Clearly, substantial additional improvement in depressive symptoms can be observed after treatment periods exceeding 8 weeks.[1,2,29–31] This notion is again supported by the results from the STAR*D trial.[29] Furthermore, a meta-analysis published by Taylor et al.[2] concluded that improvement in depressive symptoms can be observed after 1 week of treatment, but improvement continues for at least 6 weeks after treatment initiation. Our data would suggest that improvement, or the lack thereof, that is observed at later time points can be predicted by improvement under treatment at week 2. That is, most individuals meeting criteria for response or remission at later time points would demonstrate some evidence of improvement, even if full response or remission is not attained, at week 2.

Treatment regimen can be a mitigating factor that influences the onset of antidepressant action. In fact, response to many agents,[31,32] but not all,[33,34] is facilitated by dose escalation in previously nonresponsive patients. Bernardo et al.[32] reported that fast titration with venlafaxine produced more rapid improvement in depressive symptoms than did slow titration, a finding that is consistent with results of the present analysis. In addition, rapid mirtazapine dose titration during the first week of treatment enhanced all indices of predictive value. It should be noted that the effectiveness of dose escalation is not limited to the early treatment period. Heiligenstein et al.[31] reported that dose escalation of the SSRI fluoxetine improved depressive symptoms at treatment week 10 in more than two thirds of patients who had not responded at week 4.

The high negative predictive value and low false-negative rates we observed indicate that the absence of early improvement should prompt clinicians to consider changing the treatment regimen after 2 weeks of treatment, because nonimprovers at week 2 are unlikely to benefit from their current treatment. Early identification of potential treatment failures could help alter the treatment management approach to one with a higher likelihood of success. It is hoped that early monitoring and modification of depression therapy will reduce patient distress, resource utilization, medication noncompliance, and risk of suicide.

Monitoring of early improvement as a predictor of treatment outcome is of further clinical value because it can be easily implemented in the clinical setting. It does not require an expensive technical investment and can be applied worldwide. Implementation requires only an assessment of depression severity at baseline and at weekly intervals with an adequate scale. In our experience, the choice of the HAM-D-17 or MADRS scale did not significantly influence the results, which argues in favor of the robustness of early improvement as a predictor of later clinical outcome. Given the potential for saving time and costs by using early improvement as a predictor of later outcome, a weekly investment of 20 to 30 minutes for the rating of depressive symptoms in the clinical setting seems reasonable.

On the basis of the findings from this analysis of predominantly 6-week clinical trials, we recommend the following clinical guidelines for antidepressant therapy: (1) before starting treatment, a baseline assessment of the severity of depressive symptoms should be performed using a validated scale, such as the HAM-D-17, MADRS, Quick Inventory of Depressive Symptomatology–Self-Report, or 9-item Patient Health Questionnaire; (2) assessments should be made on a weekly basis to monitor changes in depressive symptoms during the course of treatment; and (3) antidepressant medications should be titrated rapidly within the first week, if possible, until therapeutic response is seen or the highest tolerated dose is achieved. It should be noted that it is unclear if the results of this analysis and the treatment guidelines outlined above can be generalized to longer duration trials. However, in the context of 4- to 6-week trials, using such a strategy to identify patients with early improvement would indicate that the treatment strategy should be continued without adaptation and monitored for continued efficacy; subsequent response or remission at 4 to 8 weeks can be expected in a large percentage of patients. If early improvement is not observed within the first 2 weeks of therapy, there is a substantially smaller chance of stable response or remission, and individual treatment adaptations should be made as early as possible and can be tailored to the patient's needs.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Sinequan, Zonalon, and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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REFERENCES

1. Rojo JE, Gibert K, Cobo J, et al. Onset of antidepressant action: a pharmacological question? Hum Psychopharmacol 2005;20:425–433
2. Taylor MJ, Freemantle N, Geddes JR, et al. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. Arch Gen Psychiatry 2006;63:1217–1223
3. Taylor MJ. Rapid onset of true antidepressant action. Curr Psychiatry Rep 2007;9:475–479
4. Katz MM, Tekell JL, Bowden CL, et al. Onset and early behavioral effects of pharmacologically different antidepressants and placebo in depression. Neuropsychopharmacology 2004;29:566–579
5. Schulberg HC, Katon W, Simon GE, et al. Treating major depression in primary care practice: an update of the Agency for Health Care Policy and Research Practice Guidelines. Arch Gen Psychiatry 1998; 55:1121–1127
6. Kennedy SH, Lam RW, Cohen NL, et al, and the CANMAT Depression Work Group. Clinical guidelines for the treatment of depressive disorders, IV: medications and other biological treatments. Can J Psychiatry 2001;46(suppl 1):38S–58S
7. Bauer M, Whybrow PC, Angst J, et al. WFSBP Task Force on Treatment Guidelines for Unipolar Depressive Disorders: World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Acute and Continuation Treatment of Major Depressive Disorder. World J Biol Psychiatry 2002;3:5–43
8. Anderson IM, Nutt DJ, Deakin JFW. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. J Psychopharmacol 2000;14:3–20
9. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder (revision). Am J Psychiatry 2000;157(suppl 4):1–45
10. National Institute for Health and Clinical Excellence. Management of depression in primary and secondary care. Available at: www.nice.org.uk/CG023NICEguideline. Accessibility confirmed September 8, 2008
11. Quitkin FM, Rabkin JD, Markowitz JM, et al. Use of pattern analysis to identify true drug response: a replication. Arch Gen Psychiatry 1987; 44:259–264
12. Quitkin FM, Stewart JW, McGrath PJ, et al. Further evidence that a placebo response to antidepressants can be identified. Am J Psychiatry 1993;150:566–570
13. Quitkin FM, McGrath PJ, Stewart JW, et al. Can the effects of antidepressants be observed in the first two weeks of treatment? Neuropsychopharmacology 1996;15:390–394
14. Katz MM, Frazer A, Bowden CL. 'Delay' hypothesis of onset of antidepressant action. Br J Psychiatry 2006;188:586
15. Nierenberg AA, Farabaugh AH, Alpert JE, et al. Timing of onset of antidepressant response with fluoxetine treatment. Am J Psychiatry 2000;157:1423–1428
16. Stassen HH, Angst J. Delayed onset of action of antidepressants: fact or fiction? CNS Drugs 1998;9:177–184
17. Stassen HH, Angst J, Delini-Stula A. Fluoxetine versus moclobemide: cross-comparison between the time courses of improvement. Pharmacopsychiatry 1999;32:56–60
18. Stassen HH, Angst J, Delini-Stula A. Delayed onset of action of antidepressant drugs? survey of results of Zurich meta-analyses. Pharmacopsychiatry 1996 May;29(3):87–96
19. Stassen HH, Delini-Stula A, Angst J. Time course of improvement under antidepressant treatment: a survival-analytical approach. Eur Neuropsychopharmacol 1993;3:127–135
20. Szegedi A, Muller MJ, Anghelescu I, et al. Early improvement under mirtazapine and paroxetine predicts later stable response and remission with high sensitivity in patients with major depression. J Clin Psychiatry 2003;64(4):413–420
21. Katz MM, Koslow SH, Maas JW, et al. The timing, specificity and clinical prediction of tricyclic drug effects in depression. Psychol Med 1987; 17:297–309
22. Nierenberg AA, McLean NE, Alpert JE, et al. Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. Am J Psychiatry 1995;152:1500–1503
23. Papakostas GI, Perlis RH, Scalia MJ, et al. A meta-analysis of early sustained response rates between antidepressants and placebo for the treatment of major depressive disorder. J Clin Psychopharmacol 2006; 26:56–60
24. Posternak MA, Zimmerman M. Is there a delay in the antidepressant effect? a meta-analysis. J Clin Psychiatry 2005;66(2):148–158
25. Stassen HH, Angst J, Hell D, et al. Is there a common resilience mechanism underlying antidepressant drug response? evidence from 2848 patients. J Clin Psychiatry 2007;68(8):1195–1205
26. Kieser M, Szegedi A. Predicting stable treatment response in patients with major depression treated with hypericum extract WS 5570/5572. Pharmacopsychiatry 2005;38:194–200
27. Gildengers AG, Houck PR, Mulsant BH, et al. Trajectories of treatment response in late-life depression: psychosocial and clinical correlates. J Clin Psychopharmacol 2005;25:S8–S13
28. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905–1917
29. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163:28–40
30. Keller MB, Gelenberg AJ, Hirschfeld RM, et al. The treatment of chronic depression, pt 2: a double-blind, randomized trial of sertraline and imipramine. J Clin Psychiatry 1998;59(11):598–607
31. Heiligenstein JH, Hoog SL, Wagner KD, et al. Fluoxetine 40–60 mg versus fluoxetine 20 mg in the treatment of children and adolescents with a less-than-complete response to nine-week treatment with fluoxetine 10–20 mg: a pilot study. J Child Adolesc Psychopharmacol 2006; 16:207–217
32. Bernardo M, Buisan E, Duran A, et al. Venlafaxine titration dosage in depressive in-patients: a series of cases. [In Spanish] Actas Esp Psiquiatr 2003;31:31–34
33. Schweizer E, Rynn M, Mandos LA, et al. The antidepressant effect of sertraline is not enhanced by dose titration: results from an outpatient clinical trial. Int Clin Psychopharmacol 2001;16(3):137–143
34. Benkert O, Szegedi A, Wetzel H, et al. Dose escalation vs. continued doses of paroxetine and maprotiline: a prospective study in depressed out-patients with inadequate treatment response. Acta Psychiatr Scand 1997;95(4):288–296

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Antidepressant chronotherapeutics for bipolar depression

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Chronotherapeutics refers to treatments based on the principles of circadian rhythm organization and sleep physiology, which control the exposure to environmental stimuli that act on biological rhythms, in order to achieve therapeutic effects in the treatment of psychiatric conditions. It includes manipulations of the sleep-wake cycle such as sleep deprivation and sleep phase advance, and controlled exposure to light and dark. The antidepressant effects of chronotherapeutics are evident in difficult-to-treat conditions such as bipolar depression, which has been associated with extremely low success rates of antidepressant drugs in naturalistic settings and with stable antidepressant response to chronotherapeutics in more than half of the patients. Recent advances in the study of the effects of chronotherapeutics on neurotransmitter systems, and on the biological clock machinery, allow us to pinpoint its mechanism of action and to transform it from a neglected or "orphan" treatment to a powerful clinical instrument in everyday psychiatric practice.

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The need for chronotherapeutics

Chronotherapeutics refers to treatments based on the principles of circadian rhythm organization and sleep physiology,[1,2] which control the exposure to environmental stimuli that act on biological rhythms, in order to achieve therapeutic effects in the treatment of psychiatric conditions.[3] These nonpharmaceutical and biologically based clinical interventions include manipulations of the sleep-wake cycle such as sleep deprivation (SD) and sleep phase advance (SPA), and controlled exposure to light and dark. The use of these techniques in everyday clinical practice is almost exclusively limited to the treatment of mood disorders, offering mental health practitioners a set of nonpharmaceutical, rapid, and effective antidepressant modalities for monotherapy or as adjuvants to conventional medication.[1,4]

Interest in the clinical use of these techniques stemmed from their efficacy, rapidity of action, and lack of side effects, and also from the possibility of achieving long-lasting therapeutic effects by combining the different chronotherapeutic interventions among themselves or with conventional psychiatric treatments.[5] Clinical treatment algorithms in everyday psychiatric settings that include chronotherapeutic techniques and the monitoring of chronobiological variables proved to be useful to predict outcomes, speed up recovery, shorten hospitalization, and reduce the clinical need for changes in drug prescriptions.[6-9] The results observed in clinical trials pro-

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duced a positive answer to early doubts about the therapeutic usefulness of chronotherapeutics[10] and about the temporary nature of the achieved benefits.[11]
These effects of chronotherapeutics have been particularly evident in difficult-to-treat conditions such as bipolar depression, which has been associated with extremely low success rates of antidepressant drugs in naturalistic settings.[12] Bipolar patients spend a substantial proportion of their time ill,[13] with depression representing their predominant abnormal mood state,[14] but with the repeated use of antidepressant drugs being related to poor prospective response to naturalistic treatment.[15] The clinical need for treatment of their disabling condition and the interplay between the risk of treatment-emergent mania[16,17] and the risk of relapse when discontinuing drug treatments[18] often leads to prolonged and highly complex medication regimens to achieve a sustained response.[19] Nevertheless, there is still a real clinical need for fast-acting antidepressant effects to counteract the rapid breakthrough depression experienced by the patients: hence the interest in chronotherapeutics, which act without the delay inherent to traditional antidepressant treatments.[3,20]
Paralleling these clinical achievements in recent years, basic research in the last decade has substantially improved knowledge about the biological mechanisms that control the molecular machinery of the master clock,[21] and link it with the neurotransmitter systems that are involved in mood regulation and targeted by antidepressant drugs.[22]
Confirming the classical belief that man and his environment are inseparable, it is now established that exposure to environmental stimuli that act on the transcription of clock genes will lead to major changes in the same brain neurotransmitter function involved in psychiatric conditions,[3] and that from a clinical point of view the choice will be restricted between the potentially detrimental random exposure to these stimuli, which could even precipitate bipolar illness episodes,[23,24] and the direct control by the psychiatrist in order to achieve a therapeutic effect.
The present review focuses on recent achievements in the chronotherapeutic treatment of bipolar depression and on the recently discovered molecular mechanisms that clearly link chronotherapeutics with the usual antidepressant drug treatments of this disorder.

Techniques

The first studies published in clinical samples used single chronotherapeutic techniques to treat depression, but the clinical need for rapid and sustained improvement of patients prompted the combination of different techniques among themselves and with usual antidepressant drug treatments.

Sleep deprivation

Antidepressant effects of sleep deprivation were first reported in 1959,[25] but the first experimental trials to test its clinical efficacy were performed in the 1970s.[26,27] The amazingly rapid effects of the treatment, which is usually able to restore euthymia in the morning soon after a single night awake, are closely linked to the wake period and are usually rapidly lost after restoring an undisturbed night sleep.[11] To achieve the best results the wake period includes the extension of daytime wakefulness into the night, and lasts about 36 hours until the evening of the day after (total sleep deprivation), but it can also be limited to the second half of the night and the following day, thus allowing sleep during the first half of the night,[28] with little disadvantage[29]: in both cases, the mood amelioration is obtained during the prolonged wake, and in the presence of light.[30] This link between mood and wake, together with the observation that during the nights of undisturbed sleep patients sleep better and deeper than usual,[31] justified the recent use of the term "wake therapy" to refer to this treatment.[2]
In the absence of combined treatments, not more than 5% of responders to wake will maintain a stable euthymia in the days of subsequent normal sleep,[20] thus limiting the diffusion of this technique alone.[32] Soon in the early studies, however, SD was observed to produce rapid benefits in the broadly defined depressive syndrome: in endogenous, reactive, unipolar, bipolar, secondary, and schizoaffective depression; in the elderly and in children; in depression secondary to Parkinson's disease or schizophrenia; or associated with pregnancy and postpartum and premenstrual dysphoric disorder,[10,20] and with better effects observed in endogenous primary depression compared with reactive and/or secondary depression, and in the treatment of Bipolar Disorder compared with Primary Depressive Disorder.[33]
In order to prevent the relapse into depression after SD, single-night SD or repeated SD was combined with serotonergic antidepressants, lithium salts, or other chronotherapeutic techniques.[4] The simple repetition of SD over time has been tested for many schedules, including twice in 1 week,[34] or twice a week for 3 weeks[35,36] or

for a month,[37] or for twice in 1 week followed by partial SD twice,[38] etc. Repeated SD once a week has also been proposed as a prophylactic treatment: preliminary studies in small samples showed that SD reduced the frequency of relapses and increased the duration of normothymia in roughly one half of the patients.[39,40]

Our group developed a treatment schedule based on repeated total SD, three times during 1 week, resulting in a lengthening of the sleep-wake period from the usual 24 to 48 hours.[41-49] When combined with light therapy and with lithium salts, the mainstay for the long-term treatment of bipolar disorder, this therapy is able to trigger an acute response also in patients drug resistant to both serotonergic and tricyclic antidepressants, and to lead to a stable euthymia for 9 months in roughly 60% of bipolar patients without a history of drug resistance.[47] Despite early concerns due to the close link between sleep loss and the onset of mania,[50] this result is achieved with a risk of switch which is around 6% and leads to easily controlled manic reactions,[51] thus comparable to the reported switch rate for placebo. Considering the 15%-to-25% risk of treatment-emergent mania linked with antidepressant drug treatment in bipolar patients,[16,17] and the 30% of responders mantaining euthymia when discontinuing drug treatments before 6 months,[18] these data warrant the highest clinical interest in using these techniques as first-choice treatments for bipolar depression.

Light therapy

The scientific approach to the treatment of depression with bright light started in the 1980s.[52-54] Early on, antidepressant bright light therapy (LT) was administered 1 to 2 hours before the usual time of awakening.[55] This phase-advancing administration of light in the early morning was then proven to have better antidepressant effects than the simple increase of the subjective photoperiod obtained by exposing the patients to light in the evening.[56] A correlation was then observed between the magnitude of phase advances to morning LT and improvement in depression ratings, with maximum effects with phase advances of 1.5 to 2.5 hours (about 7.5 to 9 hours after the dim-light melatonin onset the evening before).[57] Since scores on the Morningness-Eveningness Questionnaire (MEQ) are strongly correlated with sleep midpoint and melatonin secretion, a predictive algorithm based on MEQ scores was then developed to define the individual optimal timing of LT administration,[58] and proven successful even when used in common clinical settings, and when giving light in combination with antidepressants.[59] Over the years, other treatment algorithms have been proposed,[60] and research is currently identifying the most effective treatment schedule as a function of seasonality and other individual characteristics.[61]

Given that LT is, however, useful, even when given at midday,[62] the clinical use of LT followed a pattern of evolving applications in any kind of depressive syndrome.[63] The APA Committee on Research on Psychiatric Treatments[64] and a Cochrane review[65] concluded that light treatment for nonseasonal major depression is efficacious, with effect sizes equivalent to those in most antidepressant pharmacotherapy trials. When combined with standard antidepressant drug treatments LT hastens recovery, with benefits that can be perceived by the patients during the first week of treatment.[59,66] After 1 month of treatment, patients treated with light show a net benefit, in respect to placebo, that can be quantified in a approximately 30% better reduction in the severity of depression: remarkably, these values are very similar for early studies performed with the combination of light and tricyclic antidepressants, and for new studies combining light and selective serotonergic drugs.[59,66,67] The benefit is also clinically evident in drug-resistant patients, when adding light to ongoing albeit ineffective antidepressants.[68] Similar to SD, LT in nonseasonal major depression does not show a sustained effect after discontinuation, with a complete offset of effect after 1 month,[69] but the relapse can be easily prevented when combining LT with common antidepressant drugs.[70] Again, similarly to SD, LT caused marked benefits in the broadly defined depressive syndrome, including very different psychopathological conditions such as antepartum depression[71] as well as post-stroke depression in the elderly.[72]

In the case of bipolar depression, the efficacy of LT alone is questioned, with studies showing either better benefits than in unipolar patients,[73] or worse effects,[74] but the combination of LT with other chronotherapeutic techniques and with lithium salts was proven to lead to stable mood ameliorations and euthymia, even in drug-resistant patients.[45,47] Moreover, some observations suggested that bipolar patients could be sensitive to the antidepressant properties of light at intensities as low as 300 to 500 lux,[45,73] far below the usual 10000-lux standard used in LT of unipolar patients: a finding in agreement

with the proposed supersensitivity of the biological clock to the effects of light as a possible trait marker for bipolar disorder.[75]
Other studies explored the interaction of LT with the circadian changes of sensitivity of the biological clock to the effects of light and defined "dawn simulation" protocols based on the administration of low intensity (400 lux) LT during the last period of the patient's sleep episode, a treatment with a comparable efficacy to that of bright white LT.[76,77]

Sleep phase advance and combined treatments

Antidepressant effects of sleep phase-advance (SPA) have been predicted by chronobiological studies of depression (suggesting a misalignment between the biological clock, biological rhythms, and the sleep-wake rhythms) and first described in 1979[78]: the simple act of going to bed and waking up 5 hours earlier leads to a sustained marked improvement of mood in a bipolar depressed patient, an effect then confirmed in unipolar endogenous depression.[79] Remarkably, recent studies on large samples in the general population showed that earlier parental set bedtimes are a protective factor against depression and suicidal ideation during adolescence,[80] thus suggesting a major role for the disruption of the circadian timing in the pathophysiology of depression.[81]
Probably because of the difficult match of a phase-advanced sleep schedule with social and environmental cues and expectations, SPA has never spread into clinical settings. When combined with a previous SD, SPA is however able to sustain its effects and prevent the relapse that might occur after restoring night sleep.[82] A short SPA protocol, performed over 3 days, has been shown to be sufficient to achieve this effect and to be synergistic with lithium salts in sustaining a stable euthymia in bipolar depressed patients.[83] This protocol can easily be associated with antidepressant medications,[84] and more recent pilot trials explored the possibility of a "triple chronotherapeutics" for bipolar depression: SD followed by SPA and combined with morning LT, given as adjunctive treatment to lithium and antidepressants, significantly enhanced antidepressant response.[85]

Mechanisms of action

The mechanism of action of chronotherapeutics has been widely explored for SD, and suggests convergence of effects between SD and all known antidepressant strategies. Many effective antidepressant treatments target several mechanisms, and a multitarget approach to treatment could overall be better suited for a multifactorial illness such as depression[86]: chronotherapeutics is no exception, and is able to influence the same mechanisms that are targets for other antidepressants.

Brain monoamines and glutamate

SD potentiates all the monoaminergic systems that are targeted by antidepressant drugs and that have been involved in the pathogenesis of depression, and effects of SD on monoamines are part of its mechanism of action. Research on this topic directly measured changes in monoaminergic neurotransmission in animal models, or studied SD effects in humans with challenge methods, brain imaging, or pharmacogenetic approaches. These methods allowed definition of convergent effects in animal and humans, either healthy or depressed, of SD on serotonin (5-HT), noradrenaline (NA), and dopamine (DA).
In animal models, SD increase 5-HT neurotransmission[87] by enhancing the activity of 5-HT neurons in the dorsal raphé nucleus,[88] increasing brain extracellular 5-HT[89] and 5-HT turnover,[90-92] reducing the sensitivity of 5-HT_{1A} inhibitory autoreceptors,[88,93] and increasing the behavioral responsiveness to 5-HT precursors.[94] In a similar way, SD was shown to increase synaptic levels of NA[95] and tyrosine hydroxylase and NA transporter mRNA in the locus coeruleus,[96] and to increase DA activity and behavioral response to DA agonists,[97,98] with an increase of DA receptor binding sites during the early stages of SD (following 12 to 24 hours awake)[99] and a subsequent subsensitivity after more prolonged wake,[100] suggesting downregulation after prolonged stimulation.
Clinical psychobiology confirmed these effects in depressed humans and linked them with the efficacy of chronotherapeutics. SD increased the prolactin response to intravenous tryptophan infusion[101] and decreased plasma levels of prolactin, which is inhibited by DA agonists, thus suggesting DA hyperactivity during SD.[102,103] D2 receptor occupancy decreased in responders to SD, thus suggesting an enhanced DA release in responders,[104] levels of homovanillic acid in the spinal fluid predicted the clinical effects of SD,[105] and eye-blink rate after SD increased in responders, suggesting DA activation.[106] The NA metabolites 3-methoxy-4-hydroxyphenylglycol (MHPG) and MHPG sulfate[107] increased after SD pro-

portionally to severity of depression[108] and clinical response to treatment.[109] Human pharmacogenetics confirmed that gene variants that improve neurotransmission by increasing receptor or transporter density, or decreasing neurotransmitter degradation, also improve the clinical efficacy of SD in bipolar depression when given alone or combined with bright light therapy. This was proven for genotypes influencing the density of the 5-HT transporter[110-112] and of the 5-HT_{2A} receptor,[113] or the efficiency of the catechol-O-methyltransferase (COMT) in clearing NA and DA from the synapse.[114] Interestingly, the role of these genetic influences has effect sizes comparable to those observed on response to antidepressant drugs,[115-117] thus strongly suggesting a shared mechanism of action of chronotherapeutics and monoaminergic drugs.

Following this line of reasoning, the most striking confirmations of shared influences on monoamines come from combined treatments with chronotherapeutics and drugs. SD showed synergistic interactions with drugs that increase the activity of brain 5-HT,[42,43,85] NA,[118] and DA[46] systems; conversely, DA antagonists block the behavioral[119] and antidepressant[120] effects of SD. Similar synergistic effects have been described for light therapy, which significantly potentiates serotonergic antidepressants,[59,66] is influenced by genotypes influencing the density of the 5-HT transporter,[112] and can prevent the mood-lowering effect of acute tryptophan depletion, which reduces brain 5-HT.[121]

Finally, an increasing interest on glutamatergic neurotransmission in depression stemmed from trials reporting antidepressant effects of the NMDA antagonists ketamine[122] and the glutamatergic modulator riluzole.[123] Glutamatergic neurotransmission follows a strict circadian rhythm, and in animal models it is first enhanced and then markedly depressed during SD.[124] In vivo single proton magnetic resonance spectroscopy (1H-MRS) indicated that glutamatergic transmission is altered by SD, as shown by reduced glutamate concentrations, the changes being proportional to both perceived and observed mood amelioration in bipolar depression.[125] Remarkably, these effects were observed in the anterior cingulate cortex, a brain area which has been widely implicated in providing a neural basis for mood-congruent cognitive biases in depression,[126] and where chronotherapeutics was shown to profoundly change metabolism[127,128] and neural reactivity to stimulus words[48] in responders to treatment.

Biological clock and long-lasting effects on biological rhythms

The hypothesis that several psychiatric conditions may involve primary or secondary changes in biological clocks,[129] and the observations that biological rhythms show a range of abnormalities in mood disorders,[130] make the biological clock a primary candidate to explain the mechanism of action of chronotherapeutic techniques. The molecular machinery which constitutes the biological master clock in the suprachiasmatic nuclei (SCN) is being elucidated,[131] but the systematic study of the relationship between clock and therapeutic interventions in psychiatry is just beginning.[132]

Growing evidence supports the hypothesis that changes in brain monoaminergic functioning influence the function of the biological clock molecular machinery, and the clock and the control of biological rhythms are emerging targets for antidepressant drug treatment.[133,134] New animal models have been used to test the interactions between circadian genes and mood-related neurotransmitter systems, and, conversely, to explore the effects of light on brain circuitries and of antidepressant and mood-stabilizing drugs on the clock.[22] Serotonin modulates the response of the circadian system to light and mediates modification of the period and phase of the central clock by behavioral arousal, while, in turn, the biological clock gene network is expressed in serotonergic raphe neurons,[135] with a close interplay between the two systems leading to strong circadian and seasonal rhythms in serotonergic function.[136] Dopaminergic activity also follows a strong rhythm, and manipulations of clock genes within brain dopaminergic structures leads to abnormal animal behaviors that closely resemble human bipolar disorder,[137-139] while some genetic variants of the same clock genes are associated with a worse bipolar phenotype in human patients.[140,141] The locus coeruleus produces a relatively constant tonic noradrenergic firing throughout all behavioral states, except during rapid eye movement (REM) sleep when NA discharge is absent,[142] and it was hypothesized that modifications of NA activity during chronotherapeutics could be necessary for its effects.[99,143]

Remarkably, all antidepressant chronotherapeutic interventions cause a phase advance of biological rhythms. Light therapy in the morning is the main environmental synchronizer of the internal clock and influences timing and entrainment of the SCN circadian clock by inducing

CREB.[144] The circadian pacemaker is sensitive to short-duration light pulses with a nonlinear relationship between light duration and the amount of resetting, and a 1-hour bright white light pulse phase shifts the circadian pacemaker following a clear-cut phase-response curve[145]: phase advances are obtained when administering light in the morning, and phase delays when administering it in the evening (the so-called type I phase response).[146] SD directly targets the sleep-wake rhythm and can influence SCN function by modifying vigilance state transitions and sleep states,[147] specifically modifies the binding of the molecular components of the biological clock,[148] and is clinically synergistic with the administration of phase-advancing morning light[149]: in agreement with these findings, an actimetric advance of the activity-rest circadian cycle correlates with positive antidepressant response to SD.[49] Surprisingly, very little data are available on the effects of antidepressant drugs on the biological clock, but a single study showed that fluoxetine induces a phase advance of the SCN in rats,[150] while the antidepressant agomelatine can induce a phase advance in normal humans,[151] thus supporting the hypothesis that chronotherapeutics and drug-induced changes on monoaminergic function may result in similar long-lasting effects on the master clock of depressed patients, possibly correcting yet poorly understood abnormalities in the phase-angle relationships between biological rhythms.[81,152]

Brain plasticity and metabolism

Genes of the biological clock are expressed in many brain structures other than in the SCN[153,154] and their genetic variants can bias "non-clock" brain functions such as information processing and decision making in bipolar depression.[155] Several findings suggest that at the cellular level clock genes could provide a mechanism for the control of circadian gene expression and of responsiveness to stimuli,[156] which in psychiatric conditions may influence the complex relationship between susceptibility and precipitating factors for depression, thus biasing core characteristics of the illness such as age at onset,[157] recurrence of illness,[158] or its occurrence in specific risk periods such as the postpartum period.[159]

The close link between the clock machinery and core metabolic cellular processes is confirmed by the study of protein modulators such as glycogen synthase kinase 3-β (GSK3-β), which is a core constituent of the mammalian circadian clock and affects circadian rhythm generation by modifying the stability of circadian clock molecules.[160] This kinase is also an essential element of the Wnt/beta-catenin pathway, which is involved in the control of gene expression, cell behavior, cell adhesion, and cell polarity, and plays major roles in neurodevelopment and in regulation of neuronal polarity, neuronal plasticity, and cell survival.[161] It regulates the activity of many targets including transcriptional factors, enzymes, and cytoskeletal proteins,[162] and is considered a primary regulator in a range of cellular processes including differentiation, growth, motility, and apoptosis.[163] GSK-3 influences the susceptibility of neurons to harmful stimuli (neuronal resilience), because increasing GSK-3 activity increases apoptosis in neuronal cells, while inhibiting GSK has neuroprotective effects,[164] and because its inhibition occurs in response to brain-derived neurotrophic factor (BDNF) and other neurotrophins.[165]

These mechanisms provide a target for the convergent effects of chronotherapeutics and antidepressant drugs on the biological clock and on neurotransmitter systems. Control of the phosphorylation/activity status of GSK-3β is considered an important mechanism of serotonin (5-HT) and dopamine (DA) action on brain and behavior,[166] because GSK3-β is inhibited by lithium, valproate, and several antidepressants such as selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and tricyclic antidepressants.[165,167] Confirming the role of these mechanisms for bipolar disorder and chronotherapeutics, promoter gene variants were associated with less detrimental clinical features, including a delayed onset of illness,[168] a better clinical response to lithium,[169,170] and a better response to sleep deprivation[171]: this effect was so strong as to overcome the detrimental influence on SD response of genotypes negatively affecting serotonergic function.[111,172]

Molecular mechanisms involved in brain plasticity are likely to play a major role in antidepressant response and long-term mood stabilization of bipolar patients.[173] Accumulating evidence suggests then that plastic processes occurring during wakefulness result in a net increase in synaptic strength in many brain circuits, and that synaptic strength is downscaled to baseline levels during sleep,[174] when effective cortico-cortical connectivity is broken down.[175] In agreement with the predictions of this "synaptic homeostasis hypothesis" of sleep,[176] a recent study showed that in healthy humans prolonged wakefulness is associated with significant changes in the state of cortical circuits involving a steady

increase in the excitability of human cortical circuits that is rebalanced during sleep.[177] These effects have been related with the circadian rhythms of glutamatergic neurotransmission and with increased synaptic weights in animal models,[178] thus supporting the hypothesis that these mechanisms could provide a new basis in conceptualizing the link between chronotherapeutics and brain homeostasis in bipolar depression.

Conclusion

In conclusion, chronotherapeutics has now been proven to be a powerful clinical instrument for the treatment of depression in everyday clinical practice. Rapidity of effects and lower rates of switch into mania with respect to available antidepressant drugs make chronotherapeutic combinations a first-choice option for the hospital treatment of patients with a major depressive episode in the course of bipolar disorder. Antidepressant efficacy in nearly one half of drug-resistant patients makes it mandatory for the clinician to prescribe these treatments to these difficult-to-treat patients. Single techniques, such as light therapy, can be easily prescribed to outpatients in combination with the usual antidepressant drug treatments. In all cases, chronotherapeutic techniques should be combined with mood-stabilizing treatments, such as lithium salts, which are the mainstay of the long-term psychiatric management of bipolar disorder and which can enhance and sustain the acute antidepressant effects of chronotherapeutics. ❑

Cronoterapia antidepresiva para la depresión bipolar

La cronoterapia se refiere a los tratamientos basados en los principios de la organización del ritmo circadiano y de la fisiología del sueño, mediante el control de la exposición a los estímulos ambientales que actúan sobre los ritmos biológicos con el fin de conseguir efectos terapéuticos en el tratamiento de los cuadros psiquiátricos. Esta terapia incluye manipulaciones del ciclo sueño-vigilia como la privación de sueño y el avance de fase, junto con la exposición controlada a la luz y a la oscuridad. Los efectos antidepresivos de la cronoterapia son evidentes en cuadros de difícil tratamiento como la depresión bipolar, la cual se ha asociado con resultados de éxito extremadamente bajos para los fármacos antidepresivos en estudios naturalísticos y con una respuesta antidepresiva estable a la cronoterapia en más de la mitad de los pacientes. Avances recientes en el estudio de los efectos de la cronoterapia en los sistemas de neurotransmisión y en la maquinaria del reloj biológico, permiten identificar su mecanismo de acción y transformarla desde un rechazo o un "tratamiento huérfano" a un poderoso instrumento clínico en la práctica psiquiátrica cotidiana.

Chronothérapie antidépressive pour la dépression bipolaire

La chronothérapie se rapporte aux traitements dont les principes reposent sur l'organisation des rythmes circadiens et la physiologie du sommeil, qui contrôlent l'exposition aux stimuli environnementaux agissant sur les rythmes biologiques, afin de pouvoir traiter les pathologies psychiatriques. Elle comprend des manipulations du cycle veille-sommeil comme la privation de sommeil et l'avance de phase du sommeil ainsi qu'une exposition contrôlée à la lumière et à la nuit. Les effets antidépresseurs de la chronothérapie sont évidents dans des pathologies difficiles à traiter comme la dépression bipolaire, qui a été associée à des taux de succès extrêmement faibles des antidépresseurs dans les échantillons naturalistes et à une réponse antidépressive stable à la chronothérapie chez plus de la moitié des patients. Des progrès récents dans l'étude des effets de la chronothérapie sur les neurotransmetteurs et sur l'horloge biologique nous permettent d'identifier son mécanisme d'action et de faire de ce traitement « orphelin » ou négligé un instrument clinique puissant en pratique psychiatrique quotidienne.

REFERENCES

1. Wirz-Justice A, Terman M. Chronotherapeutics (light and wake therapy) as a class of interventions for affective disorders. *Handb Clin Neurol*. 2012;106:697-713.
2. Wirz-Justice A, Benedetti F, Berger M, et al. Chronotherapeutics (light and wake therapy) in affective disorders. *Psychol Med*. 2005;35:939-944.
3. Benedetti F, Barbini B, Colombo C, Smeraldi E. Chronotherapeutics in a psychiatric ward. *Sleep Med Rev*. 2007;11:509-522.
4. Wirz-Justice A, Benedetti F, Terman M. *Chronotherapeutics for Affective Disorders. A Clinician's Manual for Light and Wake Therapy*. Basel, Switzerland: Karger; 2009.
5. Wirz-Justice A. Chronobiology and mood disorders. *Dialogues Clin Neurosci*. 2003;5:315-325.
6. Benedetti F, Barbini B, Campori E, Colombo C, Smeraldi E. Patterns of mood variation during antidepressant treatment. *J Affect Disord*. 1998;49:133-139.
7. Benedetti F, Colombo C, Barbini B, Campori E, Smeraldi E. Morning sunlight reduces length of hospitalization in bipolar depression. *J Affect Disord*. 2001;62:221-223.
8. Bauer M, Pfennig A, Linden M, Smolka MN, Neu P, Adli M. Efficacy of an algorithm-guided treatment compared with treatment as usual: a randomized, controlled study of inpatients with depression. *J Clin Psychopharmacol*. 2009;29:327-333.
9. Bauer M, Glenn T, Whybrow PC, et al. Changes in self-reported sleep duration predict mood changes in bipolar disorder. *Psychol Med*. 2008;38:1069-1071.
10. Leibenluft E, Wehr TA. Is sleep deprivation useful in the treatment of depression? *Am J Psychiatry*. 1992;149:159-168.
11. Wu JC, Bunney WE. The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. *Am J Psychiatry*. 1990;147:14-21.
12. Post RM, Leverich GS, Altshuler LL, et al. Differential clinical characteristics, medication usage, and treatment response of bipolar disorder in the US versus The Netherlands and Germany. *Int Clin Psychopharmacol*. 2011;26:96-106.
13. Altshuler LL, Kupka RW, Hellemann G, et al. Gender and depressive symptoms in 711 patients with bipolar disorder evaluated prospectively in the Stanley Foundation bipolar treatment outcome network. *Am J Psychiatry*. 2010;167:708-715.
14. Kupka RW, Altshuler LL, Nolen WA, et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. *Bipolar Disord*. 2007;9:531-535.
15. Post RM, Leverich GS, Altshuler LL, et al. Relationship of prior antidepressant exposure to long-term prospective outcome in bipolar I disorder outpatients. *J Clin Psychiatry*. 2012;73:924-930.
16. Frye MA, Helleman G, McElroy SL, et al. Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. *Am J Psychiatry*. 2009;166:164-172.
17. Gao K, Kemp DE, Ganocy SJ, et al. Treatment-emergent mania/hypomania during antidepressant monotherapy in patients with rapid cycling bipolar disorder. *Bipolar Disord*. 2008;10:907-915.
18. Altshuler L, Suppes T, Black D, et al. Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. *Am J Psychiatry*. 2003;160:1252-1262.
19. Post RM, Altshuler LL, Frye MA, et al. Complexity of pharmacologic treatment required for sustained improvement in outpatients with bipolar disorder. *J Clin Psychiatry*. 2010;71:1176-1186.
20. Benedetti F, Colombo C. Sleep deprivation in mood disorders. *Neuropsychobiology*. 2011;64:141-151.
21. Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. *Annu Rev Physiol*. 2010;72:517-549.
22. McClung CA. Circadian rhythms and mood regulation: insights from pre-clinical models. *Eur Neuropsychopharmacol*. 2011;21(suppl 4):S683-S693.
23. Jauhar P, Weller MP. Psychiatric morbidity and time zone changes: a study of patients from Heathrow airport. *Br J Psychiatry*. 1982;140:231-235.
24. Young DM. Psychiatric morbidity in travelers to Honolulu, Hawaii. *Compr Psychiatry*. 1995;36:224-228.
25. Schulte W. Sequelae of sleep deprivation. Medizinische Klinik (Munich). 1959;54:969-973.
26. Pflug B, Tolle R. Therapy of endogenous depression using sleep deprivation. Practical and theoretical consequences. *Nervenarzt*. 1971;42:117-124.
27. Pflug B, Tolle R. Disturbance of the 24-hour rhythm in endogenous depression and the treatment of endogenous depression by sleep deprivation. *Int Pharmacopsychiatry*. 1971;6:187-196.
28. Schilgen B, Tolle R. Partial sleep deprivation as therapy for depression. *Arch Gen Psychiatry*. 1980;37:267-271.
29. Giedke H, Wormstall H, Haffner HT. Therapeutic sleep deprivation in depressives, restricted to the two nocturnal hours between 3:00 and 5:00. *Prog Neuropsychopharmacol Biol Psychiatry*. 1990;14:37-47.
30. Wehr TA, Rosenthal NE, Sack DA, Gillin JC. Antidepressant effects of sleep deprivation in bright and dim light. *Acta Psychiatr Scand*. 1985;72:161-165.
31. Benedetti F, Dallaspezia S, Cigala Fulgosi M, et al. Actimetric evidence that CLOCK 3111 T/C SNP influences depressive insomnia and activity patterns in bipolar depression. *Am J Med Genet B Neuropsychiatr Genet*. 2007;144:631-635.
32. Voderholzer U. Sleep deprivation and antidepressant treatment. *Dialogues Clin Neurosci*. 2003;5:366-369.
33. Barbini B, Colombo C, Benedetti F, Campori E, Bellodi L, Smeraldi E. The unipolar-bipolar dichotomy and the response to sleep deprivation. *Psychiatry Res*. 1998;79:43-50.
34. van den Burg W, van den Hoofdakker RH. Total sleep deprivation on endogenous depression. *Arch Gen Psychiatry*. 1975;32:1121-1125.
35. Wiegand MH, Lauer CJ, Schreiber W. Patterns of response to repeated total sleep deprivations in depression. *J Affect Disord*. 2001;64:257-260.
36. Kundermann B, Strate P, Hemmeter-Spernal J, Huber MT, Krieg JC, Lautenbacher S. Mid-term effects of serial sleep deprivation therapy implemented in cognitive-behavioral treatment on the neuroendocrine response to clomipramine in patients with major depression. *J Psychiatr Res*. 2009;43:711-720.
37. Papadimitriou GN, Christodoulou GN, Trikkas GM, Malliaras DE, Lykouras EP, Stefanis CN. Sleep deprivation psychoprophylaxis in recurrent affective disorders. *Bibl Psychiatr*. 1981;56-61.
38. van Bemmel AL, van den Hoofdakker RH. Maintenance of therapeutic effects of total sleep deprivation by limitation of subsequent sleep. A pilot study. *Acta Psychiatr Scand*. 1981;63:453-462.
39. Christodoulou GN, Malliaras DE, Lykouras EP, Papadimitriou GN, Stefanis CN. Possible prophylactic effect of sleep deprivation. *Am J Psychiatry*. 1978;135:375-376.
40. Papadimitriou GN, Christodoulou GN, Katsouyanni K, Stefanis CN. Therapy and prevention of affective illness by total sleep deprivation. *J Affect Disord*. 1993;27:107-116.
41. Benedetti F, Barbini B, Colombo C, Smeraldi E. Chronotherapeutics in a psychiatric ward. *Sleep Med Rev*. 2007;11:509-522.
42. Benedetti F, Barbini B, Lucca A, Campori E, Colombo C, Smeraldi E. Sleep deprivation hastens the antidepressant action of fluoxetine. *Eur Arch Psychiatry Clin Neurosci*. 1997;247:100-103.
43. Smeraldi E, Benedetti F, Barbini B, Campori E, Colombo C. Sustained antidepressant effect of sleep deprivation combined with pindolol in bipolar depression - a placebo-controlled trial. *Neuropsychopharmacology*. 1999;20:380-385.
44. Benedetti F, Colombo C, Barbini B, Campori E, Smeraldi E. Ongoing lithium treatment prevents relapse after total sleep deprivation. *J Clin Psychopharmacol*. 1999;19:240-245.
45. 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 Res*. 2000;95:43-53.
46. Benedetti F, Campori E, Barbini B, Fulgosi MC, Colombo C. Dopaminergic augmentation of sleep deprivation effects in bipolar depression. *Psychiatry Res*. 2001;104:239-246.
47. Benedetti F, Barbini B, Fulgosi MC, et al. Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: acute response and long-term remission rates. *J Clin Psychiatry*. 2005;66:1535-1540.

48. Benedetti F, Bernasconi A, Blasi V, et al. Neural and genetic correlates of antidepressant response to sleep deprivation: a fMRI study of moral valence decision in bipolar depression. *Arch Gen Psychiatry*. 2007;64:179-187.
49. Benedetti F, Dallaspezia S, Fulgosi MC, Barbini B, Colombo C, Smeraldi E. Phase advance is an actimetric correlate of antidepressant response to sleep deprivation and light therapy in bipolar depression. *Chronobiol Int*. 2007;24:921-937.
50. Wehr TA. Sleep loss: a preventable cause of mania and other excited states. *J Clin Psychiatry*. 1989;50(suppl):8-16.
51. Colombo C, Benedetti F, Barbini B, Campori E, Smeraldi E. Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. *Psychiatry Res*. 1999;86:267-270.
52. Kripke D. Photoperiodic mechanisms for depression and its treatment. In: Perris C, Struwe G, Jansson B, eds. *Biological Psychiatry*. Amsterdam, the Netherlands: Elsevier; 1981:1249-1252.
53. Kripke DF, Risch SC, Janowsky D. Bright white light alleviates depression. *Psychiatry Res*. 1983;10:105-112.
54. Lewy AJ, Kern HA, Rosenthal NE, Wehr TA. Bright artificial light treatment of a manic-depressive patient with a seasonal mood cycle. *Am J Psychiatry*. 1982;139:1496-1498.
55. Parry BL, Maurer EL. Light treatment of mood disorders. *Dialogues Clin Neurosci*. 2003;5:353-365.
56. Terman M, Terman JS. Bright light therapy: side effects and benefits across the symptom spectrum. *J Clin Psychiatry*. 1999;60:799-808.
57. Terman JS, Terman M, Lo ES, Cooper TB. Circadian time of morning light administration and therapeutic response in winter depression. *Arch Gen Psychiatry*. 2001;58:69-75.
58. Terman M, Terman JS. Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. *CNS Spectr*. 2005;10:647-663.
59. Benedetti F, Colombo C, Pontiggia A, Bernasconi A, Florita M, Smeraldi E. Morning light treatment hastens the antidepressant effect of citalopram: a placebo-controlled trial. *J Clin Psychiatry*. 2003;64:648-653.
60. Lewy AJ, Lefler BJ, Emens JS, Bauer VK. The circadian basis of winter depression. *Proc Natl Acad Sci U S A*. 2006;103:7414-7419.
61. Dallaspezia S, Benedetti F, Colombo C, et al. Optimized light therapy for non-seasonal major depressive disorder: effects of timing and season. *J Affect Disord*. 2012;138:337-342.
62. Wirz-Justice A, Graw P, Krauchi K, et al. Light therapy in seasonal affective disorder is independent of time of day or circadian phase. *Arch Gen Psychiatry*. 1993;50:929-937.
63. Terman M. Evolving applications of light therapy. *Sleep Med Rev*. 2007;11:497-507.
64. 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.
65. Tuunainen A, Kripke DF, Endo T. Light therapy for non-seasonal depression. *Cochrane Database Syst Rev.* 2004;CD004050.
66. Martiny K, Lunde M, Unden M, Dam H, Bech P. Adjunctive bright light in non-seasonal major depression: results from clinician-rated depression scales. *Acta Psychiatr Scand*. 2005;112:117-125.
67. Kripke DF. Light treatment for nonseasonal depression: speed, efficacy, and combined treatment. *J Affect Disord*. 1998;49:109-117.
68. Prasko J, Brunovsky M, Latalova K, et al. Augmentation of antidepressants with bright light therapy in patients with comorbid depression and borderline personality disorder. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2010;154:355-361.
69. Martiny K, Lunde M, Unden M, Dam H, Bech P. The lack of sustained effect of bright light, after discontinuation, in non-seasonal major depression. *Psychol Med*. 2006;36:1247-1252.
70. Martiny K, Lunde M, Simonsen C, et al. Relapse prevention by citalopram in SAD patients responding to 1 week of light therapy. A placebo-controlled study. *Acta Psychiatr Scand*. 2004;109:230-234.
71. Wirz-Justice A, Bader A, Frisch U, et al. A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. *J Clin Psychiatry*. 2011;72:986-993.
72. Sondergaard MP, Jarden JO, Martiny K, Andersen G, Bech P. Dose response to adjunctive light therapy in citalopram-treated patients with post-stroke depression. A randomised, double-blind pilot study. *Psychother Psychosom*. 2006;75:244-248.
73. Deltito JA, Moline M, Pollak C, Martin LY, Maremmani I. Effects of phototherapy on non-seasonal unipolar and bipolar depressive spectrum disorders. *J Affect Disord*. 1991;23:231-237.
74. Dauphinais DR, Rosenthal JZ, Terman M, DiFebo HM, Tuggle C, Rosenthal NE. Controlled trial of safety and efficacy of bright light therapy vs. negative air ions in patients with bipolar depression. *Psychiatry Res*. 2012;196:57-61.
75. Lewy AJ, Nurnberger JI Jr, Wehr TA, et al. Supersensitivity to light: possible trait marker for manic-depressive illness. *Am J Psychiatry*. 1985;142:725-727.
76. Terman M, Schlager D, Fairhurst S, Perlman B. Dawn and dusk simulation as a therapeutic intervention. *Biol Psychiatry*. 1989;25:966-970.
77. Terman M, Terman JS. Controlled trial of naturalistic dawn simulation and negative air ionization for seasonal affective disorder. *Am J Psychiatry*. 2006;163:2126-2133.
78. Wehr TA, Wirz-Justice A, Goodwin FK, Duncan W, Gillin JC. Phase advance of the circadian sleep-wake cycle as an antidepressant. *Science*. 1979;206:710-713.
79. Souetre E, Salvati E, Pringuey D, Plasse Y, Savelli M, Darcourt G. Antidepressant effects of the sleep/wake cycle phase advance. Preliminary report. *J Affect Disord*. 1987;12:41-46.
80. Gangwisch JE, Babiss LA, Malaspina D, Turner JB, Zammit GK, Posner K. Earlier parental set bedtimes as a protective factor against depression and suicidal ideation. *Sleep*. 2010;33:97-106.
81. Bhattacharjee Y. Psychiatric research. Is internal timing key to mental health? *Science*. 2007;317:1488-1490.
82. Berger M, Vollmann J, Hohagen F, et al. Sleep deprivation combined with consecutive sleep phase advance as a fast-acting therapy in depression: an open pilot trial in medicated and unmedicated patients. *Am J Psychiatry*. 1997;154:870-872.
83. 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? *J Psychiatr Res*. 2001;35:323-329.
84. Voderholzer U, Valerius G, Schaerer L, et al. Is the antidepressive effect of sleep deprivation stabilized by a three day phase advance of the sleep period? A pilot study. *Eur Arch Psychiatry Clin Neurosci*. 2003;253:68-72.
85. Wu JC, Kelsoe JR, Schachat C, et al. Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. *Biol Psychiatry*. 2009;66:298-301.
86. Millan MJ. Multi-target strategies for the improved treatment of depressive states: conceptual foundations and neuronal substrates, drug discovery and therapeutic application. *Pharmacol Ther*. 2006;110:135-370.
87. Adrien J. Neurobiological bases for the relation between sleep and depression. *Sleep Med Rev*. 2002;6:341-351.
88. Gardner JP, Fornal CA, Jacobs BL. Effects of sleep deprivation on serotonergic neuronal activity in the dorsal raphe nucleus of the freely moving cat. *Neuropsychopharmacology*. 1997;17:72-81.
89. Lopez-Rodriguez F, Wilson CL, Maidment NT, Poland RE, Engel J. Total sleep deprivation increases extracellular serotonin in the rat hippocampus. *Neuroscience*. 2003;121:523-530.
90. Hery F, Pujol JF, Lopez M, Macon J, Glowinski J. Increased synthesis and utilization of serotonin in the central nervous system of the rat during paradoxical sleep deprivation. *Brain Res*. 1970;21:391-403.
91. Cramer H, Tagliamonte A, Tagliamonte P, Perez-Cruet J, Gessa GL. Stimulation of brain serotonin turnover by paradoxical sleep deprivation in intact and hypophysectomized rats. *Brain Res*. 1973;54:372-375.
92. Asikainen M, Deboer T, Porkka-Heiskanen T, Stenberg D, Tobler I. Sleep deprivation increases brain serotonin turnover in the Djungarian hamster. *Neurosci Lett*. 1995;198:21-24.
93. Maudhuit C, Jolas T, Chastanet M, Hamon M, Adrien J. Reduced inhibitory potency of serotonin reuptake blockers on central serotoninergic neurons in rats selectively deprived of rapid eye movement sleep. *Biol Psychiatry*. 1996;40:1000-1007.
94. Santos R, Carlini EA. Serotonin receptor activation in rats previously deprived of REM sleep. *Pharmacol Biochem Behav*. 1983;18:501-507.
95. Hipolide DC, Moreira KM, Barlow KB, Wilson AA, Nobrega JN, Tufik S. Distinct effects of sleep deprivation on binding to norepinephrine and serotonin transporters in rat brain. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29:297-303.

96. Basheer R, Magner M, McCarley RW, Shiromani PJ. REM sleep deprivation increases the levels of tyrosine hydroxylase and norepinephrine transporter mRNA in the locus coeruleus. *Brain Res Mol Brain Res*. 1998;57:235-240.
97. Tufik S, Lindsey CJ, Carlini EA. Does REM sleep deprivation induce a supersensitivity of dopaminergic receptors in the rat brain? *Pharmacology*. 1978;16:98-105.
98. Mogilnicka E. REM sleep deprivation changes behavioral response to catecholaminergic and serotonergic receptor activation in rats. *Pharmacol Biochem Behav*. 1981;15:149-151.
99. Wirz-Justice A, Tobler I, Kafka MS, et al. Sleep deprivation: effects on circadian rhythms of rat brain neurotransmitter receptors. *Psychiatry Res*. 1981;5:67-76.
100. Zwicker AP, Calil HM. The effects of REM sleep deprivation on striatal dopamine receptor sites. *Pharmacol Biochem Behav*. 1986;24:809-812.
101. Salomon RM, Delgado PL, Licinio J, Krystal JH, Heninger GR, Charney DS. Effects of sleep deprivation on serotonin function in depression. *Biol Psychiatry*. 1994;36:840-846.
102. Kasper S, Sack DA, Wehr TA, Kick H, Voll G, Vieira A. Nocturnal TSH and prolactin secretion during sleep deprivation and prediction of antidepressant response in patients with major depression. *Biol Psychiatry*. 1988;24:631-641.
103. Baumgartner A, Riemann D, Berger M. Neuroendocrinological investigations during sleep deprivation in depression. II. Longitudinal measurement of thyrotropin, TH, cortisol, prolactin, GH, and LH during sleep and sleep deprivation. *Biol Psychiatry*. 1990;28:569-587.
104. Ebert D, Feistel H, Kaschka W, Barocka A, Pirner A. Single photon emission computerized tomography assessment of cerebral dopamine D2 receptor blockade in depression before and after sleep deprivation--preliminary results. *Biol Psychiatry*. 1994;35:880-885.
105. Gerner RH, Post RM, Gillin JC, Bunney WE Jr. Biological and behavioral effects of one night's sleep deprivation in depressed patients and normals. *J Psychiatr Res*. 1979;15:21-40.
106. Ebert D, Albert R, Hammon G, Strasser B, May A, Merz A. Eye-blink rates and depression. Is the antidepressant effect of sleep deprivation mediated by the dopamine system? *Neuropsychopharmacology*. 1996;15:332-339.
107. Muller HU, Riemann D, Berger M, Muller WE. The influence of total sleep deprivation on urinary excretion of catecholamine metabolites in major depression. *Acta Psychiatr Scand*. 1993;88:16-20.
108. Amin MM, Khalid R, Khan P. Relationship between sleep deprivation and urinary MHPG levels. *Int Pharmacopsychiatry*. 1980;15:81-85.
109. Matussek N, Romisch P, Ackenheil M. MHPG excretion during sleep deprivation in endogenous depression. *Neuropsychobiology*. 1977;3:23-29.
110. Benedetti F, Serretti A, Colombo C, et al. Influence of a functional polymorphism within the promoter of the serotonin transporter gene on the effects of total sleep deprivation in bipolar depression. *Am J Psychiatry*. 1999;156:1450-1452.
111. Benedetti F, Barbini B, Bernasconi A, et al. Lithium overcomes the influence of 5-HTTLPR gene polymorphism on antidepressant response to sleep deprivation. *J Clin Psychopharmacol*. 2008;28:249-251.
112. Benedetti F, Colombo C, Serretti A, et al. Antidepressant effects of light therapy combined with sleep deprivation are influenced by a functional polymorphism within the promoter of the serotonin transporter gene. *Biol Psychiatry*. 2003;54:687-692.
113. Benedetti F, Barbini B, Bernasconi A, et al. Serotonin 5-HT(2A) receptor gene variants influence antidepressant response to repeated total sleep deprivation in bipolar depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:1863-1866.
114. Benedetti F, Barbini B, Bernasconi A, et al. Acute antidepressant response to sleep deprivation combined with light therapy is influenced by the catechol-O-methyltransferase Val(108/158)Met polymorphism. *J Affect Disord.* 2010;121:68-72.
115. Benedetti F, Colombo C, Pirovano A, Marino E, Smeraldi E. The catechol-O-methyltransferase Val(108/158)Met polymorphism affects antidepressant response to paroxetine in a naturalistic setting. *Psychopharmacology (Berl).* 2009;203:155-160.
116. Benedetti F, Dallaspezia S, Colombo C, Lorenzi C, Pirovano A, Smeraldi E. Effect of catechol-O-methyltransferase Val(108/158)Met polymorphism on antidepressant efficacy of fluvoxamine. *Eur Psychiatry*. 2010;25:476-478.
117. Serretti A, Benedetti F, Zanardi R, Smeraldi E. The influence of Serotonin Transporter Promoter Polymorphism (SERTPR) and other polymorphisms of the serotonin pathway on the efficacy of antidepressant treatments. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2005;29:1074-1084.
118. Shelton RC, Loosen PT. Sleep deprivation accelerates the response to nortriptyline. *Prog Neuropsychopharmacol Biol Psychiatry*. 1993;17:113-123.
119. Gessa GL, Pani L, Fadda P, Fratta W. Sleep deprivation in the rat: an animal model of mania. *Eur Neuropsychopharmacol*. 1995;5(suppl):89-93.
120. Holsboer-Trachsler E, Hemmeter U, Hatzinger M, Seifritz E, Gerhard U, Hobi V. Sleep deprivation and bright light as potential augmenters of antidepressant drug treatment—neurobiological and psychometric assessment of course. *J Psychiatr Res*. 1994;28:381-399.
121. aan het Rot M, Benkelfat C, Boivin DB, Young SN. Bright light exposure during acute tryptophan depletion prevents a lowering of mood in mildly seasonal women. *Eur Neuropsychopharmacol*. 2008;18:14-23.
122. Diazgranados N, Ibrahim L, Brutsche NE, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry*. 2010;67:793-802.
123. Zarate CA Jr, Quiroz JA, Singh JB, et al. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. *Biol Psychiatry*. 2005;57:430-432.
124. Dash MB, Douglas CL, Vyazovskiy VV, Cirelli C, Tononi G. Long-term homeostasis of extracellular glutamate in the rat cerebral cortex across sleep and waking states. *J Neurosci*. 2009;29:620-629.
125. Benedetti F, Calabrese G, Bernasconi A, et al. Spectroscopic correlates of antidepressant response to sleep deprivation and light therapy: a 3.0 Tesla study of bipolar depression. *Psychiatry Res Neuroimaging*. 2009;173:238-242.
126. Elliott R, Rubinsztein JS, Sahakian BJ, Dolan RJ. The neural basis of mood-congruent processing biases in depression. *Arch Gen Psychiatry*. 2002;59:597-604.
127. Wu JC, Buchsbaum M, Bunney WE Jr. Clinical neurochemical implications of sleep deprivation's effects on the anterior cingulate of depressed responders. *Neuropsychopharmacology*. 2001;25(suppl 5):S74-S78.
128. Gillin JC, Buchsbaum M, Wu J, Clark C, Bunney W Jr. Sleep deprivation as a model experimental antidepressant treatment: findings from functional brain imaging. *Depress Anxiety*. 2001;14:37-49.
129. Schulz P. Biological clocks and the practice of psychiatry. *Dialogues Clin Neurosci*. 2007;9:237-255.
130. Wirz-Justice A. Biological rhythm disturbances in mood disorders. *Int Clin Psychopharmacol*. 2006;21(suppl 1):S11-S15.
131. Schibler U. The daily timing of gene expression and physiology in mammals. *Dialogues Clin Neurosci*. 2007;9:257-272.
132. Benca R, Duncan MJ, Frank E, McClung C, Nelson RJ, Vicentic A. Biological rhythms, higher brain function, and behavior: gaps, opportunities, and challenges. *Brain Res Rev*. 2009;62:57-70.
133. Benedetti F. The molecular clock as a target in the treatment of bipolar disorder. *Neuropsychopharmacology*. 2005;30:S63-S64.
134. Sprouse J. Pharmacological modulation of circadian rhythms: a new drug target in psychotherapeutics. *Expert Opin Ther Targets*. 2004;8:25-38.
135. Ciarleglio CM, Resuehr HE, McMahon DG. Interactions of the serotonin and circadian systems: nature and nurture in rhythms and blues. *Neuroscience*. 2011;197:8-16.
136. Lambert GW, Reid C, Kaye DM, Jennings GL, Esler MD. Effect of sunlight and season on serotonin turnover in the brain. *Lancet*. 2002;360:1840-1842.
137. Roybal K, Theobold D, Graham A, et al. Mania-like behavior induced by disruption of CLOCK. *Proc Natl Acad Sci U S A*. 2007;104:6406-6411.
138. McClung CA, Sidiropoulou K, Vitaterna M, et al. Regulation of dopaminergic transmission and cocaine reward by the Clock gene. *Proc Natl Acad Sci U S A*. 2005;102:9377-9381.
139. Mukherjee S, Coque L, Cao JL, et al. Knockdown of Clock in the ventral tegmental area through RNA interference results in a mixed state of mania and depression-like behavior. *Biol Psychiatry*. 2010;68:503-511.
140. Benedetti F, Radaelli D, Bernasconi A, et al. Clock genes beyond the clock: CLOCK genotype biases neural correlates of moral valence decision in depressed patients. *Genes Brain Behav*. 2008;7:20-25.

141. Benedetti F, Dallaspezia S, Fulgosi MC, et al. Actimetric evidence that CLOCK 3111 T/C SNP influences sleep and activity patterns in patients affected by bipolar depression. *Am J Med Genet B Neuropsychiatr Genet*. 2007;144B:631-635.
142. Siegel JM, Rogawski MA. A function for REM sleep: regulation of noradrenergic receptor sensitivity. *Brain Res*. 1988;472:213-233.
143. Payne JL, Quiroz JA, Zarate CA Jr, Manji HK. Timing is everything: does the robust upregulation of noradrenergically regulated plasticity genes underlie the rapid antidepressant effects of sleep deprivation? *Biol Psychiatry*. 2002;52:921-926.
144. Lee B, Li A, Hansen KF, Cao R, Yoon JH, Obrietan K. CREB influences timing and entrainment of the SCN circadian clock. *J Biol Rhythms*. 2010;25:410-420.
145. St Hilaire MA, Gooley JJ, Khalsa SB, Kronauer RE, Czeisler CA, Lockley SW. Human phase response curve (PRC) to a 1-hour pulse of bright white light. *J Physiol*. In press.
146. Khalsa SB, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to single bright light pulses in human subjects. *J Physiol*. 2003;549:945-952.
147. Deboer T, Vansteensel MJ, Detari L, Meijer JH. Sleep states alter activity of suprachiasmatic nucleus neurons. *Nat Neurosci*. 2003;6:1086-1090.
148. Mongrain V, La Spada F, Curie T, Franken P. Sleep loss reduces the DNA-binding of BMAL1, CLOCK, and NPAS2 to specific clock genes in the mouse cerebral cortex. *PLoS One*. 2011;6:e26622.
149. Benedetti F, Barbini B, Fulgosi MC, et al. Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: Acute response and long-term remission rates. *J Clin Psychiatry*. 2005;66:1535-1540.
150. Sprouse J, Braselton J, Reynolds L. Fluoxetine modulates the circadian biological clock via phase advances of suprachiasmatic nucleus neuronal firing. *Biol Psychiatry*. 2006;60:896-899.
151. Krauchi K, Cajochen C, Mori D, Graw P, Wirz-Justice A. Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature. *Am J Physiol*. 1997;272:R1178-R1188.
152. Wehr TA, Duncan WC Jr, Sher L, et al. A circadian signal of change of season in patients with seasonal affective disorder. *Arch Gen Psychiatry*. 2001;58:1108-1114.
153. Masubuchi S, Kataoka N, Sassone-Corsi P, Okamura H. Mouse Period1 (mPER1) acts as a circadian adaptor to entrain the oscillator to environmental light/dark cycles by regulating mPER2 protein. *J Neurosci*. 2005;25:4719-4724.
154. Abe H, Honma S, Namihira M, et al. Clock gene expressions in the suprachiasmatic nucleus and other areas of the brain during rhythm splitting in CS mice. *Brain Res Mol Brain Res*. 2001;87:92-99.
155. Benedetti F, Radaelli D, Bernasconi A, et al. Clock genes beyond the clock: CLOCK genotype biases neural correlates of moral valence decision in depressed patients. *Genes Brain Behav*. 2008;7:20-25.
156. Kondratov RV, Shamanna RK, Kondratova AA, Gorbacheva VY, Antoch MP. Dual role of the CLOCK/BMAL1 circadian complex in transcriptional regulation. *FASEB J*. 2006;20:530-532.
157. Benedetti F, Dallaspezia S, Colombo C, Pirovano A, Marino E, Smeraldi E. A length polymorphism in the circadian clock gene Per3 influences age at onset of bipolar disorder. *Neurosci Lett*. 2008;445:184-187.
158. Benedetti F, Serretti A, Colombo C, et al. Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. *Am J Med Genet B Neuropsychiatr Genet*. 2003;123B:23-26.
159. Dallaspezia S, Lorenzi C, Pirovano A, Colombo C, Smeraldi E, Benedetti F. Circadian clock gene Per3 variants influence the postpartum onset of bipolar disorder. *Eur Psychiatry*. 2011;26:138-140.
160. Iitaka C, Miyazaki K, Akaike T, Ishida N. A role for glycogen synthase kinase-3beta in the mammalian circadian clock. *J Biol Chem*. 2005;280:29397-29402.
161. Grimes CA, Jope RS. The multifaceted roles of glycogen synthase kinase 3beta in cellular signaling. *Prog Neurobiol*. 2001;65:391-426.
162. Kockeritz L, Doble B, Patel S, Woodgett JR. Glycogen synthase kinase-3—an overview of an over-achieving protein kinase. *Curr Drug Targets*. 2006;7:1377-1388.
163. Forde JE, Dale TC. Glycogen synthase kinase 3: a key regulator of cellular fate. *Cell Mol Life Sci*. 2007;64:1930-1944.
164. Manji HK, Moore GJ, Rajkowska G, Chen G. Neuroplasticity and cellular resilience in mood disorders. *Mol Psychiatry*. 2000;5:578-593.
165. Gould TD, Manji HK. Glycogen synthase kinase-3: a putative molecular target for lithium mimetic drugs. *Neuropsychopharmacology*. 2005;30:1223-1237.
166. Beaulieu JM, Zhang X, Rodriguiz RM, et al. Role of GSK3 beta in behavioral abnormalities induced by serotonin deficiency. *Proc Natl Acad Sci U S A*. 2008;105:1333-1338.
167. Beaulieu JM, Gainetdinov RR, Caron MG. Akt/GSK3 signaling in the action of psychotropic drugs. *Annu Rev Pharmacol Toxicol*. 2009;49:327-347.
168. Benedetti F, Bernasconi A, Lorenzi C, et al. A single nucleotide polymorphism in glycogen synthase kinase 3-beta promoter gene influences onset of illness in patients affected by bipolar disorder. *Neurosci Lett*. 2004;355:37-40.
169. Benedetti F, Serretti A, Pontiggia A, et al. Long-term response to lithium salts in bipolar illness is influenced by the glycogen synthase kinase 3-beta -50 T/C SNP. *Neurosci Lett*. 2005;376:51-55.
170. Adli M, Hollinde DL, Stamm T, et al. Response to lithium augmentation in depression is associated with the glycogen synthase kinase 3-beta -50T/C single nucleotide polymorphism. *Biol Psychiatry*. 2007;62:1295-1302.
171. Benedetti F, Serretti A, Colombo C, Lorenzi C, Tubazio V, Smeraldi E. A glycogen synthase kinase 3-beta promoter gene single nucleotide polymorphism is associated with age at onset and response to total sleep deprivation in bipolar depression. *Neurosci Lett*. 2004;368:123-126.
172. Benedetti F, Dallaspezia S, Lorenzi C, et al. Gene-gene interaction of glycogen synthase kinase 3-beta and serotonin transporter on human antidepressant response to sleep deprivation. *J Affect Disord*. 2012;136:514-519.
173. Schloesser RJ, Martinowich K, Manji HK. Mood-stabilizing drugs: mechanisms of action. *Trends Neurosci*. 2012;35:36-46.
174. Tononi G, Cirelli C. Sleep function and synaptic homeostasis. *Sleep Med Rev*. 2006;10:49-62.
175. Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G. Breakdown of cortical effective connectivity during sleep. *Science*. 2005;309:2228-2232.
176. Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. *Brain Res Bull*. 2003;62:143-150.
177. Huber R, Maki H, Rosanova M, et al. Human cortical excitability increases with time awake. *Cereb Cortex*. Epub ahead of print: February 7, 2012.
178. Vyazovskiy VV, Cirelli C, Pfister-Genskow M, Faraguna U, Tononi G. Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. *Nat Neurosci*. 2008;11:200-208.

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The unipolar–bipolar dichotomy and the response to sleep deprivation

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Abstract

Fifty-one inpatients affected by a major depressive episode were divided into four groups according to mood disorder diagnosis and previous clinical history (bipolar disorder type I; bipolar disorder type II; major depressive disorder with at least three previous depressive episodes; and single depressive episode patients) and administered three consecutive total sleep deprivation (TSD) cycles. Mood changes were rated with a reduced version of the Hamilton Depression Rating Scale and with self-administered visual analogue scales. TSD caused better clinical effects in bipolar and single-episode patients; in particular, unipolar patients lacked effects in perceived mood after the first TSD and showed worse Hamilton ratings in respect to the other groups after the three TSD treatments. Discriminant function analysis could correctly classify 80% of bipolar patients, post hoc, based on TSD response. Further researches on the clinical efficacy of TSD must take into account the heterogeneity of depression and of its biological substrate. © 1998 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Depression; Mania; Antidepressants; Nosography

1. Introduction

Total sleep deprivation (TSD) is an alternative somatic treatment for major depression (American Psychiatric Association, 1995) with a response rate of approximately 60% (Leibenluft and Wehr, 1992) and with an 85% short-term relapse rate in unmedicated responders (Wu and Bunney, 1990). Several strategies have been applied in order to sustain this transient effect: serial repetition of TSD and its association with antidepressant drugs and other non-pharmacologic treatments (e.g. Baxter et al., 1986; Shelton and Loosen, 1993; Szuba et al., 1994; Kuhs et al., 1996; Benedetti et al., 1997; Berger et al., 1997) are some of the techniques proposed with promising results.

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A major problem in the literature is the diagnostic heterogeneity of the samples treated with TSD, due to the inclusion in the study groups of patients with endogenous, reactive, unipolar, bipolar, secondary and schizoaffective depression (Leibenluft and Wehr, 1992). Depression can indeed be considered as a heterogeneous condition, the different subtypes of which may be classified by longitudinal course (e.g. Merikangas et al., 1994): sleep–wake rhythm manipulations could exert different clinical effects depending on the different mood disorder diagnoses of patients and then on the possibly different biological substrates of their clinically similar depressive syndromes. As an example, sleep loss can effectively trigger the onset of mania in bipolar patients (e.g. Wehr et al., 1987; Barbini et al., 1996) but has little or no euphorogenic effects in other diagnostic categories and in normal subjects, so that an euphorogenic response to TSD has been successfully used as a diagnostic tool in uncertain cases of mood disorder (Strouse et al., 1992). Moreover, differences in response to TSD have been proposed as a diagnostic tool in differentiating mood disorders and dementia with depressive symptoms (e.g. Buysse et al., 1988; Williams et al., 1994).

Diagnosis could then be considered a poor predictor of the clinical effect of TSD in patients affected by a major depressive episode, leading to a relative uncertainty and to sometimes contrasting reports in the literature (see review in Wu and Bunney, 1990; Leibenluft and Wehr, 1992). The topic is controversial: in agreement with the hypothesis, polarity of depression was found to influence the response by some authors (e.g. Kvist and Kirkegaard, 1980; Szuba et al., 1991), but not by others (e.g. Svendsen, 1976; Elsenga and Van den Hoofdakker, 1987); however, the presence of a variety of concomitant medications (including antidepressants, lithium, carbamazepine, neuroleptics and benzodiazepines) hampers the evaluation of these reports. The aim of the present study was to clarify this topic by evaluating the clinical effect of TSD in diagnostic subgroups of drug-free patients affected by a major depressive episode (i.e. bipolar disorder type I, bipolar disorder type II, major depressive disorder and single-episode patients).

2. Methods

2.1. Subjects

Fifty-one inpatients affected by a major depressive episode, according to DSM-IV criteria (American Psychiatric Association, 1994), were studied. A written informed consent was obtained after complete description of the study to the subjects. Inclusion criteria were: absence of other diagnoses on Axis I; absence of mental retardation on Axis II; absence of pregnancy, history of epilepsy, and major medical and neurological disorders; no treatment with lithium salts or long-acting neuroleptic drugs in the last 6 months before admission; no treatment with neuroleptics or irreversible MAOIs in the last month before admission; and absence of a history of drug or alcohol dependency or abuse within the last 6 months. Previous antidepressant drug treatments were stopped 1 week before admission. Physical examinations, laboratory tests and electrocardiograms were performed at admission.

Patients were divided in four groups according to their Axis I diagnosis and previous psychiatric history: Group 1, patients affected by bipolar disorder, type I ($n = 17$); Group 2, patients affected by bipolar disorder, type II ($n = 8$); Group 3, patients affected by major depressive disorder with at least three previous episodes in their clinical history and without a family history of bipolar disorder in first-degree relatives ($n = 17$); Group 4, patients affected by major depression, single episode ($n = 9$). Restricted inclusion criteria for Group 3 were chosen in order to enhance the stability of unipolar diagnosis, since longitudinal studies have shown that family history of bipolar disorder and a low number of previous depressive episodes are risk factors for the development of manic episodes in previously unipolar patients (see review in Goodwin and Jamison, 1990). Patients underwent a 7-day run-in period, during which semi-structured interviews based on DSM-IV for Axis I diagnoses were completed. The agreement of two independent raters (chosen among the authors of the study) was required to confirm the diagnosis. Family history was evaluated by interviewing all probands and at least two

first-degree relatives (Andreasen et al., 1977; Smeraldi et al., 1984).

2.2. Treatment and data collection

After a 7-day placebo run-in period, all subjects were administered three TSD cycles, composed of a night of TSD followed by a recovery night. On days 1, 3 and 5, patients were totally sleep-deprived and had to stay awake for 36 h, from 07.00 h until 19.00 h of the following day. They were then allowed to sleep during the nights of days 2, 4 and 6. Compliance of the subjects with the TSD procedure was ensured by the nursing staff. No concurrent psychotropic medication was administered.

Changes in mood over time were rated on the mornings of days 1, 2 and 7 by trained psychiatrists blind to the group assignment on a modified version of the 21-item Hamilton Depression Rating Scale (Hamilton, 1960) from which items that could not be meaningfully rated due to the TSD procedure and to the time frame were excluded (i.e. weight changes and insomnia: items #4–6 and 16) (HDRS-NOW; Leibenluft et al., 1993).

Changes in perceived mood were rated on days 1–3 and 7 at 08.00 h on a self-administered 12.5-cm visual analogue scale, VAS (Aitken, 1969). Patients were instructed to rate their mood between 'very sad' (on the left) and 'very happy' (on the right), with a median 'normal' point. Patients could not see, when administered the VAS, their previous self-ratings. Raw VAS data were then converted to a 0–100 rating scale (with 0, 50 and 100 denoting extreme depression, euthymia and euphoria) and normalized with respect to baseline values by expressing them as the square root of the ratio between the score on each day from day 2 to day 7 and the score at day 1 (baseline) (Benedetti et al., 1996).

2.3. Statistics

Clinical and demographic characteristics were compared between the four groups with one-way analysis of variance and chi-square tests. Levene's test of homogeneity of variances was performed on HDRS-NOW scores at day 1. To assess the clinical effects of treatment, a two-way repeated measures analysis of variance with post-hoc Newman–Keuls test was performed on ratings, with time and diagnosis as independent factors and current age and duration of illness (i.e. current age minus age at onset) as covariates (Roy-Byrne et al., 1984a). To determine if the response to TSD discriminated diagnostic subgroups, a discriminant function analysis was performed, with diagnosis as the grouping variable and improvement after TSD (i.e. difference between HDRS-NOW scores at day 1 and at day 7) as the independent variable.

Computerized analyses were performed with a commercially available statistical package (Statistica, 1993).

3. Results

Clinical and demographic characteristics of the subjects are shown in Table 1. Groups differed significantly in age (bipolar I and unipolar patients were older than bipolar II and single episode patients) and duration of illness (longer in bipolar I than in bipolar II patients). No patient switched polarity during the TSD treatment.

Homogeneity of variances before the TSD treatment was successfully tested for HDRS-NOW scores ($F = 0.11$, d.f. = 3,47, $P = 0.998$). A two-way repeated measures analysis of covariance on HDRS-NOW scores (see Table 2) showed a highly significant time effect ($F = 68.16$, d.f. = 2,94, $P < 0.0001$), a non-significant group effect ($F = 1.34$, d.f. = 3,45, $P = 0.271$) and a significant time × group interaction ($F = 2.52$, d.f. = 6,94, $P = 0.0265$). This interaction was also significant with univariate test and Greenhouse–Geisser correction ($\epsilon = 0.95$, d.f. = 5.70, 89.37, $P = 0.0269$). Covariates showed a marginal effect on HDRS scores after the first TSD ($F = 2.87$, d.f. = 2,45, $P = 0.067$) and no other relevant effect. Post-hoc comparisons showed non-significant differences between groups at days 1 and 2; at day 7, Groups 1, 2 and 4 did not significantly differ among themselves, but all showed significantly better scores than Group 3 ($P = 0.026$, $P = 0.013$ and $P = 0.007$, respectively). All patients showed significantly better day-7 than day-1 scores (Group

Table 1
Clinical and demographic characteristics of the subjects

	Group 1 (bipolar I) ($n = 17$)	Group 2 (bipolar II) ($n = 8$)	Group 3 (unipolar) ($n = 17$)	Group 4 (single episode) ($n = 9$)	Analysis of variance		
					F	d.f.	P
Sex distribution	6 m, 11 f	2 m, 6 f	5 m, 12 f	1 m, 8 f		—	
Age (years)[a]	47.29 ± 11.30	37.38 ± 10.63	50.06 ± 10.13	34.11 ± 10.02	5.91	3.47	0.00
Age of onset (years)	29.82 ± 8.73	29.88 ± 8.25	35.29 ± 8.23	34.11 ± 10.02	1.45	3.47	0.23
Duration of illness (years)	17.47 ± 9.96	7.50 ± 5.83	14.76 ± 10.09	—	3.07	2.39	0.05
Number of previous depressive episodes	4.41 ± 3.57	3.13 ± 0.64	3.76 ± 1.68	—	0.74	2.39	0.48
Number of previous manic episodes	3.00 ± 3.79	1.63 ± 1.19[b]	—	—	0.98	1.23	0.33
Duration of current episode (weeks)	15.06 ± 11.16	8.50 ± 5.83	13.29 ± 10.51	18.00 ± 14.76	1.13	3.47	0.34

[a] Newman–Keuls post-hoc comparisons: Grp 1 vs. 2, $P = 0.034$; Grp 1 vs. 4, $P = 0.013$; Grp 2 vs. 3, $P = 0.021$; Grp 3 vs. 4, $P = 0.004$.
[b] Number of previous hypomanic episodes.
Values are presented as mean ± S.D.

Table 2
Changes in HDRS-NOW scores during treatment

	Day 1 (Baseline)	Day 2 (After the first TSD)	Day 7 (Endpoint)
Group 1 (bipolar I)	22.24 ± 4.22 (15)	11.00 ± 6.51 (27)	11.53 ± 7.19 (23)
Group 2 (bipolar II)	21.13 ± 3.23 (8)	8.25 ± 4.86 (17)	9.25 ± 8.91 (26)
Group 3 (unipolar)	22.00 ± 3.91 (14)	11.65 ± 6.83 (27)	16.29 ± 7.67 (28)
Group 4 (single episode)	21.22 ± 4.18 (13)	13.78 ± 7.18 (22)	8.89 ± 8.75 (21)

Values are means ± S.D. (range).

1, $P = 0.0001$; Group 2, $P = 0.0002$; Group 3, $P = 0.0050$; Group, 4 $P = 0.0001$).

Normalized VAS scores are plotted in Fig. 1. A two-way repeated measures analysis of variance showed a highly significant time effect ($F = 6.86$, d.f. = 3,138, $P = 0.0002$), a non-significant group effect ($F = 1.22$, d.f. = 3,46, $P = 0.31$) and a non-significant time × group interaction ($F = 1.26$, d.f. = 9,138, $P = 0.26$). Inspection of Fig. 1 shows that all subjects but unipolar depressives (Group 3) exhibited a marked improvement in perceived mood after the first TSD, with a subsequent relapse after the recovery night; Student's t-tests confirmed that Group 1 had significantly better ($t = 2.18$, d.f. = 31, $P = 0.037$) and Group 4 marginally better ($t = 1.96$, d.f. = 24, $P = 0.062$) scores than Group 3 at day 2.

Discriminant function analysis showed that HDRS-NOW rated mood improvement (i.e. day-1 score minus day-7 score) significantly discriminated between diagnostic subgroups (Wilks' $\lambda = 0.848$, $F = 2.81$, d.f. = 3,47, $P = 0.049$). However, when the above-described diagnostic classification was used in four groups, 65% of bipolar type I (Group 1) and 65% of unipolar (Group 3) patients were correctly classified, while none of the bipolar type II (Group 2) and single episode (Group 4) patients were assigned to the proper group; in particular, six out of eight (75%) bipolar II patients were assigned to the bipolar I group. When bipolar types I and II patients were pooled together in one group, the discriminant power increased (Wilks' $\lambda = 0.851$, $F = 4.21$, d.f. = 2,48, $P = 0.021$): 80% of bipolar and 53% of unipolar patients were correctly classified; again, single-episode patients were assigned either to the bipolar (7/9) or to the unipolar (2/9) group.

4. Discussion

Our study showed that in patients affected by a major depressive episode TSD caused different

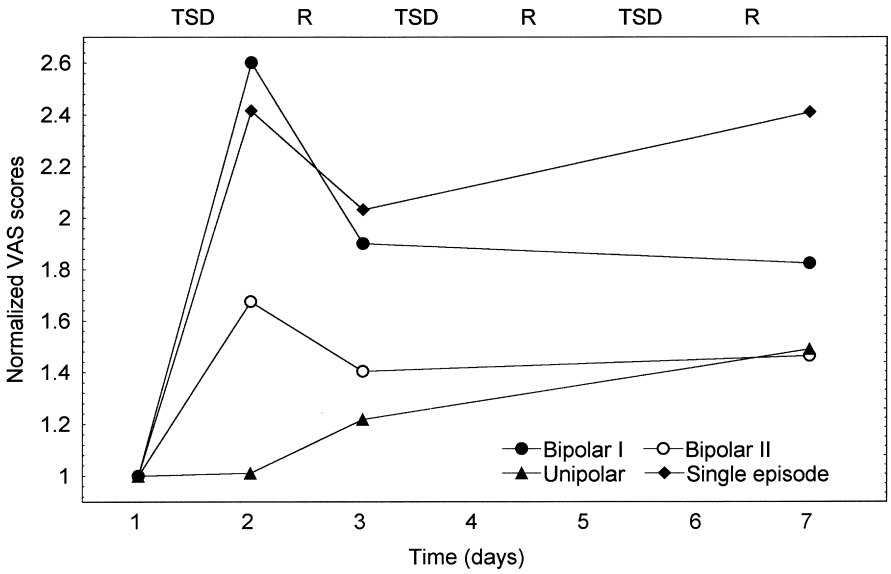

Fig. 1. Mean transformed VAS scores in the four groups. TSD, total sleep deprivation; R, recovery night.

clinical effects depending on mood disorder diagnoses. After TSD, mood levels improved in all diagnostic subgroups, but Hamilton ratings of unipolar patients were significantly worse than those of bipolar I, bipolar II and single-episode patients. The significance of the unipolar/bipolar dichotomy in respect to TSD effects was confirmed by discriminant function analysis which, based on the clinical response to sleep deprivation, failed to separate bipolar I and II patients while it significantly discriminated between bipolar and unipolar patients. All patients showed significantly higher mood levels after the three TSD cycles than at baseline; this finding disagrees with patterns of decreasing responses to TSD following repeated TSD treatments reported by some authors (e.g. Roy-Byrne et al., 1984b), but not by others (e.g. Benedetti et al., 1996).

The present data confirm previous reports of a better effect of TSD in bipolar than in unipolar depression (e.g. Szuba et al., 1991), but also suggest a difference in patterns of perceived mood changes after TSD in the two diagnostic subgroups (Fig. 1). Some speculations on the possible biological substrates of these differences are possible, though no definite conclusions on this subject can yet be drawn from our data or from the literature.

Wehr et al. (1987) hypothesized that abrupt changes in the sleep–wake rhythm can trigger manic or hypomanic phases in bipolar patients through a self-reinforcing mechanism of sleep loss and progressive mood improvement; preliminary findings on the patterns of sleep and wake during the onset of mania are in agreement with this hypothesis (Wehr, 1989; Wright, 1993; Nowlin-Finch et al., 1994; Barbini et al., 1996). This phenomenon is by definition absent in unipolar subjects, thus suggesting the presence of different biological substrates in the two diagnostic groups. In bipolar patients TSD seems to exert its effect by acting on the same mechanisms which can cause the switch into a manic phase (e.g. Wehr, 1992): the susceptibility to develop mania could involve a different sensitivity to the neurochemical changes induced by sleep deprivation (e.g. Gerner et al., 1979; Ebert et al., 1994; Salomon et al., 1994; Asikainen et al., 1995), or sleep deprivation could cause different neurobiological effects in bipolar and unipolar patients. Moreover, since we did not measure sleep during the recovery nights, we cannot exclude the possibility that differences among diagnostic groups in timing

and architecture of sleep during the recovery nights could have influenced the results (e.g. Berger et al., 1997).

The attempt to discriminate unipolar and bipolar patients on the basis of biological variables has not yet proved successful. In agreement with the permissive hypothesis of serotonin (5-HT) dysfunction, platelet 5-HT uptake was found to be lower in bipolar than in unipolar patients (see review in Goodwin and Jamison, 1990). A recent review of the available data, however, pointed out that none of the variables examined appeared to differentiate the two groups consistently (Yatham et al., 1997). Moreover, the occurrence of mania, which discriminates the two diagnostic groups, seems to be related to alterations in dopaminergic function (e.g. Post et al., 1980; Bunney and Garland, 1982), with CSF homovanillic levels raising before the switch into a manic phase (Wehr and Goodwin, 1981) and urinary dopamine levels predicting manic mood (Joyce et al., 1995).

Interestingly, current hypotheses on the neurochemical mechanisms of action of TSD focus on the same neurotransmitters considered for a biological differentiation of unipolar and bipolar illness. Several findings suggested an involvement of the brain dopaminergic system: lower levels of homovanillic acid in the spinal fluid before TSD were associated with better clinical effects of TSD (Gerner et al., 1979); plasma levels of prolactin, which is inhibited by dopamine (DA) agonists, were reported to decrease after TSD (Kasper et al., 1988; Baumgartner et al., 1990) with a different prolactin response to sulpiride in TSD responders and non-responders (Ebert et al., 1993); single photon emission computed tomography before and after TSD showed a significantly different D_2 receptor occupancy in responders and non-responders, thus suggesting an enhanced dopamine release in responders (Ebert et al., 1994); and animal research suggested a major role for enhanced DA activity in the behavioral effects of sleep deprivation (Zwicker and Calil, 1986; Gessa et al., 1995). The involvement of the 5-HT system is suggested by preclinical research: sleep deprivation induces an increase in the electrophysiological activity of brain 5-HT neurons in cats (Gardner et al., 1997); an increase in brain 5-HT turnover in rats and hamsters (Hery et al., 1970; Cramer et al., 1973; Asikainen et al., 1995) with an increase in behavioral responsiveness to 5-HT precursors (Santos and Carlini, 1983); and an enhanced prolactin response to tryptophan in human females (Salomon et al., 1994).

To clarify the topic with sounder evidence, however, further research is needed to try to link the different effects of TSD on mood of bipolar and unipolar patients with different changes in biological parameters. It should be noted that a more precise definition of this subject could be very useful in choosing the appropriate pharmacological strategy to sustain the transient effects of TSD.

Whatever the answer to these issues, we can say with confidence that further research on the clinical effects of TSD cannot ignore the possibility of a differential effect in unipolar and bipolar depressed patients. It is arguable that differences in response due to this diagnostic heterogeneity could be responsible for the sometimes conflicting literature data (Leibenluft and Wehr, 1992).

Finally, discriminant function analysis failed to recognize single-episode patients as a distinct category but, based on the response to TSD, assigned them either to the bipolar or to the unipolar group. Longitudinal naturalistic studies show that at least 50% of patients affected by an initial major depressive episode will have one or more further mood disorder episodes during their lifespan (e.g. NIMH-NIH, 1985; Angst, 1992) and that a not negligible percentage of patients with a diagnosis of unipolar depression will develop manic or hypomanic episodes (Akiskal et al., 1995). TSD has been proposed as a diagnostic tool to classify uncertain clinical cases (e.g. Buysse et al., 1988; Strouse et al., 1992; Leibenluft and Wehr, 1992; Williams et al., 1994): the presence of a ‘bipolar-like’ or a ‘unipolar-like’ response to TSD could be useful in predicting the further evolution of single-episode patients. The follow-up data of our sample and further studies using discriminant function analysis to classify independent and larger samples will help to clarify this point.

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References

Akiskal, H.S., Maser, J.D., Zeller, P.J., Endicott, J., Coryell, W., Keller, M., Warshaw, M., Clayton, P., Goodwin, F., 1995. Switching from 'unipolar' to bipolar II. An 11-year prospective study of clinical and temperamental predictors in 559 patients. Archives of General Psychiatry 52, 114–123.

Aitken, R.C.B., 1969. Measurement of feelings using visual analog scale. Proceedings of the Royal Society of Medicine 62, 989–993.

American Psychiatric Association, 1994. Diagnostic and Statistic Manual of Mental Disorders, 4th ed. (DSM-IV) American Psychiatric Press, Washington, DC.

American Psychiatric Association, 1995. Practice Guidelines for Treatment of Patients with Bipolar Disorder. American Psychiatric Press, Washington, DC.

Andreasen, N.C., Endicott, J., Spitzer, R.L., 1977. The family history method using diagnostic criteria: reliability and validity. Archives of General Psychiatry 34, 1229–1233.

Angst, J., 1992. How recurrent and predictable is depressive illness? In: Montgomery, S., Rouillon, R. (Eds.), Long-term Treatment of Depression. Wiley, New York, pp. 1–10.

Asikainen, M., Deboer, T., Porkka-Heiskanen, T., Stenberg, D., Tobler, I., 1995. Sleep deprivation increases brain serotonin turnover in the Djungarian hamster. Neuroscience Letters 198, 21–24.

Barbini, B., Bertelli, S., Colombo, C., Smeraldi, E., 1996. Sleep loss, a possible factor in augmenting manic episode. Psychiatry Research 65, 121–125.

Baumgartner, A., Riemann, D., Berger, M., 1990. Neuroendocrinological investigations during sleep deprivation in depression. Biological Psychiatry 28, 569–587.

Baxter, L.R., Liston, E.H., Schwartz, J.M., Altshuler, L.L., Wilkins, J.N., Richeimer, S., Guze, B.H., 1986. Prolongation of the antidepressant response to partial sleep deprivation by lithium. Psychiatry Research 19, 17–23.

Benedetti, F., Barbini, B., Campori, E., Colombo, C., Smeraldi, E., 1996. Dopamine agonist amineptine prevents the antidepressant effect of sleep deprivation. Psychiatry Research 65, 179–184.

Benedetti, F., Barbini, B., Lucca, A., Campori, E., Colombo, C., Smeraldi, E., 1997. Sleep deprivation hastens the antidepressant action of fluoxetine. European Archives of Psychiatry and Clinical Neuroscience 247, 100–103.

Berger, M., Vollmann, J., Hohagen, F., König, A., Lohner, H., Voderholzer, U., Riemann, D., 1997. Sleep deprivation combined with consecutive sleep phase advance as a fast acting therapy in depression: an open pilot trial in medicated and unmedicated patients. American Journal of Psychiatry 154, 870–872.

Bunney, W.E., Jr., Garland, B.L., 1982. A second generation catecholamine hypothesis. Pharmacopsychiatrica 15, 111–115.

Buysse, D.J., Reynolds, C.F. III, Kupfer, D.J., Houck, P.R., Hoch, C.C., Stack, J.A., Berman, S.R., 1988. Electroencephalographic sleep in depressive pseudodementia. Archives of General Psychiatry 45, 568–575.

Cramer, H., Tagliamonte, A., Tagliamonte, P., Perez-Cruet, J., Gessa, G.L., 1973. Stimulation of brain serotonin turnover by paradoxical sleep deprivation in intact and hypophysectomized rats. Brain Research 54, 372–375.

Ebert, D., Kaschka, W., Stegbauer, P., 1993. Prolactin response to sulpiride before and after sleep deprivation in depression. Biological Psychiatry 33, 666–669.

Ebert, D., Feistel, H., Kaschka, W., Barocka, A., Pirner, A., 1994. Single photon emission computerized tomography assessment of cerebral dopamine D2 receptor blockade in depression before and after sleep deprivation. Preliminary results. Biological Psychiatry 35, 880–885.

Elsenga, S., Van den Hoofdakker, R.H., 1987. Response to total sleep deprivation and clomipramine in endogenous depression. Journal of Psychiatric Research 21, 151–161.

Gessa, G.L., Pani, L., Serra, G., Fratta, W., 1995. Animal models of mania. Advances in Biochemistry and Psychopharmacology 49, 43–66.

Gardner, J.P., Fornal, C.A., Jacobs, B.L., 1997. Effects of sleep deprivation on serotonergic neuronal activity in the dorsal raphe nucleus of the freely moving cat. Neuropsychopharmacology 17, 72–81.

Gerner, R.H., Post, R.M., Gillin, J.C., 1979. Biological and behavioral effects of one night's sleep deprivation in depressed patients and normals. Psychiatry Research 15, 21–40.

Goodwin, J.H., Jamison, K.R., 1990. Manic Depressive Illness. Oxford University Press, New York–Oxford.

Hamilton, M., 1960. A rating scale for depression. Journal of Neurology, Neurosurgery and Psychiatry 23, 56–62.

Hery, F., Pujol, J.F., Lopez, M., Macon, J., Glowinski, J., 1970. Increased synthesis and utilization of serotonin in the central nervous system of the rat during paradoxical sleep deprivation. Brain Research 21, 391–403.

Joyce, P.R., Fergusson, D.M., Woollard, G., Abbott, R.M., Horwood, L.J., Upton, J., 1995. Urinary catecholamines and plasma hormones predict mood state in rapid cycling bipolar affective disorder. Journal of Affective Disorders 33, 233–243.

Kasper, S., Sack, D.A., Wehr, T.A., 1988. Nocturnal TSH and prolactin secretion during sleep deprivation and prediction of antidepressant response in patients with major depression. Biological Psychiatry 24, 631–641.

Kuhs, H., Farber, D., Borgstadt, S., Mrosek, S., Tölle, R., 1996. Amitriptyline in combination with repeated late sleep deprivation versus amitriptyline alone in major depression. A randomised study. Journal of Affective Disorders 37, 31–41.

Kvist, J., Kirkegaard, C., 1980. Effect of repeated sleep deprivation on clinical symptoms and the TRH test in en-

dogenous depressives. Acta Psychiatrica Scandinavica 62, 494–502.

Leibenluft, E., Wehr, T.A., 1992. Is sleep deprivation useful in the treatment of depression? American Journal of Psychiatry 149, 159–168.

Leibenluft, E., Moul, D.E., Schwartz, P.J., Madden, P.A., Wehr, T.A., 1993. A clinical trial of sleep deprivation in combination with antidepressant medication. Psychiatry Research 46, 213–227.

Merikangas, K.R., Wicki, W., Angst, J., 1994. Heterogeneity of depression. Classification of depressive subtypes by longitudinal course. British Journal of Psychiatry 164, 342–348.

National Institute of Mental Health — National Institutes of Health 1985. Consensus development conference statement. Mood disorders: prevention of recurrences. American Journal of Psychiatry 142, 469–472.

Nowlin-Finch, N.L., Altshuler, L.L., Szuba, M.P., Mintz, J., 1994. Rapid resolution of first episodes of mania: sleep related? Journal of Clinical Psychiatry 55, 26–29.

Post, R.M., Jimerson, D.C., Bunney, W.E., Goodwin, F.K., 1980. Dopamine and mania: behavioral and biochemical effects of the dopamine receptor blocker pimozide. Psychopharmacology 67, 297–305.

Roy-Byrne, P., Uhde, T.W., Post, R.M., Joffe, R.T., 1984a. Relationship of response to sleep deprivation and carbamazepine in depressed patients. Acta Psychiatrica Scandinavica 69, 379–382.

Roy-Byrne, P.P., Uhde, T.W., Post, R.M., 1984b. Antidepressant effect of one night's sleep deprivation: clinical and theoretical implications. In: Post, R.M., Ballenger, J.C. (Eds.), Neurobiology of Mood Disorders. William and Wilkins, Baltimore, pp. 817–835.

Salomon, R.M., Delgado, P.L., Licinio, J., Krystal, J.H., Heninger, G.R., Charney, D.S., 1994. Effects of sleep deprivation on serotonin function in depression. Biological Psychiatry 36, 840–846.

Santos, R., Carlini, E.A., 1983. Serotonin receptors activation in rats previously deprived of REM sleep. Pharmacology, Biochemistry and Behavior 18, 501–507.

Shelton, R.C., Loosen, P.T., 1993. Sleep deprivation accelerates the response to nortrptyline. Progress in Neuropsychopharmacology and Biological Psychiatry 17, 113–123.

Smeraldi, E., Petroccione, A., Gasperini, M., Macciardi, F., Orsini, A., 1984. The search for genetic homogeneity in affective disorders. Journal of Affective Disorders 7, 99–107.

Statistica, 1993. Windows version 4.5. StatSoft, Tulsa.

Strouse, T.B., Szuba, M.P., Baxter, L.R., 1992. Response to sleep deprivation in three women with postpartum psychosis. Journal of Clinical Psychiatry 53, 204–206.

Svendsen, K., 1976. Sleep deprivation treatment in depression. Acta Psychiatrica Scandinavica 54, 184–192.

Szuba, M.P., Baxter, L.R., Fairbanks, L.A., Guze, B.H., Schwartz, J.M., 1991. Effect of partial sleep deprivation on the diurnal variation of mood and motor activity in major depression. Biological Psychiatry 30, 817–829.

Szuba, M.P., Baxter, L.R., Altshuler, L.L., Allen, E.M., Guze, B.H., Schwartz, J.M., Liston, E.H., 1994. Lithium sustains the acute antidepressant effects of sleep deprivation: preliminary findings from a controlled study. Psychiatry Research 51, 283–295.

Wehr, T.A., 1989. Sleep loss: a preventable cause of mania and other excited states. Journal of Clinical Psychiatry 50, 8–16.

Wehr, T.A., 1992. Improvement of depression and triggering of mania by sleep deprivation. Journal of the American Medical Association 267, 548–551.

Wehr, T.A., Goodwin, F.K., 1981. Biological rhythms and psychiatry. In: Arieti, S., Brodie, H.K.H. (Eds.), American Handbook of Psychiatry, vol. 7. II ed. Basic Books, New York, pp. 46–74.

Wehr, T.A., Sack, D.A., Rosenthal, N.E., 1987. Sleep reduction as a final common pathway in the genesis of mania. American Journal of Psychiatry 144, 201–204.

Williams, C.J., Yeomans, J.D., Coughlan, A.K., 1994. Sleep deprivation as a diagnostic instrument. British Journal of Psychiatry 164, 554–556.

Wright, J.B., 1993. Mania following sleep deprivation. British Journal of Psychiatry 163, 679–680.

Wu, J.C., Bunney, W.E., 1990. The biological basis of the antidepressant response to sleep deprivation and relapse: review and hypothesis. American Journal of Psychiatry 147, 14–21.

Yatham, L.N., Srisurapanont, M., Zis, A.P., Kusumakar, V., 1997. Comparative studies of the biological distinction between bipolar and unipolar depression. Life Sciences 61, 1445–1455.

Zwicker, A., Calil, H., 1986. The effects of REM sleep deprivation on striatal dopamine receptor sites. Pharmacology, Biochemistry and Behavior 24, 809–812.

Cover Sheet for "**Are Bright Lights and Regulated Sleep Times Effective** Treatment for Depression**?**" (IRB #7361)

Overview: This outline is a guide for you to use while considering whether to participate in this research study. The consent that follows includes much more information about the study and its risks, which you will need to make a decision. Please read this outline and the consent carefully, and only sign it if you are comfortable doing so.

● You are being asked to participate in a research treatment study because you are depressed.
● You**r** treat**ment will involve keeping specified sleep times and sitting in front of bright lights wearing tinted or untinted goggles.**.

Type of treatment: The treatment portion of this study will last up **6** weeks followed by six month during which helpful treatment can be continued or other treatment can be tried. Prior to treatment, blood and urine tests as well as a heart test and physical examination will determine whether you are healthy and not pregnant (if you are a fertile female)**. Treatment will be with bright lights and specific changes to your sleep, partially determined by how you answer questions about when you do or like to do things and partially by when you would like to be asleep. The specific timing and manipulation of allowed sleep, bright lights and use of goggles will be randomly (like flipping a coin) determined. In order to manipulate your sleep, varying amounts of time remaining awake between allowed sleep will be required, for some patients required wake time might reach as long as 42 hours on a single occasion.** During the first week you will complete **rating** forms **and speak with a study doctor by telephone** daily and then weekly for the remainder of **6** weeks. **Thereafter**, your study doctor will continue to treat you for an additional six months during which there will be monthly determinations of how you are doing. During this time, while your study doctor will manage your treatment, you or your insurance will pay for any medicine or other treatment such as a light box. After this six months, if psychiatric treatment is still needed, your doctor will help you find further treatment.

Alternatives to participation: You do not have to participate in this research study to receive treatment for depression. If you decide not to participate, the doctor who evaluated you will help you find an alternative.

Risks: There are risks and discomforts associated with participating in this study (please read the "Risks" section of the detailed consent for a complete listing and explanation of risks). These include:
● Your depression may not improve
● Bright light can over-stimulate some people and can cause patients with bipolar disorder to switch from being depressed to being "high" (that is, hypomanic or manic)
● Missing sleep can also over-stimulate and induce switching to a "high" mood
Compensation: None
Voluntary Participation: Participation in this study is entirely voluntary. You do not have to participate if you do not want to and can stop participating at any time.

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PLOS ONE

The Day-to-Day Acute Effect of Wake Therapy in Patients with Major Depression Using the HAM-D_6 as Primary Outcome Measure: Results from a Randomised Controlled Trial

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Abstract

Background: This paper reports day-to-day data for from a one-week *intervention phase*, part of a 9-weeks randomised parallel study with patient having major depression (data from weekly visits have been reported). Wake therapy (sleep deprivation) has an established antidepressant effect with onset of action within hours. Deterioration on the following night's sleep is, however, common, and we used daily light therapy and sleep time stabilisation as a preventive measure. In particular, we evaluated the day-to-day acute effect of and tolerance to sleep deprivation and examined predictors of response.

Methods: Patients were assessed at psychiatric inpatient wards. In the wake group (n = 36), patients did three wake therapies in combination with light therapy each morning together with sleep time stabilisation. In the exercise group (n = 38), patients did daily exercise. Hamilton subscale scores were primary outcome (not blinded), secondary outcome was self-assessment data from the Preskorn scale and sleep.

Results: Patients in the wake therapy group had an immediate, large, stable, and statistically significant better antidepressant effect than patients in the exercise group with response rates at *day5* of 75.0%/25.1% and remission rates of 58.6%/6.0%, respectively. The response and remission rates were diminished at *day8* with response rates of 41.9%/10.1% and remission rates of 19.4%/4.7%, respectively. Patients and ward personnel found the method applicable with few side effects. Positive diurnal variation (mood better in the evening) predicted a larger response to wake therapy. In the wake group napping on days after intervention predicted greater deterioration on *day8*.

Conclusions: The intervention induced an acute antidepressant response without relapse between wake nights but with a diminishing effect after intervention. Development is still needed to secure maintenance of response. Avoiding napping in the days after wake therapy is important.

Trial Registration: Clinical trials.gov NCT00149110

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Introduction

The objective of this study was to investigate if a chronotherapeutic intervention combining sleep deprivation (wake therapy) with light therapy and sleep time stabilisation could induce a rapid and augmented antidepressant response and remission in patients with major depression. The medium-term effect over a nine week period has been published elsewhere [1], whereby the wake therapy group manifested a sustained better response and remission than the exercise group. The present paper reports data from the one-week study period where patients were randomised to either wake therapy or exercise in an inpatient setting. In this study period patients had daily ratings of depression severity and did self-evaluation of sleep in order to reflect a timely assessment of any mood fluctuation and sleep changes. This was important as wake therapy is known to induce mood swings and alterations in sleep quality, length and phase.

Systematic clinical investigation has been performed on various aspects of the acute response to wake therapy for more than 40 years, and a large evidence base confirms the rapid antidepressant effect [2], [3], [4], [5]. The term wake therapy is used synonymous to sleep deprivation but has a more positive image for the patient. Deterioration or relapse after the first nights sleep after wake therapy (termed "recovery sleep") has been and still is a problem, and several new methods have been tested, mainly in bipolar depressed patients. These include the use of wake therapy in combination with: bright light therapy [6], bright light therapy and sleep phase advance [7], bright light therapy and lithium [8], pindolol [9], bright light therapy and transcranial magnetic stimulation [10]. A manual [11] and an instruction chapter [12] assist clinicians in the practical details of chronotherapy with an emphasis on preventing relapse. The prevention of deterioration or relapse during a course of wake therapy is important with respect to its applicability, safety and acceptance. A fast response to an antidepressant intervention is very desirable but a steep relapse is equally undesirable. What we want from antidepressant therapy is a rapid and stable improvement.

The effect of wake therapy is linked to the phenomenon of diurnal variation [13], [14]. Slight alterations of sleep timing can cause dramatically changes in mood and at the extreme end of this is the positive response to an entire night of sleep deprivation. As the antidepressant improvement gained over night has been known to be unstable, the present protocol aimed at inducing day-to-day stability through the use of sleep time stabilisation and light therapy. Our earlier report of the results showed that this was attained as we found a smaller day-to-day variation of sleep parameters [1]. Napping is know from the literature to be depressiogenic after wake therapy [15] and was thus advised against.

This paper thus focuses on the acute effect of the interventions used in the one-week *intervention phase* as assessed throughout the intervention days on the inpatient ward, and on testing potential predictors of wake therapy response.

As the acute changes during or after wake therapy is very important for safety and tolerance we designed the *intervention phase* so as to be able to detect rapid changes in depression severity.

Thus the first objective regarding the *intervention phase* was:

- To investigate whether the combination of wake therapy, light therapy and sleep time stabilisation can prevent any deterioration *between* wake nights and/or *after* the end of the series of 3x wake therapy.

As some discrepancy exists regarding the impact of diurnal variation on the effect of wake therapy response, patient self-assessed their mood over the course of the day for 6 days prior to the intervention week. Thus we were able to test our second objective:

- To investigate if the acute effect of wake therapy was influenced by the presence of diurnal variation of mood as assessed prior to the intervention?

As the literature shows that napping after sleep deprivation is depressiogenic we sampled information regarding napping during the intervention days to test our third objective:

- To investigate to what extent daytime napping in the *intervention phase* caused deterioration of any achieved improvement?

Methods

General

The protocol for this trial and supporting CONSORT checklist are available as supporting information; see Checklist S1 and Protocol S1.

Methods have been described in detail in [1] which presented the medium-term results from weekly visits from a 9-weeks study period. Patients diagnosed with major depression were randomised in a ratio of 1:1 into two parallel groups: the *wake* group or the *exercise* group. Inclusion criteria were: age above 18, major depressive episode, patients with bipolar disorder to be in mood stabilising treatment for at least one month in a recommended dosage and a HAM-D_{17} score $\geq$13. Exclusion criteria were: psychotic disorder, organic brain disorder, mental retardation, alcohol or drug abuse, pregnancy or insufficient contraception, light-induced migraine or epilepsy, retinal blindness or severe cataract, glaucoma, retinal diseases, antipsychotic drugs treatment, marked suicidal ideation, and severe agitation.

The study started with a one-week *run-in phase* where medication with duloxetine was begun and diurnal variation assessed.

Then followed a one-week *intervention phase* where all patients were admitted to an in-patient ward on a Monday (*day1)*. Patients randomised to the *wake* group carried out (A) three wake therapies alternating with recovery sleep nights, (B) daily morning bright light therapy and (C) sleep timing control. Patients randomised to the e*xercise* group were also admitted on a Monday (*day1*) and started a daily exercise program instructed by physiotherapists. Patients were all discharged on the following Saturday (*day6*) when patients in the *wake* group had carried out all 3 wake therapies. During each of the five days of the inpatient stay we assessed patients at the ward in the morning. After discharge patients were seen at the psychiatric research unit on the following Monday (*day8*).

This was followed by a 7-week *continuation phase* where patient in the *wake* group continued with sleep time stabilisation, daily morning light therapy and duloxetine 60 mg daily dosage and patients in the *exercise* group continued with an individual exercise program of at least 30 minutes duration and duloxetine in a daily dosage of 60 mg. In this paper we report data from the one-week *intervention phase*.

The individual study days in the *intervention phase* and their relation to study procedures are named as shown in Figure 1: Monday is *day1,* Tuesday is *day2,* Wednesday is *day3,* Thursday is *day4,* Friday is *day5,* Saturday is *day6,* Sunday is *day7*, and the next day, Monday, is *day8*.

The intervention phase has, for the purpose of data analyses, been subdivided into a *admittance period* signifying the period from being admitted to the in-patients ward on a Monday (*day1*) and till

		Intervention Phase														
Period		**Admittance period**										**Discharge period**				
Day of week		**Mo.**		**Tu.**		**We.**		**Th.**		**Fr.**		**Sa.**		**Su.**		**Mo.**
Day number		**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**
Night number	**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**	
Wake number			**I**				**II**				**III**					
Recovery sleep number					**I**				**II**				**III**			
Interview		**x**		**x**		**x**		**x**		**x**						**x**
Self-assessment		**x**		**x**		**x**		**x**		**x**		**x**		**x**		**x**
Week number		**1**														**2**

Figure 1. Consort diagram of subject flow.
doi:10.1371/journal.pone.0067264.g001

being discharged on a Saturday (*day6*), and a *discharge period* signifying the period from discharge on a Saturday (*day6*) till assessments at the psychiatric research unit on the following Monday (*day8*).

Wake Therapy

Wake therapies were scheduled for Mondays (*day1*), Wednesdays (*day3*) and Fridays (*day5*). Patients were instructed to stay up the entire wake nights and were encouraged not to sleep on the following day until 8 pm. Patients were allowed to walk freely in and outside the ward, take baths, talk to the staff, watch television, cook meals, listen to music, read, use the computer, and drink coffee etc. The ward staff was instructed to encourage patients to stay awake but without putting any pressure onto them. On Tuesday, Thursday and Saturday nights (recovery sleep I, II and III), patients were scheduled to go to sleep no later than 8 pm and to wake up no later than 8 am. This was used as a precaution, because oversleeping in the morning on recovery nights is known, from the literature, to worsen mood [16]. This adjustment to early sleep was intended to act like a milder version of a sleep phase advance, as this has been shown to facilitate antidepressant response [17].

Light Therapy

Daily light therapy was administered daily for 30 minutes while on the in-patient ward; using a light box (SMIFA Biolamp, giving 10.000 lux white light at 40 cm distance from the screen). Individual timing was scheduled from an algorithm based on the patient's score on the Morningness-Eveningness Questionaire (MEQ) [18] (but limited to 7 AM in the morning as the earliest). At 4 AM patients were administered 30 minutes of light to alleviate tiredness. Oral and written information on the light therapy procedure was given.

Sleep Time Stabilisation

Guidance for sleep time stabilisation was based on daily entries in the sleep logs of sleep onset, sleep offset, subjective sleep quality (range 0 to 10 and 10 = best) and daytime naps and entries were used at daily and weekly visits to guide patients to keep a stable sleep-wake cycle. Patients who needed to take naps were instructed to schedule these at around 4 pm and not to exceed 30 minutes.

Exercise

A daily exercise programme was started on admittance to the inpatient ward. Each participant planned a daily exercise program of minimum 30 minutes duration with the physiotherapist. Patients filled in daily logs with name of activity, perceived exertion [19] and duration of exercise. Patients in this group followed the ordinary bedtime and sleep length regime in the open ward. At the hospital, exercise was taken between 9 am and 4 pm.

Medication

Patient received a fixed daily dosage of 60 mg duloxetine in the morning, begun at the run-in phase, a week prior to admittance to the in-patient ward.

Structure of Reporting

Reporting followed the Consort guideline (Figure 2) [20].

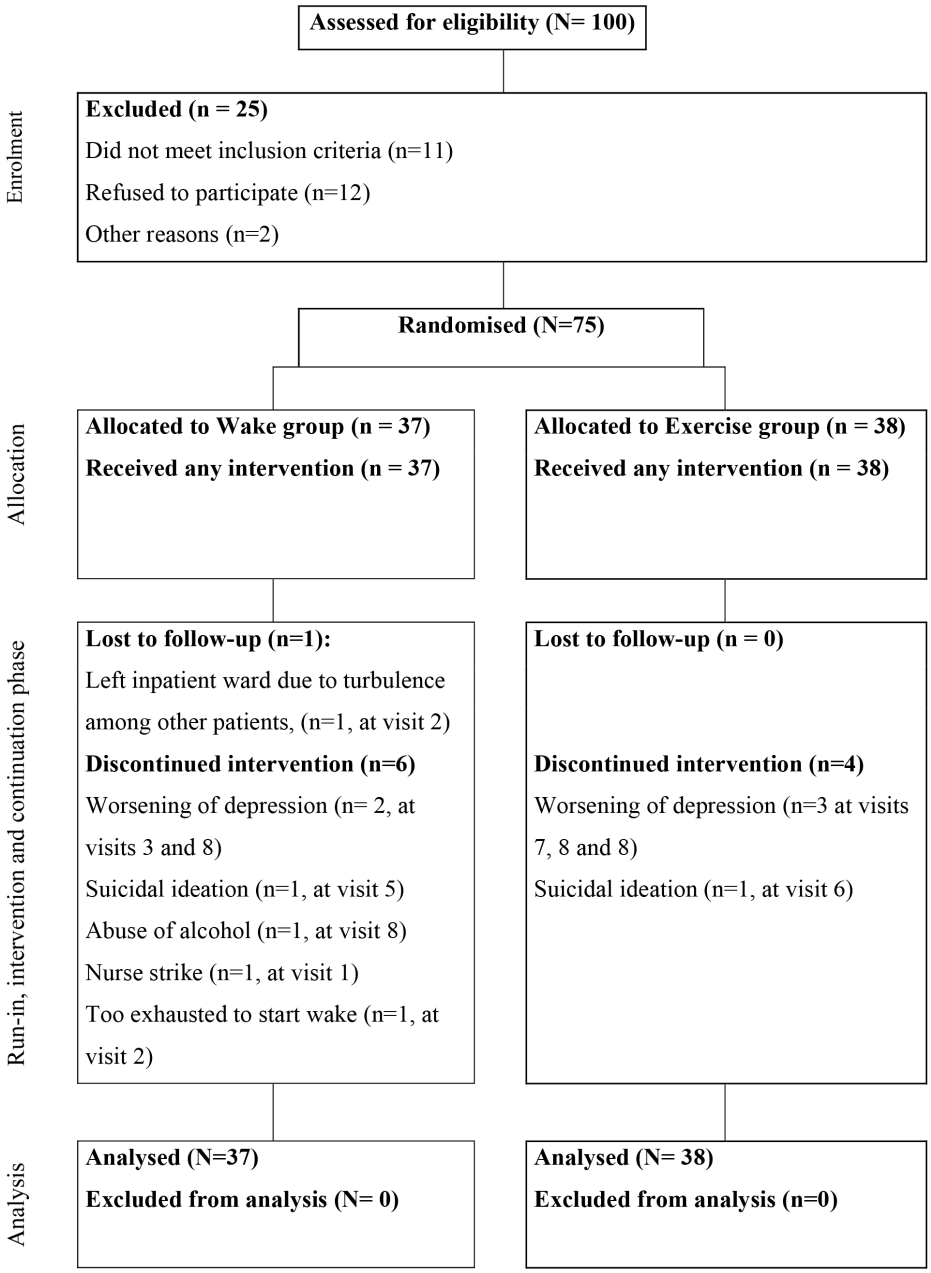

Figure 2. Flow chart and description of study procedures in the *intervention phase.*
doi:10.1371/journal.pone.0067264.g002

Approval, Monitoring and Ethics

Approvals were given by the committee on Biomedical Research Ethics, the Danish Medicines Agency and the Danish Central Data Register. Monitoring was done by the national GCP unit in Copenhagen. The study was carried out according to the declaration of Helsinki and the ICH-GCP guidelines [21].Written study information and oral description of the study were given to the patients before written informed consent was obtained.

Recruitment

Patients were recruited from general practitioners and psychiatrists, open wards at the local mental health centre and a few patients through advertisements.

Random Allocation Sequence

A randomisation list was made by an external statistician who by computer generated a random list with a block size of four (block size was blinded). A GCP qualified research coordinator labelled envelopes with consecutive numbers and inserted group specific instruction letters according to the randomization list (kept locked up). The envelope was handed over to the patient after signing the informed consent form.

Blinding

Blinding of assessors at the daily assessments on the ward was not possible, as patients in the wake group would show signs of not having slept during wake nights. Assessments on the ward were

thus done by other raters than assessments at weekly visits that were done by Hamilton raters blinded to treatment assignment.

Sample Size

Sample size for the whole 9-week study was calculated from an expected reduction in HAM-D_{17} scores of 14 points from 24 to10 points (*wake group*) and of 11 points from 24 to 13 points (*exercise group*), and with a standard deviation of 6 points, a power of 80% to detect a significant difference ($p = 0.05$, two sided), in all 64 patients were needed in each group. This corresponds to an effect size of 0.50 (difference between groups/pooled standard deviation). As the expected difference between groups was hypothesized to emerge immediately when the wake and light therapy was given in the *intervention phase*, the sample size calculation from the main study also applied to this paper.

Interim Analysis

No interim analyses were planned or performed.

Stopping Rules

Criteria for discontinuation of study treatment was: a wish to discontinue treatment, intolerable or clinically significant side effects, a score of 15 or more on the Mania Scale (MAS), continued clinical worsening of depression, change of mood stabilizer in bipolar patients, and non-compliance with elements of the study.

Study Registration

Study is registered at ClinicalTrials.gov with identifier NCT00149110.

Outcomes

Outcome measures are described in detail in [1]. To assess depression severity we used the clinician-reported Hamilton depression rating scale 17 items version (HAM-D_{17}). In the present analysis, focusing on the *intervention phase*, we have used the HAM-D_6 [22], [23], [24], [25] subscale. This is a validated and unidimensional depression scale without any sleep items. Sleep items would be inaccessible in a wake therapy trial. The HAM-D_6 contains six core items of depression from the HAM-D_{17}, namely depressed mood, guilt feelings, work and interests, psychomotor retardation, psychic anxiety, and somatic general (tiredness and pain). The total score of the HAM-D_6 can theoretically go from 0 (not depressed) to 22 (extremely depressed): a score of 12 equal severe depression, a score of 9 equals moderate depression. Remission on the HAM-D_6 was defined as a score of 4 or less [26], response was defined as a reduction of 50% or more from baseline (*day1*) [27]. Deterioration rates were defined as scores equal to or above score values at *day1*. Deterioration was used as a measure of instability of depression severity. This HAM-D_6 subscale does not include sleep items, making it appropriate for assessing depression severity over a course of wake therapies. The HAM-D_6 interviews were performed at the ward in the morning on *day1* till *day5* and at the research unit on *day8*. The self-assessment scales (Preskorn and sleep logs) were administered on all days in the *intervention phase*. The Preskorn scale, constructed as a VAS scoring from 0 (no depression) to 10 (worst depression ever), was used to self-monitor mood changes during the day at the *run-in phase* and from day to day in the *intervention phase*. The Bech-Rafaelsen Mania scale (MAS) [22] was used to monitor any emergence of manic symptoms and was used on the same days as the HAM-D_6.

Patients in the *wake* group filled in daily light therapy logs, daily sleep logs with sleep onset, sleep offset, and self-perceived quality of sleep [28], and the Stanford Sleepiness Scale [29], [30] for every hour of the wake nights.

Hospital staff filled in semi-qualitative evaluations of treatment elements during the *intervention phase* and patients did a similar evaluation at the following post intervention visit (*day8*).

During the *run-in phase*, patient self-assessed their mood on the Preskorn scale shortly after wake-up, then at 9 am, noon, 3 pm, 6 pm, 9 pm, and just before lights out - over a period of six days.

The rating window (time frame covered by the scale) [26] is for the HAM-D_6 traditionally the past three days and this was used for assessment on *day1* and *day8*. On *day2* till *day5* the window for the HAM-D_6 was limited to the past hour to improve sensitivity to changes in depression severity. The Preskorn scale was self-assessed at noon on all study days in the *intervention phase* (to minimize influence from diurnal variation).

Hamilton assessors were not blinded to patient's treatment allocation. Assessors were certified for good inter-rater and test-retest reliability.

In the *intervention phase* we expected a rapid reduction in depression severity in the *wake* group and a more gradual reduction on the *exercise* group. The day-to-day variation in depression severity was unknown but thought to be of interest, as a large variation would be considered a substantial burden and hazard to patients.

The Morningness-Eveningness Questionaire (MEQ) was used to time light therapy according to individual patient chronotype [31]. In this paper we used it to examine any relation with depression outcome.

Patients were asked, at the beginning of the *run-in phase,* if in their present depressive episode retrospectively they had experienced a significant drop in mood after daytime naps, in order to investigate this as a predictor for effect of wake therapy.

Data Analysis

All patients with data from any days of the *intervention phase* were included in analyses. Available data from HAM-D_6 and Preskorn scales were computed within a Mixed Model Repeated Measures analysis [32]. This included for continuous endpoints (depression scores) a Random-effects Regression Model (RRM) and for dichotomous endpoint (response, remission, deterioration) a Generalized Estimation Equation model (GEE). Thus, for RRM, the model included depression score as output variable and baseline, day, treatment group, the interaction between day and treatment group as covariates. For GEE, the model included response, remission or deterioration fractions as output variables and baseline, day and treatment group as covariates. For tables and graphs estimated scores are presented. Baseline values (*day1*) are used to calculate estimated scores at subsequent days. Baseline values are mean scores from all patients, and are thus presented in tables as a single value for both groups. The model gives p-values for the whole of the *intervention phase* and post-hoc p-values for each day.

In this paper we have used *day1* of the *intervention phase* as baseline for analysis of days of the *intervention phase* (*day1 till 5*). The presented results from *day8* were calculated with *week0* (see Figure 1) as baseline with the model specified in [1] because *day8* is not part of the *intervention phase*.

To facilitate comparisons with other studies the unbiased effect size (Cohen's) was calculated as described by Hegdes and Olkin [33]. For the Cohen effect size we used the method of last observation carried forward (LOCF) whereas in the RRM and GEE available data were used.

Analyses of diurnal variation of mood, based on Preskorn data from 7 times a day each day for 6 days self- assessed in the *run-in*

phase, have been analysed in a similar mixed model with Preskorn scores as outcome variable and patient and interaction of patient with time as covariates. The resultant parameter estimate for time is used to represent the degree of diurnal variation and is in turn used in a RRM model as a covariate to analyse the influence of diurnal variation on depression scores. A positive diurnal variation of mood (with mood better in the evening) is defined as a time parameter estimate of less than zero (score reduction on the Preskorn scale = improvement) and a negative diurnal variation of mood (with mood worse in the evening) is defined as a parameter estimate of time greater than zero (score increase on the Preskorn scale = deterioration) both on the Preskorn scale. The MEQ sum score was entered as a covariate to examine its influence on depression outcome. Sleep parameters were analysed in a general linear model (GLM) with values at *day1* as baseline covariates except for the effect of sleep quality and napping that was analysed in a RRM model.

For the analyses of the impact of diurnal variation and naps on HAM-D_6 scores at *day8* we included a separate covariate for *day8* as available data showed a non-linear deviation from other intervention days.

Primary outcome was remission rates at *day5* based on the HAM-D_6 and outcomes for the other days are considered post-hoc. Secondary outcomes were response rates, deterioration rates and mean scores on the MAS, Preskorn and sleep parameters.

Analyses were performed by SAS 9.2 software. All time points are shown in the format of hour: minutes. Brackets after numbers are standard deviations unless otherwise stated. The level of statistical significance was set at a 5% level, two-sided.

Results

General

Patients were included from September 2005 to August 2008, last patient last visit March 2009. In all, 100 patients were screened and 75 patients were included in the study with 37 patients randomised to the *wake* group and 38 patients to the *exercise* group. Inclusion was stopped at 75 patients due to time constraints and funding limits. In the *wake* group one patient was kept waiting for the intervention, due to a nurse's strike, and was in remission when the strike ended, and was thus discontinued and is not included in analysis. One patient in the *wake* group decided at visit two, before being admitted to the inpatient ward, not to go through with the wake therapies and was discontinued from the study but is included in analyses. One patient in the *wake* group did not fill in sleep logs and left the inpatient ward after one wake therapy due to perceived uneasiness on the ward but is included in the analyses. Thus 36 of the patients allocated to the wake group and all 38 patients allocated to the exercise group were included in the data analyses. In the wake therapy group only 34 patients had available sleep data. Due to logistic reasons the number of patients assessed with the HAM-D_6 in the exercise group was fewer on days 4 and 5. Numbers are given in tables. No patients discontinued in the *exercise* group. The number of performed sleep deprivations in the *intervention phase* was 35 for wake I, 34 for wake II and 28 for wake III. Thus overall 97 wake therapy nights were carried out in the *intervention phase*. Patient performed exercise with a mean duration of 51.2 (SD = 45.0) minutes/day. The mean Borg scale score was 13.1 (SD = 6.1) corresponding to moderate exertion.

Deterioration and Depression Outcome

The fraction of patients having a deterioration defined as a HAM-D_6 scale score above the entry level of 12 points, at any of the assessed days, was very low and below 4.2% in the *exercise* group and 1.8% in the *wake* group. The difference in deterioration between groups was statistically non-significant for the whole period.

Table 1 shows estimated post *day1* remission and response rates for assessed intervention days. Clinically relevant and statistically significant larger response and remission rates were seen in the *wake* compared to the *exercise* group from *day2* and reaching a maximum at *day5* with response rates in the wake/exercise groups of 75.0%/25.1% and remission rates of 56.8%/6.0%. The difference between groups was statistically significant (response: Odds ratio 9.0; CL 3.7–21.8, $p<.0001$ and, remission: Odds ratio 20.8; CL 5.6–77.1, $p<.0001$) and post hoc for each assessed day (see Table 1).

The response rates at *day8* (= week2), as analysed on the 9-weeks dataset was reduced to 41.9%/10.1% in the wake/exercise groups and remission rates were reduced to 19.4%/4.7%.The difference between groups at *day8* was statistically significant response: Odds ratio 6.4; CL 2.3–17.4, $p = .0002$ and, remission: Odds ratio 4.9; CL 1.4–17.0, $p = .01$).

Table 2 shows estimated post d*ay1* HAM-D_6 scores for assessed intervention days. A significant and clinically larger reduction in scores was seen in the *wake* group compared to the *exercise* group from *day2* (the day after the first wake therapy night) with a score difference of 2.5 (SE 0.7), (95% CL, 1.1–3.9, $p = .0007$) and the score differences increased on the following days to a maximum of 4.6 (SE 0.6) on *day5* (95% CL, 3.4–5.9,$p<.0001$) solely due to a further reduction in scores in the *wake* group, whereas the scores in the *exercise* group were unchanged. The scores at *day5* were 4.1 (SE 0.4) in the *wake* group and 8.7 (SE 0.5) in the *exercise* group. The difference in HAM-D_6 scores between groups was significant for the interaction between groups and days ($F_{181} = 8.8$, $p = .004$) and post hoc for each assessed day. The post hoc scores, estimated from the nine weeks dataset, at *day8* were 7.5 (SE 0.5) in the wake group and 9.7 (SE 0.4) in the exercise group ($F_{529} = 3.4$, $p<0.0007$), (see Table S2). The difference between groups had an effect size (Cohen's) of 1.43 (CL 0.92–1.94) at *day5* and 0.53 (CL 0.06–0.99) at *day8*.

Table 3 shows estimated baseline-adjusted Preskorn scale scores. A better outcome was seen in the wake group compared to the exercise group from *day1* through till *day8* and in contrast to results from the HAM-D_6 scale, no tapering of the difference between groups or deterioration from *day5* till *day8* was seen. The difference between scores in the groups was significant for the whole period ($F_{69} = 11.5$, $p = .001$) and post hoc for all days.

MAS scale scores (excluding item five, sleep) showed that no patient reached any level of mania. The maximum score was below 5 (below cut-off for mild mania).

Significantly more of those patient that had obtained response at day two were also in response at day eight compared to patients non-responding at day two (Fisher's Exact test; $p = 0.05$). The positive predictive value (the probability that patients responding after the first wake therapy maintained the response at day eight) was 56.3% and the negative predictive value (the probability that patients not responding after the first wake therapy did also not respond at day eight) was 75.0%.

Diurnal Variation, Mood and Chronotype

Data on diurnal variation of mood, as assessed by the Preskorn scale, was present for 72 patients from the run-in week (reduced scores indicates improvement in the Preskorn scale). A statistically significant variation of mood was found for time of day ($F_{344} = 4.9$, $p<.0001$) with no significant differences between treatment groups. The diurnal variation (mean of 6 days) ranged from a

Table 1. Estimated Post-*Day1* mean Response and Remission rates based on HAM-D_6 scores for Each Treatment Group by day.

	Response Per cent (n)				
	Wake %	**Exercise %**	**Odds Ratio**	**95% CL**	**P Value**
	(n)	**(n)**			
Day1(baseline)	0 (0/36)	0 (0/38)	1	-	-
Day2 (after wake I)	58.7 (16/31)	13.7 (8/35)			
Day3 (after recovery sleep I)	64.6 (23/35)	16.9 (3/34)	9.0*	3.7–21.8	<.0001
Day4 (after wake II)	70.1 (21/31)	20.7 (6/26)			
Day5 (after recovery sleep II)	75.0 (24/30)	25.1 (4/22)			
	Remission Per cent (n)				
	Wake %	**Exercise %**	**Odds Ratio**	**95% CL**	**P Value**
	(n)	**(n)**			
Day1 (baseline)	0 (0/36)	0 (0/38)	1	-	-
Day2 (after wake I)	38.6 (11/31)	2.9 (1/35)			
Day3 (after recovery sleep I)	44.6 (18/35)	3.7 (2/34)	20.8*	5.6–77.1	<.0001
Day4 (after wake II)	50.7 (15/31)	4.7 (2/26)			
Day5 (after recovery sleep II)	56.8 (17/30)	6.0 (0/22)			

Numbers of patients with response and remission given in parenthesis.
Abbreviations: HAM-D_6 = Hamilton Depression Rating Scale subscale, Response as a reduction of more than 50% from *day1*, Remission was defined as a HAM-D_6 score below 5, CL = confidence limits.
*OR was from the regression model without interaction between day and intervention and the main effect of intervention was reported.
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maximum score increase of 3.8 points (worsening during the day) to a maximum score reduction of 3.6 (improvement during the day). When dividing into positive *or* negative diurnal variation we found that positive diurnal variation (morning worst) was present in 58.3% of patient and negative diurnal variation (evening worst) scores was present in 41.7% of patients.

We analysed whether diurnal variation of mood at the run-in phase was predictive of the HAM-D_6 depression scores during the intervention phase and found that the degree of diurnal variation had a significantly *differential* impact on scores in the two groups ($F_{63} = 14.2$, $p = 0.0004$ for the interaction).

We then examined the magnitude of impact of diurnal variation of mood separately for the two groups, by using the 1. Quartile (positive diurnal variation), the median, and the 3. Quartile (negative diurnal variation) values of the diurnal parameter estimate range ($Q_1 = -0.1976$, median = 0.0363, and $Q_3 = 0.1001$) as covariates in the model with *day1* as baseline. At *day5* patients in the *wake* group with positive diurnal variation (Q_1) had an estimated HAM-D_6 score of 3.5 (SE 0.5), patients with a

Table 2. Estimated Mean Post-*Day1* HAM-D_6 scores for Each Treatment Group by day. Numbers of patients given in parenthesis.

	Wake (SE)	**Exercise (SE)**	**Difference Between Groups**		
	[n]	**[n]**			
Day	**Mean (SE)**	**Mean (SE)**	**Score (SE)**	**CL**	**P value**
Day1	12.1 (0.2)		-		NA
	[Wake 37 Exercise 38]				
Day2 (after wake I)	6.2 (0.5)	8.7 (0.5)	2.5 (0.7)	1.1–3.9	.0007
	[31]	[35]			
Day3 (after recovery sleep I)	5.5 (0.4)	8.7 (0.4)	3.2 (0.6)	2.0–4.4	<.0001
	[35]	[3]			
Day4 (after wake II)	4.8 (0.4)	8.7 (0.4)	3.9 (0.5)	2.8–5.0	<.0001
	[31]	[26]			
Day5 (after recovery sleep II)	4.1 (0.4)	8.7 (0.5)	4.6 (0.6)	3.4–5.9	<.0001
	[30]	[22]			

Abbreviations: HAM-D6 = Hamilton Depression Rating Scale, NA = not applicable, SE = standard error, CL = confidence limits.
doi:10.1371/journal.pone.0067264.t002

Table 3. Estimated Mean Post-D*ay1* Preskorn scores for Each Treatment Group by day.

	Wake	Exercise	Difference Between Groups		
Day	**Mean (SE)**	**Mean (SE)**	**Score (SE)**	**CL**	**P value**
Day1	5.6 (0.3)[Wake 34 Exercise 38]		-		NA
Day2 (after wake I)	4.1 (0.2) [34]	5.2 (0.2) [38]			
Day3 (after recovery sleep I)	4.1 (0.2) [34]	5.1 (0.2) [38]			
Day4 (after wake II)	4.0 (0.2) [34]	5.0 (0.2) [38]			
Day5 (after recovery sleep II)	3.9 (0.2) [34]	4.9 (0.2) [37]	1.0 (0.3)*	0.4–1.7	0.001
Day6 (after wake III)	3.8 (0.2) [34]	4.9 (0.2) [38]			
Day7 (after recovery sleep III)	3.7 (0.3) [34]	4.8 (0.3) [37]			
Day 8 (week 2)	3.7 (0.3) [32]	4.7 (0.3) [37]			

Numbers of patients given in square brackets.
Abbreviations: NA = not applicable, SE = standard error, CL = confidence limits.
*Score difference was from the regression model without interaction between day and intervention and the main effect of intervention was reported.
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small diurnal variation (median) had a score of 4.2 (SE 0.4), and patients with a negative diurnal variation of mood (Q3) had a score of 4.7 (SE 0.5).

Correspondingly at *day5* patients in the exercise group with positive diurnal variation (Q_1) had a mean score of 9.6 (SE 0.6), patients with a small diurnal variation (median) has a score of 8.9 (0.5) and patients with a negative diurnal variation (Q3) a score of 8.4 (SE 0.6). Positive diurnal variation thus improved outcome in the wake group but worsened outcome in the exercise group and negative diurnal variation worsened outcome in the wake group and improved outcome in the exercise group, compared to patients without any clinical diurnal variation of mood (median).

The total scores from the Morningness-Eveningness Questionnaire (MEQ) was analysed as a covariate in the RRM model. Analysis showed no significant impact on depression scores.

Sleep and Influence of Naps on Depression Outcome

At the start of study patients were asked to rate retrospective whether they, in their current depressive episode, had experienced any mood drop after having a daytime nap. Results from this assessment showed that a ''nap-mood-drop'' had been present in 47.1% of patient and had lasted a mean of 92.7 (69.5) minutes after end of nap; equally prevalent in both groups. The presence of a mood drop after daytime napping had a significantly negative influence on HAM-D_6 scores ($F_{65} = 3.9$, $p = 0.05$) in the intervention phase with no difference between groups.

Results from the sleep logs are given in Table S3. This shows that, during the *intervention phase*, sleep onset was advanced in both treatment groups but significantly more in the wake group with 79.6 (99.4) minutes compared to 39.7 (125.6) minutes in the exercise group (between groups $F_1 = 10.1$, $p = .002$). Sleep offset was advanced in the wake group by 30.0 (89.1) minutes but not in the exercise group where a slight sleep delay of 3.0 (132.8) minutes was found (between groups $F_1 = 0.6$, $p = 0.43$). Sleep duration was increased in both groups: 49.6 (126.9) minutes in the wake group and 42.7 (123.0) minutes in the exercise group (between groups: $F_1 = 2.6$, $p = 0.11$). The mean sleep duration for patients in the *wake* group on nights after wake therapy (recovery sleep nights I, II, III: *night3*, *night5* and *night7*), was: *night3* with 10:35 (1:11) hour: minutes, *night5* with 10:14 (1:41) hour: minutes and *night7* with 9:51 (1:58) hour: minutes. Sleep duration on these nights were significantly longer than corresponding sleep days in the exercise group that were: *night3* with 7:17 (1:20) hour: minutes (between groups: $F_1 = 119.2$, $p<.0001$), *night5* with 7:47 (1:35) hour: minutes (between groups: $F_1 = 36.0$, $p<.0001$), and *night7* with 7:17 (1:48) hour: minutes (between groups: $F_1 = 29.4$, $p<.0001$). Scores on self-perceived quality of sleep increased in both groups but significantly more in the wake group ($F_1 = 10.5$, $p = 0.002$). The total mean sleep length for the eight nights (including sleep for those not taking the third wake therapy) was 49:45 (6:03) hour: minutes in the wake group and 60:02 (7:45) hour: minutes in the exercise group (excluding naps in both groups).

Any change of sleep-offset from end of the *admittance period* to the end of the *discharge period* did not have any significant influence on HAM-D_6 scores at *day8* ($F_{71} = 0.08$, $p = 0.77$).

Sleep logs showed that 41.2% (n = 14/34, with a total of 25 naps) of patients in the *wake* group and 52.6% (20/38, with a total of 60 naps) of patients in the *exercise* group napped in the *intervention phase*. The mean duration of the 25 naps in the *wake* group was 96.0 (65.5) minutes and the mean duration of the 60 naps in the *exercise* group was 75.3 (45.4) minutes. In the *wake* group, the total amount of napping time, during the *intervention phase*, was 2400 minutes distributed with 675 minutes (n = 9) in the *admittance period* (*day1* till *day5*) and 1725 minutes (n = 9) in the *discharge period* (*day6* till *day8*). In the exercise group, the total amount of napping time was 4520 minutes distributed with 2380 minutes (n = 16) in the *admittance period* (*day1* till *day5*) and 2140 minutes (n = 15) in the *discharge period* (*day6* till *day8*). The mean sleep midpoint of naps was 14:31 (2:55) in the *wake* group and 13:52 (2:50) in the *exercise* group. Only 14.7% (n = 5) of patients in the *wake* group were napping on the days after a wake night; one patient after the first wake, three patients after the second wake night and one patient after the third wake night. All differences between groups on nap statistics were non-significant.

We then examined the effect of napping on depression outcome (HAM-D_6 scores) in the *intervention phase* and found that napping significantly worsened depression scores ($F_{70} = 4.4$, $p = 0.04$) in the whole group. Further analysis showed that this worsening was predominantly due to napping in the *discharge period* where napping significantly worsened depression outcome ($F_{70} = 9.2$, $p = 0.003$) where as napping in the *admittance period* had a small and nonsignificant worsening effect on depression scores. ($F_{70} = 1.1$, $p = 0.3$). Furthermore the worsening of depression scores seen in the *discharge period* was predominantly in the wake group ($F_{69} = 5.8$, $p = 0.02$).

To illustrate the effect of napping in the *discharge period* on depression scores in the two treatment groups we calculated the baseline adjusted (*day1*) estimated HAM-D_6 scores for all days in the *intervention phase* for patients who napped (n = 24) and for patients who did not nap in this period. Results are shown in Figure 3. The main finding is that patients in the *wake* group who napped in the *discharge period* had a very large deterioration from *day5* till *day8* whereas patients not napping in the *wake* group had a much smaller deterioration in the same period. Also, in the wake group, we found that patients napping in the *discharge period* had a moderately *lesser* effect of wake therapy during the *admittance period* ($F_{65} = 3.8$, $p = 0.06$) compared to those patients without napping. Difference in depression scores in the exercise group between those napping and those not napping were nonsignificant.

Patient and Staff Evaluations

Table 4 shows patients and staffs evaluation of study procedures. In general there was a high level of global satisfaction with the study procedures. Additional semi-qualitative data (not shown in Table 4) showed that conversations with investigators were rated especially beneficial in 37.9% of wake patients and 46.0% of exercise patients. In the wake group 20.7% found wake therapy especially beneficial and 48.0% found it difficult. In the exercise group 35.1% found exercise especially beneficial and 24.3% found it difficult.

The following supplemental data provide further information about the study:

Supplemental tables and figures:

Table S1: sociodemographics showing data for antidepressants, depression history, and age and length of depression in past 5 years. No significant differences were found between groups.

Table S2: baseline-adjusted estimated mean HAM-D_6 scores by treatment group from the medium-term 9-weeks study for comparison. The magnitude of difference between groups remained stable for the whole period. The difference in HAM-D_6 scores between groups was significant ($F_{529} = 8.9$, $p = .003$) and also post hoc for all weeks. The interaction between group and week was insignificant indicating a parallel reduction in scores in the two groups;

Figure S1: time course of depression ratings on the HAM-D_6 scale for individual patients and days in the *interventions phase* by treatment group;

Figure S2: sleepiness as measured on all wake nights by the Stanford Sleepiness Scale (mean± standard deviation), LOCF. Mean sleepiness at 11 PM was 2.3 (1.1) (corresponding to: "functioning at high levels, but not at peak; able to concentrate") and increased by each hour to a maximum of 4.0 (1.9) (corresponding to: "somewhat foggy, let down") at 6 PM and then gradually diminished to 3.3 (1.6) (corresponding to: "awake, but relaxed; responsive but not fully alert") at 8 PM.

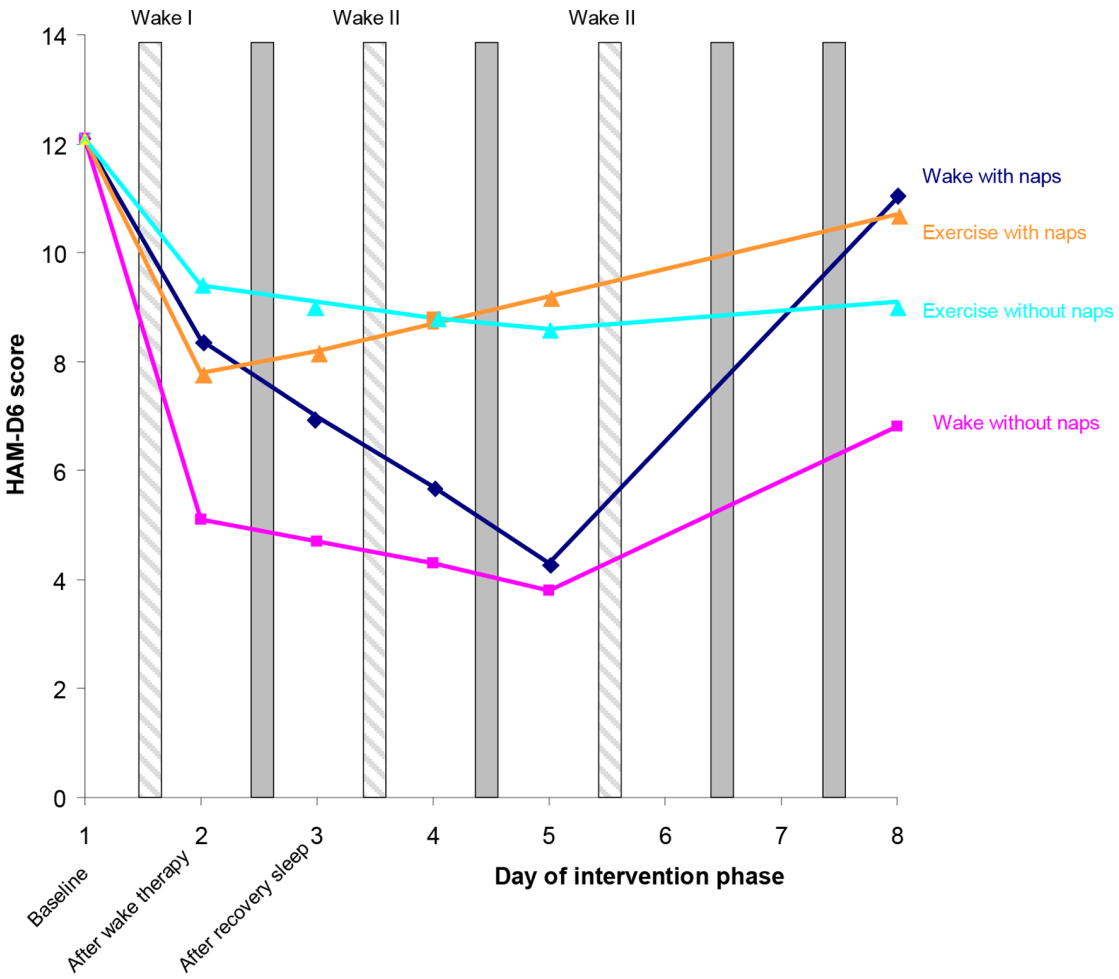

Figure 3. Estimated Mean Post-*day1* HAM-D_6 scores by napping status in the discharge period (*day6* till *day8*) by treatment group.
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Table 4. Patient and staff evaluations of procedures (wake, sleep time stabilisation, light and exercise) used in intervention week.

	Wake	Exercise
Patients' evaluation	**Per cent (n)**	**Per cent (n)**
Felt global improvement	87.9 (29/33)	81.1 (30/37)
Satisfied with study procedures	81.8 (27/33)	94.6 (35/37)
Did you find any study procedure especially beneficially	87.9 (29/33)	100 (37/37)
Did you find any study procedure especially disagreeable	72.7 (24/33)	70.3 (26/37)
Day-time staff evaluation		
Staff evaluated that patient improved during stay at ward	82.6 (19/23)	52.6 (10/19)
Staff evaluated that some of the used study procedures were difficult for patient	73.9 (17/23)	52.6 (10/19)
Staff evaluated that some of the used study procedures were beneficial for patient	86.4 (19/22)	89.5 (17/19)
Staff indicated that study procedures are applicable in ward	95.9 (21/22)	57.9 (11/19)
Staff indication that study procedures could be used in ward as a treatment option for patients with depression	81.8 (18/22)	94.7 (18/19)
Night-watch staff evaluation		
Staff evaluated that patient improved during stay at ward	47.4 (9/10)	NA
Staff evaluated that used study procedures were difficult for patient	52.4 (11/21)	NA
Staff evaluated that used study procedures were beneficial for patient	75.0 (15/20)	NA
Staff indicated that study procedures are applicable in ward	70.0 (14/20)	NA
Staff indication that study procedures could be used in ward as a treatment option for patients with depression	85.0 (17/20)	NA

Per cent refers to positive responses.
doi:10.1371/journal.pone.0067264.t004

Discussion

The presented results confirm our *first* hypothesis: that a combination of wake therapy, light therapy and sleep time stabilisation can induce a rapid and marked response and remission without any relapse or deterioration between intervention days. It is thus a replication of the results found by other authors [34].

By necessity, the rating period during the intervention days is short and scores cannot be directly compared with scores from weekly assessments (*day1* and *day8*) where the standard retrospective rating period of three days has been used. However, there is no doubt that the marked response and remission rates seen immediately after the first wake therapy and augmented on the following intervention days are diminished somewhat on the following weekly assessment (*day8*). Thus the full goal of the study is not accomplished. In this respect it is important to notice that the dreaded mood fluctuations between wake nights and after recovery sleep, seen in some earlier studies using wake therapy, were not seen in this study.

The regime was well tolerated but as mentioned in the previous report [1] a few patients experienced anxiety attacks following wake therapy nights. Sleep loss due to wake therapies when compared to sleep duration in the *exercise* group was moderate and confirms that wake therapy does not cause a huge sleep deficit but is more a reallocation of sleep.

Concerning our second hypothesis, we found, as expected, that the presence of a positive diurnal variation (better in the evening) was associated with a better treatment response in the wake group. It is not established whether the diurnal variation of mood can be regarded as a continuum, as we implicitly have done, of a single latent biological parameter or whether there is a more complex and individual biology at the core of the phenomenon.

Gordijn et al found that variability in itself more than any definite type of variation predicted response to sleep deprivation [35]. In our opinion a positive diurnal variation should though still be recommended as a positive predictor when considering a patient for wake therapy regimens.

The effect size on *day5* of 1.45 is considered very large and larger than seen in drug therapy trials and comes within 5 days.

Regarding our third hypothesis we could confirm [15] that napping, after the wake therapy regimen, is associated with a much greater tendency for deterioration than for patients not napping. Thus, when using this wake paradigm, advice should be given and control measures employed to avoid any napping in the days following wake therapy. We cannot from this study with certainty conclude that napping by itself was the cause of the greater deterioration as inherent patient characteristics could play a role. The finding that patients who did nap after the end of the wake therapy regimen also had less effect during the wake therapies, suggests that the tendency to nap may be linked to some degree to the non-response to wake therapy.

The sleep logs showed a significant advance of the sleep-wake cycle in the wake group, which might also have contributed to the antidepressant effect.

Performing a series of three wake therapies is quite demanding on the patients and even though there is a substantial gain in the short and a moderate gain after nine weeks it would still be very useful to be able to predict which patients will benefit the most from this intervention. Our analysis showing a high negative predictive value suggests that non-response to an initial wake therapy gives little hope of response after further wake therapies. This finding could be useful guiding the clinicians.

It is a limitation of the study that the statistical analysis had to be performed within a larger dataset and with the use of another baseline than for the 9-weeks study. As the scores at week 1 (*day1*)

were quite similar across groups we do not suspect this to be a major problem. Fewer patients were assessed in the exercise group with the HAM-D_6 at days 4 and 5 primarily due to logistic reasons pertaining to exercise training sessions. As this was not related to depression severity we do not believe this has biased the results.

Due to the rather small sample size statistical significance of sub-analyses might be due to change findings of multiple testing and should thus be interpreted with caution.

Depression ratings from the days of the intervention week were based on a 'last hour' time window and this might bias towards lower scores compared to scores from longer time windows. This would give an artificially deterioration at end of intervention week where rating were based on a last 'three days time' window.

Some imprecision might come from performing 'last hour' rating on slightly different time point of the day.

As patients in this study were predominantly treatment resistant [1] the findings cannot be generalised to non-treatment resistant patient and as the majority of patient were unipolar we cannot generalise findings to bipolar patients.

Supporting Information

Figure S1 Individual patient's available data from the HAM-D6 scale for the 8 days of the interventions phase for each patient by treatment group.
(DOC)

Figure S2 Sleepiness as measured on wake nights by the Stanford Sleepiness Scale (mean± standard deviation) for 94 wake nights (data missing from 3 nights), LOCF.
Scoring: 1 = Feeling active, vital, alert, or wide awake, 2 = Functioning at high levels, but not at peak; able to concentrate, 3 = Awake, but relaxed; responsive but not fully alert, 4 = Somewhat foggy, let down, 5 = Foggy; losing interest in remaining awake; slowed down, 6 = Sleepy, woozy, fighting sleep; prefer to lie down, 7 = No longer fighting sleep, sleep onset soon; having dream-like thoughts.
(DOC)

Table S1 Sociodemographics.
(DOC)

Table S2 Baseline-adjusted estimated mean HAM-D6 scores by treatment group from the medium-term 9-weeks study.
(DOC)

Table S3 Results from the sleep logs.
(DOC)

Checklist S1 Consort checklist.
(DOC)

Protocol S1 Study protocol.
(DOC)

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Author Contributions

Conceived and designed the experiments: KM ER VL ML LS BT LL PB. Performed the experiments: KM ER VL ML LS BT LL PB. Analyzed the data: KM ER VL ML LS BT LL PB. Contributed reagents/materials/analysis tools: KM ER VL ML LS BT LL PB. Wrote the paper: KM ER VL ML LS BT LL PB.

References

1. Martiny K, Refsgaard E, Lund V, Lunde M, Sørensen L, et al. (2012) A 9-Week randomized trial comparing a chronotherapeutic intervention (wake and light therapy) to exercise in major depressive disorder patients treated with duloxetine. J Clin Psychiatry 73: 1234–1242.
2. Kuhs H, Tölle R (1991) Sleep deprivation therapy. Biol Psychiatry 29: 1129–1148.
3. Wu JC, Bunney WE (1990) The biological basis of an antidepressant response to sleep deprivation and relapse: Review and hypothesis. Am J Psychiatry 147: 14–21.
4. Wirz-Justice A, van den Hoofdakker RH (1999) Sleep deprivation in depression: what do we know, where do we go? Biol Psychiatry 46: 445–453.
5. Giedke H, Schwärzler F (2002) Therapeutic use of sleep deprivation in depression. Sleep Med Rev 6: 361–377.
6. Neumeister A, Goessler R, Lucht M, Kapitany T, Bamas C, et al. (1996) Bright light therapy stabilizes the antidepressant effect of partial sleep deprivation. Biol Psychiatry 3: 16–21.
7. Wu JC, Kelsoe JR, Schachat C, Bunney BG, DeModena A, et al. (2009) Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. Biol Psychiatry 66: 298–301.
8. Colombo C, Lucca A, Benedetti F, Barbini B, Campori E, et al. (2000) Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. Psychiatry Res 95: 43–53.
9. Smeraldi E, Benedetti F, Barbini B, Campori E, Colombo C (1999) Sustained antidepressant effect of sleep deprivation combined with pindolol in bipolar depression. A placebo-controlled trial. Neuropsychopharmacol 20: 380–385.
10. Kreuzer PM, Langguth B, Schecklmann M, Eichhammer P, Hajak G, et al. (2012) Can repetitive transcranial magnetic stimulation prolong the antidepressant effects of sleep deprivation? Brain Stimul 5: 141–147.
11. Wirz-Justice A, Benedetti F, Terman M (2009) Chronotherapeutics for Affective Disorders: A Clinician's Manual for Light and Wake Therapy. Basel: S. Karger AG Switzerland. 116 p.
12. Wirz-Justice A, Terman M (2012) Chronotherapeutics (light and wake therapy) as a class of interventions for affective disorders. In: Vinken PJ, Bruyn GW, editors. Handb Clin Neurol 106: 697–713.
13. Wirz-Justice A (2008) Diurnal variation of depressive symptoms. Dialogues Clin Neurosci 10: 337–343.
14. Boivin DB, Czeisler CA, Dijk DJ, Duffy JF, Folkard S, et al. (1997) Complex interaction of the sleep-wake cycle and circadian phase modulates mood in healthy subjects. Arch Gen Psychiatry 54: 145–152.
15. Riemann D, Wiegand M, Lauer CJ, Berger M (1993) Naps after total sleep deprivation in depressed patients: are they depressiogenic? Psychiatry Res 49: 109–120.
16. Kuhs H, Tölle R (1991) Sleep deprivation therapy. Biol Psychiatry 29: 1129–1148.
17. Voderholzer U, Valerius G, Schaerer L, Riemann D, Giedke H, et al. (2003) Is the antidepressive effect of sleep deprivation stabilized by a three day phase advance of the sleep period? A pilot study. Eur Arch Psychiatry Clin Neurosci 253: 68–72.
18. Horne JA, Ostberg O (1976) A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 4: 97–110.
19. Borg GA (1982) Psychophysical bases of perceived exertion. Med Sci Sports Exerc 14: 377–381.
20. Schulz KF, Altman DG, Moher D, for the CONSORT Group. (2010) CONSORT Statement: updated guidelines for reporting parallel group randomised trials. Ann Int Med 152: 726–732.
21. EMEA. The European Agency for the Evaluation of Medicinal Products (1997) Note for guidance on Good Clinical Practice (CPMP/ICH/135/95). London: EMEA.
22. Bech P (2012) Clinicial Psychometrics. Oxford: Wiley-Blackwell.
23. Bech P, Allerup P, Gram LF, Reisby N, Rosenberg R, et al. (1981) The Hamilton Depression Scale. Evaluation of objectivity using logistic models. Acta Psychiatr Scand 63: 290–299.
24. O'Sullivan RL, Fava M, Agustin C, Baer L, Rosenbaum JF (1997) Sensitivity of the six-item Hamilton Depression Rating Scale. Acta Psychiatr Scand 95: 379–384.
25. Bech P, Kastrup M, Rafaelsen OJ (1986). Mini-compendium of rating scales for states of anxiety depression mania schizophrenia with corresponding DSM-III syndromes. Acta Psychiatr Scand 326: 1–37.

26. Bech P (2012) The three-fold Hamilton Depression Scale: an editorial comment to Isacsson G, Adler M. Randomized clinical trials underestimate the efficacy of antidepressants in less severe depression. Acta Psychiatr Scand 125: 423–424.
27. Bech P, Licht RW, Stage KB, Abildgaard W, Bech-Andersen G, et al. (2005) In "Kompendium, Rating scales for Affektive Lidelser", Psychiatric Research Unit, Mental Health Centre North Zealand, University Hospital of Copenhagen, Denmark 2nd edition.
28. Sleep logs are found on the website for Clinimetric Center for Mental Health (CCMH). Available: www.ccmh.dk/vejledninger/søvnskema Assessed 2013 May 26.
29. Glenville M, Broughton R (1978) Reliability of the Stanford Sleepiness Scale compared to short duration performance tests and the Wilkinson Auditory Vigilance Task. Adv Biosci 21: 235–244.
30. MacLean AW, Fekken GC, Saskin P, Knowles JB (1992) Psychometric evaluation of the Stanford Sleepiness Scale. J Sleep Res 1: 35–39.
31. Terman M, Terman JS (2010) Light Therapy. In: Principles and Practice of Sleep Medicine, 5th edition. Edited by Kryger MH, Roth T, Dement WC. St. Louis: Elsevier/Saunders 1682–1695.
32. Brown H, Prescott R (1999) Applied Mixed models in Medicine. Chichester: Wiley.
33. Hedges LV, Olkin I (1985) Statistical methods for meta-analysis. New York, NY: Academic Press. 78–85.
34. Wirz-Justice A, Benedetti F, Berger M, Lam RW, Martiny K, et al. (2005) Chronotherapeutics (light and wake therapy) in affective disorders. Psychol Med. 35: 939–944.
35. Gordijn MC, Beersma DG, Bouhuys AL, Reinink E, Van den Hoofdakker RH (1994). A longitudinal study of diurnal mood variation in depression; characteristics and significance. J Affect Disord 31: 261–273.

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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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ABSTRACT

Previous studies have demonstrated that combined total sleep deprivation (Wake therapy), 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 $= 44 \pm 16.4$ SD, 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 h), followed by a three-night sleep phase advance along with four 30-min 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 ± 4.2 SD at baseline to a mean of 9.4 ± 7.3 SD on day five ($p = .002$) with six of the ten individuals meeting criteria for remission. CSSRS scores dropped from a mean of 19.5 ± 8.5 SD at baseline to a mean of 7.2 ± 5.5 SD 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.

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1. Introduction

Major depressive disorder is a neuropsychiatric condition that consists of core symptoms including a persistently depressed mood, anhedonia, sleep disruption, anergia, poor concentration, guilt, hopelessness, appetite changes, and suicidal ideation. Currently there are no commonly used rapid treatments for depression. 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 and Pankratz, 2000). Depression is a major medical issue both domestically and abroad. Depression is

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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 et al., 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 and Tolle (1971), and reviewed extensively by (Wu and Bunney (1990); Wirz-Justice et al. (2005); 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; Smeraldi et al., 1999; Martiny et al., 2012; Shelton and Loosen, 1993; Szuba et al., 1994; Wu et al., 2009), sleep phase advance (Riemann et al., 1999; Echizenya et al., 2013), and bright light therapy (Echizenya et al., 2013; Martiny et al., 2012, 2013; Neumeister et al., 1996; Wu et al., 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 et al., 2013; Martiny et al., 2012; Wu et al., 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., 2014). 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 a substance of abuse, 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 first briefly explained the chronotherapy intervention to patients who were admitted. Study team members then met with interested patients to obtain informed consent. All interested patients who met inclusion criteria, and did not meet exclusion criteria were included in the study. A total of 21 potential participants were referred, with three not being interested in the study, and four meeting 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) (Fig. 1). The mean age of participants was 44 ± 16.4, six of whom were women, and none of whom 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. We initially recruited two participants with a diagnosis of bipolar disorder, however both of those participants were excluded from analysis due to protocol deviations as described above. 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. The medications that were either started or continued by the treating team were as follows: 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

The Triple Chronotherapy procedure we used closely resembled the one described in the manual written by Wirz-Justice at al (Wirz-Justice et al., 2013). Recruited participants filled out the

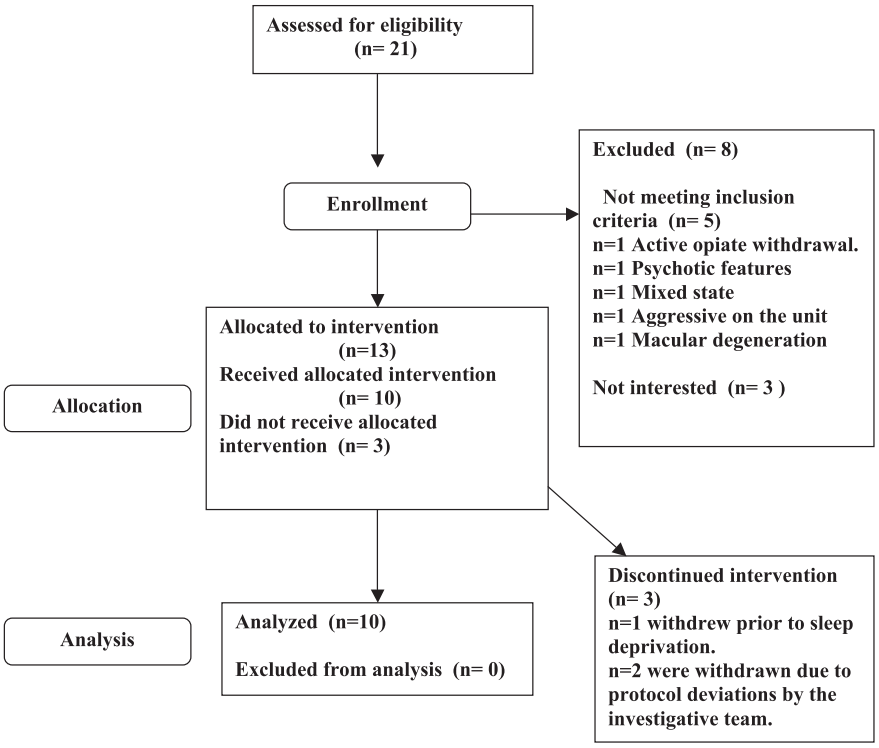

Fig. 1. Screening and enrollment flowchart.

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 min at 10,000lux, with the timing set by MEQ. The start time of light exposure varied between 6am and 8am. Following the four-day intervention, participants were asked to remain on as close a schedule as possible to 10pm to 5am (although this was not monitored as we considered the intervention to have been completed). We did recommend that they expand their time in bed to a maximum of 8 h if they were experiencing daytime sleepiness with 7 h in bed. Light therapy was generally discontinued, however participants were offered recommendations on the appropriate use of light therapy if they desired to continue it once they left the hospital (Fig. 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 (Sheehan et al., 1998) to confirm diagnoses, administered a 17-Item Hamilton depression rating scale (HAMD17) (Hamilton, 1960), Columbia Suicide Severity Rating Scale (CSSRS) (Posner et al., 2011), and a Young Mania Rating scale (YMRS) (Young et al., 1978), 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) (Rush et al., 1996), the Patient Health Questionaire-9 (PHQ9) (Spitzer et al., 1999), the Epworth Sleepiness scale (ESS) (Johns, 1993), the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), and the Scale for Suicidal Ideation (SSI) (Beck et al., 1979). 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 (HAM-D6) (O'Sullivan et al., 1997), 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. We defined remission from depression as a HAM17 score of less than 7. We defined response from either depression (HAM17), or suicidal ideation (CSSRS) as a greater than 50% drop in score from baseline.

Table 1
Demographics.

$N = 10$	
Age	Mean = 44 ± 16.4 SD
Gender	4 Male, 6 Female
Race/Ethnicity	9 (90%) Caucasian 1 (10%) African American
Duration of current episode	15.4months ± 13.2 SD
Number of lifetime episodes	7.8 ± 5.8 SD
Number of failed medications/ECT	5.5 ± 5.7 SD One failure of ECT

2.4. Data analysis

Because of the small sample size ($n = 10$), we chose to use more valid and more conservative non-parametric statistical tests. We used Wilcoxon's signed rank 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).

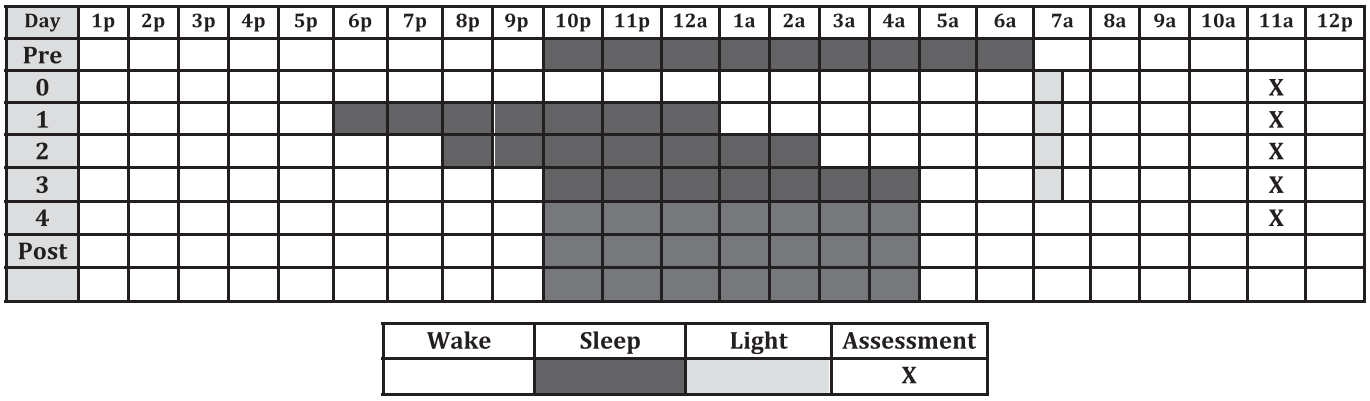

Fig. 2. Chronotherapy procedure.

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 ± 4.2 SD at day 0, to a final score of 9.4 ± 7.3 SD on day 4. Six out of ten participants met criteria for remission on the Ham17 (60%). Sixty-percent met criteria for response (Figs. 3 and 4). The Columbia Suicide Severity Index went from an average of 19.5 ± 8.5 SD on day 0 to a final score of 7.2 ± 5.5 SD on day 4. Sixty percent of participants met criteria for a response on the CSSRS (Fig. 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 et al., 2014). 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 et al., 2001; Colombo et al., 2000; Shelton and Loosen, 1993; Szuba et al., 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

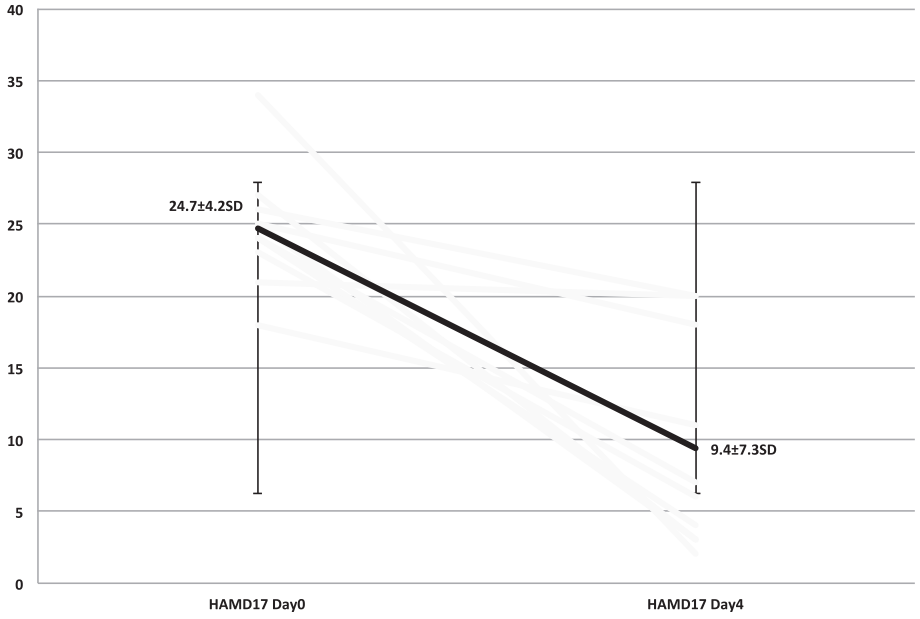

Fig. 3. Hamilton Depression Rating Scale 17-item.

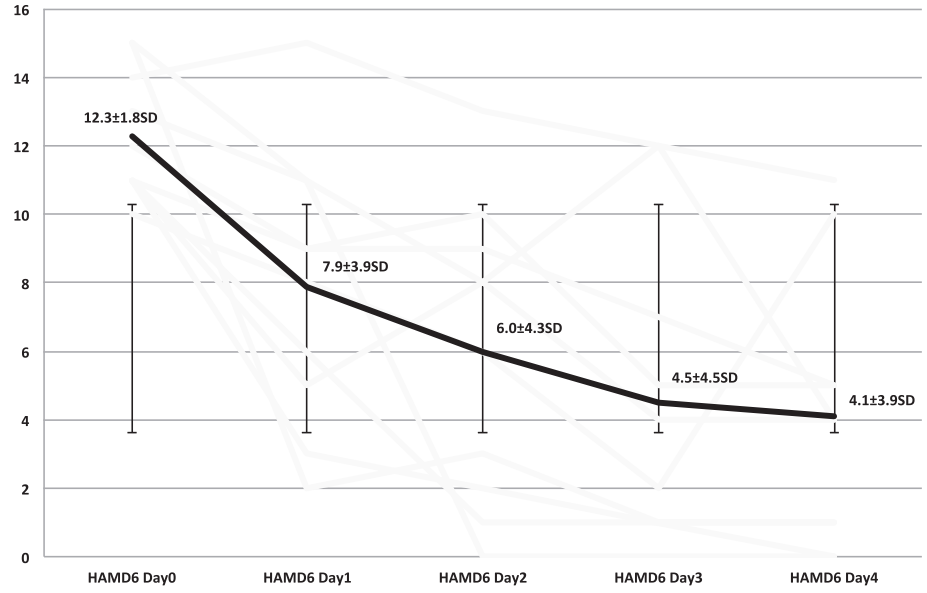

Fig. 4. Hamilton Depression Rating Scale 6-item.

following the first night of recovery sleep. There was a small statistically non-significant ($p = 0.74$) increase in suicidal ideation on day 2 compared to day 1, however this small increase was mostly accounted for by our non-responders, was still considerably below reported suicidal ideation prior to starting the procedure, and not likely to be clinically significant. 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 et al., 2013; Martiny et al., 2012; Wu et al., 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. Although our findings in the context of the other literature in the field are very encouraging, we believe further study must take place prior to widespread clinical adoption. 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

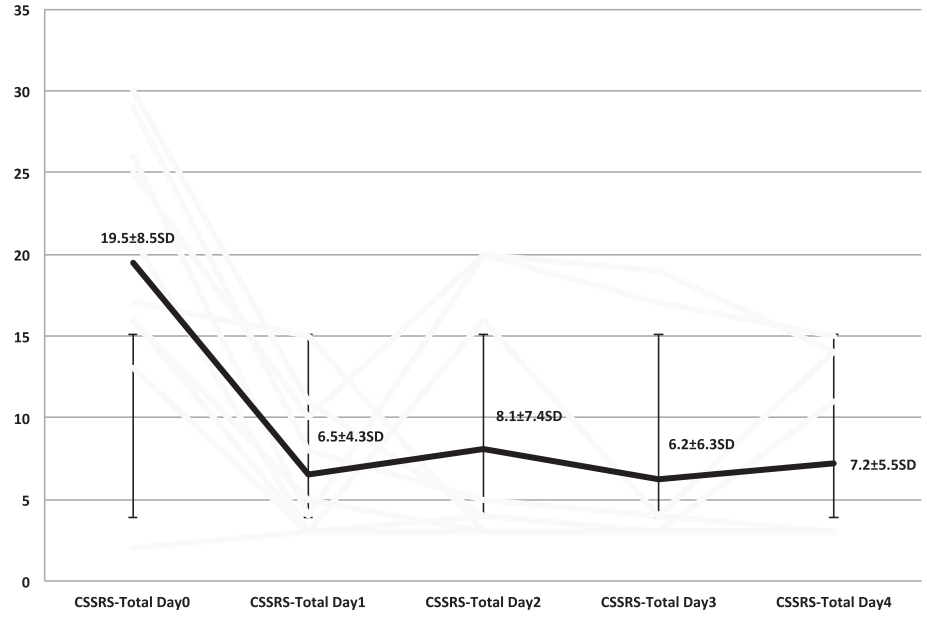

Fig. 5. Columbia Suicide Severity Rating Scale total.

Table 2
Measures score (±Standard deviation).

Measure	Baseline	Day 1	Day 2	Day 3	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(±8.0) $p < .004$	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.

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, 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.

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Support was provided by the Medical University of South Carolina Resident Research Training Program (DART program), which was funded by National Institute on Drug Abuse (NIDA) R25 DA020537-06 (PI's Back and Brady). Besides providing mentorship that assisted in experimental design and implementation, the funding source did not influence the project.

Author contributions

Gregory L. Sahlem was the Primary investigator of the study. He contributed in experimental design, regulatory procedures, data collection, data analysis, and manuscript preparation.

Benjamin Kalivas contributed in experimental design, data analysis, and manuscript preparation.

James B. Fox contributed in recruitment, and manuscript preparation.

Kayla Lamb contributed to regulatory procedures, and manuscript preparation.

Amanda Roper contributed in experimental design, and manuscript preparation.

Emily N. Williams contributed in experimental design, recruitment, and manuscript preparation.

Nolan R. Williams contributed in experimental design, and manuscript preparation.

Jeffrey E. Korte was the statistician on the project. He contributed in data analysis and manuscript preparation.

Zachary D. Zuschlag contributed in recruitment and manuscript preparation. Salim El Sabbagh contributed in recruitment and manuscript preparation.

Constance Guille was a mentor for the project and contributed in experimental design and manuscript preparation.

Kelly S. Barth was a mentor for the project and contributed in recruitment and manuscript preparation.

Thomas W. Uhde was a mentor for the project and contributed in experimental design, and manuscript preparation.

Mark S. George was a mentor for the project. He contributed in experimental design, regulatory procedures, data analysis, and manuscript preparation.

E.Baron Short was a mentor for the project. He contributed in experimental design, regulatory procedures, data analysis, and manuscript preparation.

Conflict of interest

There is no Conflict of Interest.

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References

Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. J Consult Clin Psychol 1979;47:343–52.
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? J Psychiatr Res 2001;35:323–9.
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. J Clin Psychiatry 2005;66:1535–40.
Benedetti F, Barbini B, Colombo C, Smeraldi E. Chronotherapeutics in a psychiatric ward. Sleep Med Rev 2007;11:509–22.
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. J Clin Psychiatry 2014;75(2):133–40.
Bostwick MP, Pankratz VS. Affective disorders and suicide risk: a reexamination. Am J Psychiatry 2000:1925–32.
Buysse DJ, Reynolds 3rd CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.
Caddy C, Giaroli G, White TP, Shergill SS, Tracy DK. Ketamine as the prototype glutamatergic antidepressant: pharmacodynamic actions, and a systematic review and meta-analysis of efficacy. Ther Adv Psychopharmacol 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 Res 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. J Affect Disord 2013;144:28–33.
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;7(3):421–31.
Hamilton M. A rating scale for depression. J Neurol, Neurosurg psychiatry 1960;23:56–62.
Heron M. Deaths: leading causes for 2010. Natl Vital Stat Rep 2013;62.
Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 1976;4:97–110.
Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale. Chest 1993;103:30–6.
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: J Am Med Assoc 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: J Am Med Assoc 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. J Clin psychiatry 2012;73:1234–42.
Martiny K, Refsgaard E, Lund V, Lunde M, Sorensen L, Thougaard B, et al. The day-to-day acute effect of wake therapy in patients with major depression using the HAM-D6 as primary outcome measure: results from a randomised controlled trial. PloS one 2013;8:e67264.
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. Biol Psychiatry 1996;39:16–21.
O'Sullivan RL, Fava M, Agustin C, Baer L, Rosenbaum JF. Sensitivity of the six-item Hamilton depression rating scale. Acta Psychiatr Scand 1997;95:379–84.
Pflug B, Tolle R. Disturbance of the 24-hour rhythm in endogenous depression and the treatment of endogenous depression by sleep deprivation. Int Pharmacopsychiatry 1971;6:187–96.
Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia–Suicide severity rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011:1266–77.
Riemann D, Konig A, Hohagen F, Kiemen A, Voderholzer U, Backhaus J, et al. How to preserve the antidepressive effect of sleep deprivation: a comparison of sleep phase advance and sleep phase delay. Eur Arch Psychiatry Clin Neurosci 1999;249:231–7.
Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med 1996;26:477–86.
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. Am J 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 setting. Neuropsychopharmacol: official Publ Am Coll Neuropsychopharmacol 2007;32:244–54.
Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(Suppl. 20):22–33. quiz 4–57.
Shelton RC, Loosen PT. Sleep deprivation accelerates the response to nortriptyline. Prog Neuro-Psychopharmacology Biological Psychiatry 1993;17:113–23.
Smeraldi E, Benedetti F, Barbini B, Campori E, Colombo C. Sustained antidepressant effect of sleep deprivation combined with Pindolol in bipolar depression: a placebo-controlled trial. Neuropsychopharmacology 1999;20(4):380–5.
Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA: J Am Med Assoc 1999;282:1737–44.
Szuba MP, Baxter Jr LR, 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 Res 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.
Wirz-Justice A, Benedetti F, Terman M. Chronotherapeutics for affective disorders: a clinician's manual for light and wake therapy. 2nd, rev. ed. Basel: Karger; 2013.
Wu JC, Bunney WE. The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. Am J 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. Biol Psychiatry 2009;66:298–301.
Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry: J Ment Sci 1978;133:429–35.

INSTITUTIONAL REVIEW BOARD

NEW YORK STATE PSYCHIATRIC INSTITUTE

MEMORANDUM

November 07, 2016

TO: Dr. Jonathan Stewart

FROM: Dr. Edward Nunes, IRB Co-Chair

SUBJECT: Protocol #7361: ARE BRIGHT LIGHTS AND REGULATED SLEEP EFFECTIVE TREATMENT FOR DEPRESSION?

A Full Board reviewed the above protocol on November 07, 2016 and recommended approval pending your response to the following items. Please submit (through PRISM) **(1) a copy of this memo, (2) your point-by-point response (question and answer format), (3) the revised Protocol Summary Form (PSF) with revisions bolded, (4) the Consent Forms (CF).**

1. Please confirm that either an ophthalmologist or an internist will conduct the funduscopic exam, as it was felt that this exam needs to be conducted by a physician experienced in it. Although you are the expert in this area, and you included the funduscopic exam in the protocol, members of the Board also wondered whether such exam is necessary given the likely low risk of light therapy. However, if you wish to remove the requirement for an eye exam, that would require re-review by the Board, and your request would need to be accompanied by a review of what is known about the risks of light therapy to the eye.`
2. Please include in the PSF and CF that a pregnancy test will be conducted both at baseline and again at 4 weeks for women of child bearing potential.
3. Please revise the Delay to Treatment section of the PSF to confirm that study participation concludes after 6 weeks, and the 6 months after study participation is considered clinical treatment.
4. Because low thyroid function is mentioned in the CF, please update exclusion criterion #3 to state, “Unstable medical condition (such as low thyroid function)”.

EN/alw

Ophthalmologic Examination of Patients With Seasonal Affective Disorder, Before and After Bright Light Therapy

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• PURPOSE: We assessed the potential ocular hazards of bright light therapy for patients with seasonal affective disorder, after both short- and long-term treatment, and identified prospective patients with pre-existing ocular abnormalities.

• METHODS: Fifty patients with seasonal affective disorder received daily exposure to artificial light in the morning or evening for 30 minutes at an illuminance level of 10,000 lux (irradiant dose, 0.016 J/cm^2). Ophthalmologic examinations were performed before and after short-term treatment (two to eight weeks) and after three to six years of use during the fall and winter months. Over the four years of patient intake, the eye examination included subsets of the following tests: visual acuity, intraocular pressure, slit-lamp biomicroscopy, direct and indirect ophthalmoscopy, color vision, visual field, fundus photography, Amsler grid, ocular motility, pupillary reactions, contrast sensitivity, stereopsis, and the macular stress test.

• RESULTS: No ocular changes were detected after short-term treatment. Long-term treatment (three to six years) of 17 patients, with cumulative exposure durations of 60 to 1,250 hours, also resulted in no ocular abnormalities.

• CONCLUSIONS: Light therapy yields about 75% clinical remissions. It is effective as an antidepressant and appears safe for the eyes. Current knowledge is insufficient to specify any definite ocular contraindications for bright light therapy, although we recommend that patients with pre-existing ocular abnormalities and those using photosensitizing drugs undergo treatment only with periodic ophthalmologic examination.

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THE THERAPEUTIC USE OF ARTIFICIAL BRIGHT light is a recently developed, yet already widely applied, treatment for the winter depression of seasonal affective disorder.[1] Patients with seasonal affective disorder regularly become depressed in late fall or winter and show spontaneous remission in spring and summer. Within the United States the syndrome is more prevalent at higher latitudes. Nationally, it is estimated that about 11 million people are affected at syndromal levels, and about 25 million people are affected at subsyndromal levels. Hallmark symptoms of the disorder include fatigue, increased sleep, carbohydrate craving, and dysphoric mood. When patients are undergoing light therapy, these symptoms are typically reduced or eliminated within one week.[2] In order to maintain remission, daily treatments are often continued throughout the fall and winter months. The antidepressant effect of light appears to be mediated by the eyes, not the skin.[3]

As originally studied at the National Institute of Mental Health,[4] the treatment regimen used 2,500

lux (at eye level) of full-spectrum light designed to simulate the solar spectrum, including near and middle ultraviolet radiation. However, the eyes were partially shielded from ultraviolet light by a plastic diffusing screen. Daily treatment sessions usually required exposure for two hours or longer at this intensity level. Since 1987, however, we have used lamps that minimize ultraviolet radiation, with a raised illuminance of approximately 10,000 lux, and 30-minute treatment sessions.[5] Terman and associates[6] have described in detail potential ocular hazards of light treatment, particularly in association with preexisting ocular abnormality or concurrent use of photosensitizing drugs. A recent consensus report on the safety of light therapy devices concluded that no hazard has been identified "for a standard fluorescent lighting apparatus designed to produce 2,500 to 10,000 lux, given low levels of ultraviolet emission."[7] Remé, Menozzi, and Krueger[8] have proposed a set of standards for such illumination sources.

In the first clinical trials of light therapy, Rosenthal and associates[4] found no pretreatment to posttreatment ocular changes, on the basis of slit-lamp examinations, dark adaptometry, and fundus examinations. In more extensive comparisons between patients with seasonal affective disorder and normal controls, a large set of ophthalmologic tests yielded no statistically significant differences.[9] Lam and associates,[10,11] however, found small but significant reductions in visual sensitivity, as measured by electroretinogram b-wave amplitude[10] and electrooculographic Arden ratio,[11] in comparison with normal control subjects. These studies were designed to elucidate underlying ocular mechanisms involved in the pathogenesis of seasonal affective disorder and were not performed to screen for ocular abnormalities.

Whether all patients seeking bright light treatment should receive an ocular screening examination is a controversial matter.[12-14] Comprehensive ophthalmologic examination of patients with seasonal affective disorder has not yet been reported, and data that would form a basis for identifying patients at risk for ocular damage from light are lacking. Over the course of the present study, we selected and administered a set of basic diagnostic tests to identify pre-existing ocular abnormalities, to exclude patients from light treatment if the baseline examination indicated clinically significant abnormality, and to evaluate retest results after an initial short-term treatment phase and after several years of treatment.

PATIENTS AND METHODS

RESEARCH VOLUNTEERS WERE SCREENED FOR PROSPECTIVE study according to National Institute of Mental Health diagnostic criteria for seasonal affective disorder[4] and the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R)[15] (major depressive disorder, recurrent [296.3] or bipolar disorder not otherwise specified [296.7], both with seasonal pattern [winter type]). Patients entered clinical trials of light therapy between 1987 and 1991, after providing informed consent. Exclusion criteria included the following: (a) current treatment with psychotropic or photosensitizing medication, recent history of suicide attempt, panic or eating disorder unrelated to depression, or other DSM-III-R axis I disorder; (b) current use of alcohol, marijuana, cocaine, or stimulant drugs, including diet pills; (c) ocular abnormality including corneal or retinal pathology, cataract, or narrow-angle or primary open-angle glaucoma; and (d) nonocular conditions including skin cancer, head injury, epilepsy, diabetes, or diseases requiring treatment with beta-adrenergic blockers. At the time of entry into the study, all patients met clinical severity criteria[16] for moderate to severe depression.

Before acceptance into the program, patients underwent a standard physical examination supplemented by electrocardiogram, urinalysis, and blood tests (complete blood cell count, including platelets, thyroid panel, cholesterol [high density lipoprotein, cholesterol/high-density lipoprotein ratio and triglycerides]), to rule out potentially complicating medical conditions.

Of 64 patients recruited into the study, two were excluded because of ophthalmologic indications. Because of scheduling constraints, five patients received only pretreatment ocular examinations and six received only posttreatment examinations (all with normal results). One patient refused a second examination with pupil dilation. To determine potential

short-term treatment effects, we analyzed the ocular results for the 50 patients who received both pretreatment and posttreatment ocular examinations during the year of entry into the study. This group included 13 men and 37 women, ages 18 to 62 years (mean ± S.D., 39.28 ± 11.38 years).

For long-term follow-up, all 30 (60%) patients who retained light boxes were contacted for reexamination in the fall of 1993. Of those patients, 17 returned for ocular examinations. Of the 13 who did not return, six had moved and could not be reached, four had discontinued use of the lights, and three were unable to schedule appointments. Thus, we examined 17 (85%) of 20 of the patients whom we could verify had continued with light therapy for three to six consecutive fall and winter seasons through 1993.

The pretreatment screening examination included a medical history of systemic and ocular diseases, a review of potentially photosensitizing current medications, and notation of any ocular complaints. The Table shows the distribution of tests administered across the four years of the treatment study (1987 to 1991) and the follow-up examination (1993).[17] In the first two years, six basic tests were performed, accompanied by fundus photography of the central 30 degrees. Visual acuity was assessed by using the Snellen visual acuity chart with and without spectacle correction. Color vision was assessed using the American Optical or Ishihara plates. Static visual field was evaluated using the Humphrey automated perimeter (full-field 81-point screening test). Intraocular pressure was determined with Goldmann applanation tonometry, and the anterior segment was examined by slit-lamp biomicroscopy. After pupil dilation with tropicamide 1% and oxymetazoline hydrochloride 2.5%, the central and peripheral fundus was observed by direct and indirect ophthalmoscopy.

In the third and fourth years of the study fundus photography was discontinued as a cost-saving measure, because no abnormality had been detected by this means in previous patients. Visual field testing was discontinued in the fourth year because of the unavailability of an automated perimeter. Several tests were added to elucidate further potential changes of the central fundus and optic and oculomotor nerve function, as shown in the Table. A test of stereopsis was added to detect defects in visual acuity that might be reflected in higher-order cerebral function. The Vistech 6000 chart was used to assess contrast sensitivity. Color vision was probed with more specificity by using the Farnsworth-Munsell 100 hue test and the Farnsworth panel D15. Additionally, patients completed a side effects checklist for assessment of potential subjective visual disturbances, based on the Systematic Assessment for Treatment Emergent Events,[18] which included eye irritation or swelling; blurred, double, or poor vision; photophobia; and the presence of other (unspecified) ocular problems.

Patients received the initial ocular examination during the pretreatment baseline period while they were depressed, with posttreatment evaluations after approximately two weeks of light treatment at 10,000 lux. In some cases, scheduling constraints delayed the posttreatment examination for up to two months, after completion of a second treatment phase (and thus, increased cumulative light exposure). For the follow-up examination after three to six years, a subset of seven diagnostic tests was used, as shown in the Table.

The time of day that light treatment sessions occurred was randomly assigned, in morning or evening intervals either between 5:30 and 7:30 AM or 5:30 and 7:30 PM. Daily 30-minute sessions were scheduled, at an illuminance of 10,000 lux. Treatment duration was approximately two weeks, followed by a withdrawal period of approximately ten days before switching to treatment at the alternate time of day.

The lighting fixture (Ultra-Brite 10,000 system, Medic-Light, Inc., Lake Hopatcong, New Jersey) was a metal box containing fluorescent lamps (using ultraviolet-attendated, full-spectrum cool white, or triphosphor types) with a reflector and plastic diffusing screen mounted on a frame. It was set on a table top in an overhead frame at a 55-degree tilt from the horizontal, so that the light projected downward toward the face. This angular arrangement was designed to maximize illuminance while reducing glare and direct exposure to the eye, in contrast to vertical, straight-on illumination. Patients were instructed to face the apparatus but not to look into it, concentrating instead on the illuminated table surface. A wide-angle digital illuminance meter measured light intensity to be approximately 10,000 lux at the level of the eyes. Reflection of light upward from a standard

TABLE

INVENTORY OF TEST ADMINISTRATION*

	YEAR 1 (N = 17)	YEAR 2 (N = 13)	YEAR 3 (N = 12)	YEAR 4 (N = 8)	FOLLOW-UP EXAMINATION (N = 17)
Visual acuity (uncorrected and best-corrected)	Yes	Yes	Yes	Yes	Yes
Intraocular pressure	Yes	Yes	Yes	Yes	Yes
Slit-lamp biomicroscopy	Yes	Yes	Yes	Yes	Yes
Direct or indirect ophthalmoscopy	Yes	Yes	Yes	Yes	Yes
Color vision†	Yes	Yes	Yes	Yes	No
Visual field	Yes	Yes	Yes	No	No
Fundus photography	Yes	Yes	No	No	No
Side-effects checklist	No	Yes	Yes	Yes	No
Amsler grid	No	No	Yes	Yes	Yes
Ocular motility	No	No	Yes	Yes	Yes
Pupillary reactions	No	No	Yes	Yes	Yes
Contrast sensitivity	No	No	Yes	Yes	No
Stereopsis	No	No	Yes	Yes	No
Macular stress test	No	No	Yes	Yes	No
Color vision‡	No	No	Yes	Yes	No

*Yes indicates that the test was administered; no, that the test was not administered.
†American Optical or Ishihara Color Plates.
‡Farnsworth-Munsell D15 and 100 Hue.

white or black table surface did not markedly affect global illuminance.

In addition to the ocular examination, patients completed a usage-pattern questionnaire for which they retrospectively estimated the duration of light treatment per month across all years of the study.

RESULTS

DEPRESSION SCORES, WHICH WERE DETERMINED BY clinical raters without knowledge of the treatment condition (either morning or evening light or withdrawal) showed statistically significant pretreatment to posttreatment reductions. At baseline, the mean Hamilton depression scale score was 16.3 ± 4.2. After treatment it was 5.5 ± 5.5 ($P = .0001$ by two-tailed *t*-test for correlated samples). The atypical symptoms score (for hyperphagia, hypersomnia, fatigue, and the like) was 13.5 ± 4.6 at baseline; after treatment, it was reduced to 3.8 ± 4.6 ($P = .0001$). according to the rating scale criteria of Terman, Terman, and Rafferty[16] 38 (76%) of the 50 patients showed pretreatment to posttreatment score reductions of at least 50%, to scores of 7 or less on both Hamilton and atypical scales (lowest posttreatment score of morning and evening conditions). This remission rate, categorically defined, matches or surpasses that of most previous studies that have used 2,500-lux morning light with two-hour daily exposures.[2-5]

At baseline, mild and moderate myopia (mild, 1 to 5 diopters; moderate, 6 to 10 diopters; and severe, greater than 10 diopters) was observed in 22 (44%) of 50 patients. One patient had anisometropic amblyopia (−10 diopters myopia). There was one patient with peripheral retinal degeneration (lattice and paving stone), two patients with peripapillary atrophy with tilted disk, and two patients with iris nevi and choroidal nevus (previously unknown to the patients). Two patients had old chorioretinal scars that were completely asymptomatic.

Three patients showed red-green color vision deficiencies, all of which had been previously diagnosed. In one patient an idiopathic preretinal fibrosis (cellophane maculopathy) was documented by fundus photography in both pretreatment and posttreatment tests. This patient had a mild color vision defect and altered Amsler grid perception secondary to the preretinal fibrosis. Neither condition is known to be exacerbated by exposure to light.

Visual field testing did not disclose any abnormalities that would be cause for exclusion from the study. Contrast sensitivity testing throughout the spatial frequency range of 1.5 to 18 cycles per degree disclosed 20 of 40 eyes (in 12 of 20 patients) with borderline high thresholds, but none of these were considered pathologic. Stereopsis testing disclosed no sensory anomalies other than preexisting amblyopia and myopia. Previous use of potentially photosensitizing psychotropic drugs (tricyclics, phenothiazines, or lithium) was noted for 20 patients (40%), with several of them having taken more than one such drug.

Over the course of this study, two patients were excluded from entry into the study on the basis of the baseline examination, in which uveitis and glaucoma were diagnosed.

None of the patients showed any pathologic change in their eyes that could be attributed to light therapy. Best-corrected visual acuity showed no detectable change in 43 of the patients, and small improvements that were seen in seven patients were within the range of test-retest reliability. Ocular motility was normal, as were direct and indirect pupillary reactions.

All patients showed Goldmann applanation intraocular pressures lower than 22 mm Hg, with symmetric readings to within 2 mm Hg seen in more than 90% of the patients. Pretreatment and posttreatment pressure varied by less than 4 mm Hg, which is within the expected range of test-retest variability, in all but four patients, who nonetheless were normal.

Ophthalmoscopic examination (direct or indirect) demonstrated sharp borders with symmetric cup/disk ratios of the optic nerve, all of which were within normal limits. Bilateral foveal reflexes were good and retinas were normal. Two patients had pre-existing retinal scars that did not change during treatment.

With the exception of the patient with preretinal fibrosis, assessment of macular function using the Amsler grid showed no scotoma nor metamorphopsia; the patient in question also showed no change from the pretreatment test. Furthermore, for the macular stress test administered to each eye, *t*-tests showed no significant changes in mean recovery time.

The results of color vision testing were normal for all but three patients known to have red-green deficiencies. The perception of color did not change after light therapy. That these patients responded well to light therapy is of potential theoretical interest in view of possible wavelength specificity in the response of patients with seasonal affective disorder.[19,20]

Contrast sensitivity testing disclosed 14 potentially abnormal eyes, three of which showed normal results at baseline before light treatment. All these eyes bordered on normal, however, and were not considered pathologic (for example, with a selective low-frequency deficit). By contrast, nine eyes that showed high threshold at baseline were normal after treatment. Statistically, we could detect no significant pretreatment to posttreatment change (McNemar test, chi-squared = 3.0, 1 degree of freedom, not significant). Visual fields, tested by automated perimetry, remained normal after treatment, except for the one patient whose defect was consistent with a retinal scar caused by earlier cryotherapy and who showed no posttreatment change.

Stereoscopic acuity was evaluated in 20 patients before and after light treatment. The test score did not change in 12 patients. Five patients showed an improvement of one to four points, and three showed a decrease of one to two points. Thus, 17 (85%) patients examined showed improvement or no change. There were no associated ocular changes detected in any of the patients who had reduced stereopsis scores, and it was judged that these results fell within the range of test-retest variability. Because of these negative results and the indirect aspect of the measure, which infers ocular function on the basis of cortical fusion of images from the two eyes, we subsequently dropped the test of stereopsis from the screening battery.

A summary of ocular symptoms reported on the self-rating checklist is shown in Figure 1. All symptoms showed mean severity levels on a scale of one to five (one indicates absent; five, severe) of less than two (absent to mild) at both baseline and posttreatment examinations. Surprisingly, reports of photophobia decreased significantly after treatment ($P = .019$). Reports of swollen eyes and blurred vision showed trends toward reduction ($P = .058$ and .096, respectively). Several patients reported worsening of eye irritation, poor vision, photophobia, or a combination of them. Most prominent among complaints was eye irritation (reported by four [11.8%] of 34 patients). However, the complaints were not associat-

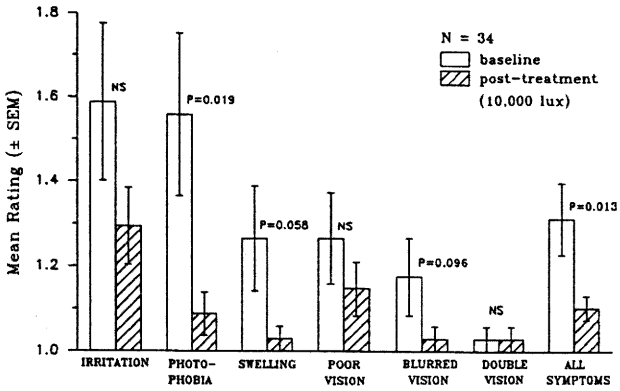

Fig. 1 (Gallin and associates). Severity of ocular symptoms (mean ± S.E.M.) as reported on the Systematic Assessment for Treatment Emergent Events[18] at baseline, that is, while depressed, and after light treatment.

ed with objective findings during ophthalmologic examinations, and the symptoms reported were always mild. Furthermore, these complaints were offset by an even larger proportion of patients (17.7%, six of 34) with reduced eye irritation after treatment. Overall, reports of ocular symptoms were significantly reduced at the posttreatment examination ($P = .013$). Whether this represents true improvement or a tendency toward fewer complaints while not depressed is unclear.

Among the 17 patients who returned for the follow-up examination, eight completed three consecutive years of fall and winter light usage, five completed four years, three completed five years, and one completed six years. On average, treatment was undertaken for 5.7 ± 2.2 months per year (range, two to nine months). In addition to the fall and winter, three patients used the light during the spring and summer months when it rained or when the sky was overcast for several days. Figure 2 shows cumulative retrospective estimates of annual hours of light exposure. There were wide differences across patients, with cumulative exposure duration averaging 194.9 ± 141.3 hours (range, 49.1 to 567.8 hours). Corresponding cumulative irradiant doses were 6.2 ± 4.5 J/cm^2 (range, 1.6 to 18.2 J/cm^2). The patient with maximum exposure received approximately 1,250 hours of light treatment over five years (40 J/cm^2), primarily because of frequent use of the apparatus as a desk lamp during the past two years.

There were no ocular abnormalities or clinically significant changes found in visual acuity, ocular motility, intraocular pressure, Amsler grid perception, and slit-lamp and fundus examinations.

DISCUSSION

THIS STUDY SYSTEMATICALLY SCREENED FOR OCULAR abnormalities in patients with seasonal affective disorder before and after bright light therapy, with follow-up after continued use for three to six years. No ocular abnormalities attributable to the treatment were found. Furthermore, although several patients reported slight increases in ocular irritation, response to the Systematic Assessment for Treatment Emergent Events questionnaire indicated a larger proportion of patients who noted reduced ocular irritation after light exposure. Other tests in the ophthalmologic examination failed to demonstrate clinically significant changes. Ocular status remained normal for all patients.

Patients with pre-existing ocular abnormalities (including cataract, glaucoma, cystic macular edema,

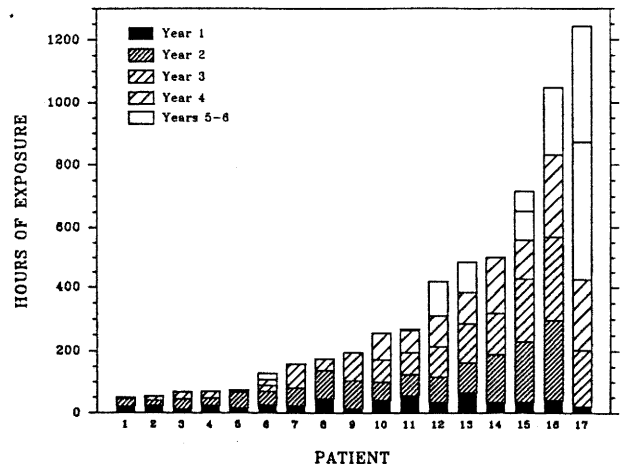

Fig. 2 (Gallin and associates). Cumulative light exposure duration (stacked histogram) for 17 patients who continued fall through winter treatments at 10,000 lux for three to six years. Durations for year 1 were determined from daily log sheets. Durations for later years were determined from patients' retrospective estimates of average weekly light exposure for each month of the year. Patient 17 did not use light treatment in year 2, but resumed it in years 3 to 6.

lattice and paving stone degeneration, early stage hypertensive retinopathy, and optic nerve head swelling) were excluded from the study on the basis of their medical history. Therefore, we cannot state whether such treatment would exacerbate the underlying condition. Current knowledge is insufficient to specify any definite ocular contraindications for bright light therapy, although we recommend that patients at potential risk undergo treatment only with ophthalmologic monitoring.

Mild to moderate myopia was found in 22 (44%) of the 50 patients, which is approximately twice the general prevalence in the United States population.[21] This finding has been confirmed in another study of patients with seasonal affective disorder, with 50% prevalence (Gorman CP, unpublished data presented at 5th Annual Meeting of the Society for Light Treatment and Biological Rhythms, June 1993). Whether myopia is linked to seasonal affective disorder, or the increased incidence reflects the particular age distribution or socioeconomic characteristics typical of these patients, is a matter for further inquiry.

The obvious hazards of exposure to ultraviolet light were minimized in this study by the use of lamps with very low ultraviolet emission levels. The SPX-35 lamp mounted in the 10,000-lux light box configuration, for example, produces less than 0.01 $\mu W/cm^2/nm$ throughout the ultraviolet range, which is approximately two orders of magnitude lower than irradiance in the visible range. For cool-white light, the 10,000-lux, 30-minute light therapy regimen provides an irradiant dose of 0.016 J/cm^2 in one session,[5] equivalent to that of the earlier 2,500-lux, two-hour regimen. It must be acknowledged that, while not subject to close supervision of an experimental protocol, patients will often receive far higher doses (for example, the maximum of 0.09 J/cm^2 per day found for Patient 17; Fig. 2). Even at such an extreme level, however, we detected no ocular change after several years of exposure.

Patients using photosensitizing medications that might lead to acute ocular or dermal reactions were excluded from this study. Such medications absorb primarily in the UVA (320 to 400 nm) and UVB (290 to 320 nm) ranges, with some extending into the visible blue-green (400 to 550 nm) range.[5] Although the light sources used were selected for minimal ultraviolet radiation, we noted localized rashes in patients using Retin-A skin cream, as well as photoreactivation of herpes simplex blisters in one patient, presumably attributable to residual ultraviolet exposure, which quickly resolved by use of a topical sunblock. Thus, additional short-wavelength filtering or use of sun blocks and ultraviolet- and blue-blocking spectacles may be an important safety precaution for patients using bright light therapy while taking photosensitizing medications.

The advisability of ophthalmologic examinations for patients undergoing bright light therapy has been debated in the literature. Vanselow and associates[12] described a study candidate for whom a pre-existing perimacular pigment epithelial scar was discovered in initial screening and who was denied light treatment. Waxler and associates[14] questioned the need for such exclusion, because the light is not known to cause or exacerbate retinopathy. They argued that because the light levels that are used for therapy are far lower than naturally occurring outdoor light, which can reach approximately 100,000 lux, routine ophthalmologic screening is not necessary. Two of us responded, however, that such examinations are needed to reduce the likelihood that unknown pre-existing ocular abnormalities would subsequently be attributed to the light.[13] Furthermore, light exacerbation of degenerative processes in the retina, especially that of age-related maculopathy, remains a topic of investigation both clinically and experimentally,[22,23] and light-induced retinal lesions have been observed both in humans[24] and animals.[25]

The argument that light therapy poses no more hazard than does normal outdoor light has often been used to downplay the potential risk. However, many individuals are normally exposed only briefly to outdoor light,[26] and the treatment procedure can be different from normal patterns of exposure to light. Furthermore, the geometric arrangement of the lighting fixture, in close proximity to the patient and with a relatively inescapable field of illumination, contrasts with outdoor exposure conditions in which head and body movement create a more varied exposure pattern. We have found several patients for whom the daily light-therapy session entails exposures greatly exceeding the spontaneous pattern either indoors or outdoors. Even though we have identified no adverse

treatment effects either during the initial year or at the three- to six-year follow-up examinations, longer-term sequelae cannot be ruled out. Cumulative photoinduced retinal changes may take decades to reach a pathologic threshold, and it may be difficult to distinguish such cases from, for example, age-related degenerative changes.

Although our exclusion criteria were strict, in light of the present results, exclusions might now be narrowed, providing access to patients with ocular abnormalities who might nonetheless benefit from light therapy without increased ocular risk. For example, patients with suspected glaucoma might receive such treatment, although patients with progressive retinal diseases, such as diabetic retinopathy, macular degeneration, or retinitis pigmentosa, would continue to be excluded. Even then, however, if a patient cannot tolerate or has not responded to antidepressant medications, then bright light treatment might be administered in conjunction with ophthalmologic monitoring. A promising alternative, at a far lower dose, is low-intensity dawn light simulation, which appears efficacious as a bedside treatment during the final hours of sleep.[27]

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REFERENCES

1. Terman M. Light treatment. In: Kryger M, Roth T, Dement W, editors. Principles and practice of sleep medicine, 2nd ed. Philadelphia: WB Saunders, 1993:1012–29.
2. Terman M, Terman JS, Quitkin FM, McGrath PJ, Stewart JW, Rafferty B. Light therapy for seasonal affective disorder: a review of efficacy. Neuropsychopharmacology 1989;2:1–22.
3. Wehr TA, Skwerer RG, Jacobsen FM, Sack DA, Rosenthal NE. Eye versus skin phototherapy of seasonal affective disorder. Am J Psychiatry 1987;144:753–7.
4. Rosenthal NE, Sack DA, Gillin JC, Lewy AJ, Goodwin FK, Davenport Y, et al. Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. Arch Gen Psychiatry 1984;41:72–80.
5. Terman JS, Terman M, Schlager D, Rafferty B, Rosofsky M, Link MJ, et al. Efficacy of brief, intense light exposure for treatment of winter depression. Psychopharmacol Bull 1990;26:3–11.
6. Terman M, Remé CE, Rafferty B, Gallin PF, Terman JS. Bright light therapy for winter depression: potential ocular effects and theoretical implications. Photochem Photobiol 1990;51:781–92.
7. Society for Light Treatment and Biological Rhythms. Consensus report on the safety of light therapy devices. Light Treatment Biol Rhythms 1991;3:48–50.
8. Remé CE, Menozzi M, Krueger H. Standards for specifying parameters of bright light stimulation for therapeutic applications: a proposal. Light Treatment Biol Rhythms 1991; 3:40–3.
9. Oren DA, Moul DE, Schwartz PJ, Alexander JR, Yamada EM, Rosenthal NE. An investigation of ophthalmic function in winter seasonal affective disorder. Depression 1993;1:29–37.
10. Lam RW, Beattie CW, Buchanan A, Mador JA. Electroretinography in seasonal affective disorder. Psychiatry Res 1992;43:55–63.
11. Lam RW, Beattie CW, Buchanan A, Remick RA, Zis AP. Low electrooculographic ratios in patients with seasonal affective disorder. Am J Psychiatry 1991;148:1526–9.
12. Vanselow W, Dennerstein L, Armstrong S, Lockie P. Retinopathy and bright light therapy [letter]. Am J Psychiatry 1991;148:1266–7.
13. Remé CE, Terman M. Does light therapy present an ocular hazard? [letter]. Am J Psychiatry 1992;149:1762–3.
14. Waxler M, James RH, Brainard GC, Moul DE, Oren DA, Rosenthal NE. Retinopathy and bright light therapy [letter]. Am J Psychiatry 1992;149:1610–1.
15. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-III-R), 3rd edition, revised. Washington, DC: American Psychiatric Press, 1987.
16. Terman M, Terman JS, Rafferty B. Experimental design and measures of success in the treatment of winter depression by bright light. Psychopharmacol Bull 1990;26:505–10.
17. Gallin PF, Remé CE, Burde RM, Rafferty B, Terman M. The Columbia-Presbyterian eye check-up for users of light treatment. New York, New York State Psychiatric Institute, 1993.
18. National Institute of Mental Health. Systematic assessment for treatment emergent effects (SAFTEE). Rockville, Maryland: National Institute of Mental Health, 1986.
19. Brainard GC, Sherry D, Skwerer RG, Waxler M, Kelly K, Rosenthal NE. Effects of different wavelengths in seasonal affective disorder. J Affect Disord 1990;20:209–16.
20. Oren DA, Brainard GC, Johnston SH, Joseph-Vanderpool JR, Sorek E, Rosenthal NE. Treatment of seasonal affective disorder with green light and red light. Am J Psychiatry 1991;148:509–11.
21. Curtin BJ, Whitmore WG. The optics of myopia. In: Tasman W, Jaeger EA, editors. Duane's clinical ophthalmology. Volume 1. Chapter 1. Philadelphia: JB Lippincott, 1993:1–10.
22. Young RW. Solar radiation and age-related macular degeneration. Surv Ophthalmol 1988;32:252–69.

23. Taylor HR, West S, Munoz B, Rosenthal FS, Bressler SB, Bressler NM. The long-term effects of visible light on the eye. Arch Ophthalmol 1992;110:99–104.
24. Hope-Ross MW, Mahon GJ, Gardiner TA, Archer DB. Ultrastructural findings in solar retinopathy. Eye 1993;7:29–33.
25. Organisciak DT, Winkler BS. Retinal light damage: practical and theoretical considerations. In: Osborne NN, Chader GJ, editors. Progress in retinal and eye research. Volume 13. Oxford: Pergamon Press, 1994:1–29.
26. Okudaira N, Kripke DF, Webster JB. Naturalistic studies of human light exposure. Am J Physiol 1983;245:R613–5.
27. Terman M, Schlager DS. Twilight therapeutics, winter depression, melatonin, and sleep. In: Montplaisir J, Godbout R, editors. Sleep and biological rhythms. Oxford: Oxford University Press, 1990:113–28.

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CONSENT FORM

Are Bright Lights and Regulated Sleep Times Effective Treatment for Depression?

Purpose and Overview

The purpose of this study is to find out whether sleeping only at regulated times and sitting in front of a bright light wearing different colored or clear goggles is effective treatment for depression. You are being asked to participate in this study because you are depressed and do not have mood swings (bipolar disorder).

Voluntary

Participation in this research study is voluntary. If you decide not to participate, or if you later decide to stop participating, or your doctor removes you from study participation for any reason, you will not lose any benefits to which you are otherwise entitled. A decision not to participate or withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute or Columbia University.

Alternatives to Participation

There are alternatives to your participating in this study. If you previously participated in another treatment study, you may be eligible for further treatment without taking part in this study. You can go to a private doctor or to a psychiatry clinic where you may receive any of the medications marketed for depression. Electroconvulsive treatment and focused psychotherapy are also accepted treatments for depression. Electrical stimulation of a nerve in the neck (called the vagus nerve) has also been approved by the FDA.

Study Procedures

In order to find out if you can be treated in this study, you will receive a complete psychiatric evaluation by a study psychiatrist. If the study psychiatrist decides you can participate, you will be given this consent form to read. If you then agree to participate and are satisfied that your questions have been answered, you will then sign the consent form. A member of the research team will then complete research rating forms, you will complete self-report ratings, about 15 cc (approximately a tablespoon) of blood will be drawn for routine laboratory testing (for example, to make sure your kidneys and liver are healthy), a doctor will perform a physical examination (for example, listen to your heart and lungs, look into your eyes) and you will provide a urine specimen (to be checked for kidney function, pregnancy if you are a woman of child-bearing age, and street drugs such as heroin and cocaine). These tests will determine if you have a medical disorder such as low thyroid function that might be the cause of your depression or that should be treated prior to your entry into this. If you have one of these medical problems, your doctor will discuss this with you at the first visit after it is found, or telephone you if it requires quicker attention.

You have been offered participation in this study because you are depressed. Once you have agreed and signed the study consent form, you will be asked to answer questions about your mood, prior treatment, the times of the day you like to do things, a variety of common psychiatric symptoms and your interest and functioning in several life circumstances, like work and family. You will wear an activity monitor (which looks like a wrist watch) and keep a log of your sleep, mood and energy for about seven weeks. After 1-2 weeks (you can choose to wait up to 30 days before re-evaluation), you will be re-evaluated. If you remain significantly depressed at this re-evaluation, and remain agreeable,

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you will begin sleeping only at assigned times (regulated sleep therapy) plus sitting in front of bright lights wearing goggles. The timing of your allowed sleep and whether the goggles you wear will be clear or amber will be determined randomly (as if by a flip of a coin). Whatever timing and goggles you are assigned you will continue for the next six weeks, initially with daily telephone evaluations and from the end of week 1 through the end of week 6 weekly in person. At the time you are randomized and again at weeks 1 and 6 visits you will also be evaluated by a rater who does not know whether you have begun treatment or what treatment you may be receiving. It is important that you not let on whether you have begun treatment, or, if you have, what that treatment has been.

Light and Regulated Sleep Therapy

Treatment will be with bright lights and regulated sleep times. To help us determine whether this approach is effective treatment and which times for sleep and bright lights and how best to use the bright lights, by chance different patients will receive different instructions. All will be given specific times they are allowed to sleep and specific times to sit in front of the bright lights. Time sitting in front of the bright lights will begin at 30 minutes, but if you have trouble tolerating the light your doctor may tell you to decrease this time shorter (to as little as 10 minutes), and if you tolerate the light but remain depressed your doctor may tell you to increase the time (up to 60 minutes). For some the specific sleep times may include a 48 hour period during which they are not allow to sleep as long as 42 hours. You will be provided goggles both to wear in the evening during saliva collection for melatonin and when sitting in front of the bright lights. Some goggles will be clear and some will be amber. Prior to being told your specific times for allowed sleep and use of the bright lights, you will complete the Morningness-Eveningness Questionnaire; your answers will suggest where your biologic clock is currently set and partially determine the times you will be allowed to sleep and instructed to use the bright lights. You will also report the time you want to be sleeping which will also determine the sleep instructions and timing of your bright light use.

Risks and Inconveniences

General. A general risk is that you may remain depressed. It has not been determined whether the combination of wake therapy, light therapy and regular allowed sleep is effective for your disorder. Second, suicide is a risk in patients who are depressed. Patients with bipolar disorder may become manic. These risks will be minimized by: (a) exclusion of patients known to have bipolar disorder; (b) not participating in the study if you or your doctor consider you to be at significant risk to harm yourself or in need of hospitalization; (c) discontinuing study participation should you become significantly worse or significantly suicidal; (d) offer of hospitalization in the case of significant worsening/suicidal thoughts/behavior; (e) weekly visits and 24 hour phone availability of an experienced research psychiatrist.

Remaining awake for long periods. The major risk of remaining awake for long periods is mania. This possibility will be minimized by only including patients without a history of mania or hypomania (a period of being “high” without being manic), constant availability of access to a research psychiatrist by telephone. An additional risk is being drowsy at times alertness is required, such as driving or operating heavy machinery. Therefore, if assigned extended periods of wakefulness or if you feel sleepy, you should not drive or operate heavy machinery.

Light Therapy. Patients may become over-stimulated, and those with bipolar disorder may become manic. As this study will not include patients known to have bipolar disorder, this risk seems minimal, but likely not zero, especially since not all patients with bipolar disorder are known to have it. More commonly, over-stimulation is described as “like too much coffee” and can be eliminated by decreasing

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bright light exposure, either by decreasing the time in front of the light or increasing the distance from the light, or both. Occasionally, light exposure may also cause headache, nausea or eye irritation. Again, these will be counteracted by increasing the distance for the light, decreasing the time you sit at the light or both. Long-term research studies have found that light therapy is safe for the retina of the eye. Nevertheless, **as a precaution, we will examine your retina to see whether there are already signs of damage, and you will not receive light therapy if you have retinal conditions such as retinitis pigmentosa or macular degeneration**. As the lights used are similar to early morning light in intensity but without any ultraviolet radiation, they may be considered safer than going outside on a sunny day.

Additional Risks

Participation in this study may involve risks that we currently do not know. Some discomfort may be associated with the drawing of blood samples. A maximum of 1 tablespoon of blood will be taken unless there is a medical reason to obtain extra blood. There is a minor risk of bleeding, bruising, or infection at the site of the needle insertion. With any treatment there is the risk that the treatment may not help and the depression might become worse. Also, if a treatment is effective or partially effective there is the risk of worsening of symptoms if the treatment is stopped or the dose is reduced.

Benefits

Your depression may improve.

You will be informed if significant new information becomes known about treatment of depression or about the treatments used in this study, especially if such information might affect the willingness of some subjects to continue their participation.

Confidentiality

All study information is kept in locked cabinets at the Depression Evaluation service at the New York State Psychiatric Institute or in a secure HIPAA compliant computer accessable only by study staff. Records will be kept confidential to the extent permitted by law. Your name and other personal identifying information will be stored in an electronically secure database at New York Psychiatric Institute. Any publications will present only group data and not include information that could identify you. Records will be available to research staff, and to Federal, State and Institutional regulatory personnel (who may review records as part of routine audits). Also, you should be aware that there are legal advocacy organizations that have the authority under New York State law to access otherwise confidential subject records, though they cannot re-disclose this information without the subject's consent. Electronically stored/transmitted data will be password protected with access only to study personnel.

There are limits to confidentiality. For example:

If your answers indicate a serious problem that may jeopardize your safety or health, then the researchers will contact your physician or emergency personnel as seems appropriate to your well-being. Also, suspected or known neglect or sexual or physical abuse of a child, or threatened violence to self or others will be reported to the appropriate authorities.

Study Compensation

Tests that are part of the research study are provided free of charge, and neither

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you nor your insurance company or other third party payer will be billed for these, including hospitalization, if at the New York State Psychiatric Institute. Any tests not required by the research will be paid for by you or your insurance company. In addition, following 6 weeks, regardless of initial treatment assignment, all participants will continue to be followed and complete monthly ratings for an additional six months; during this post-6 week six months, the cost of any prescription, whether for medication or light box will be your responsibility. After this six month post-12 week treatment period, should you and your doctor determine that further psychiatric treatment is indicated, your doctor will help you find an appropriate treater.

In Case of Injury

Federal regulations require that we inform participants about our institution's policy with regard to compensation and payment for treatment of research-related injuries. In case of injury, New York State Psychiatric Institute will provide short term emergency medical treatment, which has been determined to be necessary by New York State Psychiatric Institute's doctors. In addition, we will provide assistance in arranging follow up care in such instances. New York State Psychiatric Institute and Research Foundation for Mental Hygiene do not provide compensation or payment for treatment of research related injuries. However, you should be aware that you do not give up your legal right to seek such compensation through the court by participating in this research.

Questions

Your study doctor will answer any questions you may have now or in the future to the best of his/her ability. If you should have additional questions, you can contact the Principal Investigator, Jonathan W. Stewart, M.D., (646-774-8070).

If you have any questions about your rights as a research participant, want to provide feedback, or have a complaint, you may call the NYSPI Institutional Review Board (IRB). (An IRB is a committee that protects the rights of participants in research studies). You may call the IRB Main Office at (646)774-7155 during regular office hours. You will be notified of significant new findings that may relate to your willingness to continue to participate.

Women of Child-bearing Age

While these treatments are considered to be fairly safe during pregnancy, the study excludes women who are pregnant. Therefore, a pregnancy test will be performed and if it is positive, you cannot participate. Also, we ask that you use reasonable precautions not to become pregnant while participating and if you choose to be treated with medication after the initial six weeks of treatment. Because the safety of missing a night of sleep, keeping specific sleep schedules or bright lights are unknown in pregnancy, you should not be pregnant or become pregnant while using these treatments. Should you become pregnant, you should immediately contact a study psychiatrist and discontinue any treatment until informed otherwise by a study psychiatrist. After the six weeks research treatment, you will again be asked to produce a urine specimen which will be tested for pregnancy. If do not produce a urine at the six week time point, continuing treatment will not be denied.

By signing this form, you are indicating that you have discussed this research study and consent form with an investigator, and he/she has answered all of your questions about the study to the best of his/her ability. Your study doctor will answer to the best of his/her ability any questions you may have about the study, your psychiatric condition or your reaction to the study procedures. If you have any further questions, you may call Jonathan W. Stewart, M.D., the Principal Investigator of this study, at 646-774-8070.

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You will receive a copy of this consent form to keep.

Documentation of Consent

I voluntarily agree to participate in the research study described above.

Print name: _____

Signed: _____

Date: _____

I have discussed the proposed research with this participant including the risks, benefits, and alternatives to participation (including the alternative of not participating in the research). The participant has had an opportunity to ask questions and in my opinion is capable of freely consenting to participate in this research.

Print name: _____

Person Designated to Obtain Consent

Signed: _____

Date: _____

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Cover Sheet for "Are Bright Lights and Regulated Sleep Times Effective Treatment for Depression?" (IRB #7361)

Overview: This outline is a guide for you to use while considering whether to participate in this research study. The consent that follows includes much more information about the study and its risks, which you will need to make a decision. Please read this outline and the consent carefully, and only sign it if you are comfortable doing so.

- You are being asked to participate in a research treatment study because you are depressed.
- Your treatment will involve keeping specified sleep times and sitting in front of bright lights wearing tinted or untinted goggles..

Type of treatment: The treatment portion of this study will last up 6 weeks followed by six month during which helpful treatment can be continued or other treatment can be tried. Prior to treatment, blood and urine tests as well as a heart test and physical examination will determine whether you are healthy and not pregnant (if you are a fertile female). Treatment will be with bright lights and specific changes to your sleep, partially determined by how you answer questions about when you do or like to do things and partially by when you would like to be asleep. The specific timing and manipulation of allowed sleep, bright lights and use of goggles will be randomly (like flipping a coin) determined. In order to manipulate your sleep, varying amounts of time remaining awake between allowed sleep will be required, for some patients required wake time might reach as long as 42 hours on a single occasion. During the first week you will complete rating forms and speak with a study doctor by telephone daily and then weekly for the remainder of 6 weeks. Thereafter, your study doctor will continue to treat you for an additional six months during which there will be monthly determinations of how you are doing. During this time, while your study doctor will manage your treatment, you or your insurance will pay for any medicine or other treatment such as a light box. After this six months, if psychiatric treatment is still needed, your doctor will help you find further treatment.

Alternatives to participation: You do not have to participate in this research study to receive treatment for depression. If you decide not to participate, the doctor who evaluated you will help you find an alternative.

Risks: There are risks and discomforts associated with participating in this study (please read the "Risks" section of the detailed consent for a complete listing and explanation of risks). These include:

- Your depression may not improve
- Bright light can over-stimulate some people and can cause patients with bipolar disorder to switch from being depressed to being "high" (that is, hypomanic or manic)
- Missing sleep can also over-stimulate and induce switching to a "high" mood

Compensation: None

Voluntary Participation: Participation in this study is entirely voluntary. You do not have to participate if you do not want to and can stop participating at any time.

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New York State Psychiatric Institute (NYSPI)
Authorization to Use or Disclose Health Information during a Research Study

Protocol Number: 7361 **Principal Investigator:** Jonathan W. Stewart, M.D.

Name of Study: Are Bright Lights and Regulated Sleep Times Effective Treatment for Depression?

Before researchers can use or share any identifiable health information ("Health Information") about you as part of the above study (the "Research"), the New York State Psychiatric Institute (NYSPI) is required to obtain your authorization. You agree to allow the following individuals and entities to use and disclose Health Information about you as described below:

- New York State Psychiatric Institute (NYSPI), your doctors and other health care providers, if any, and
- The Principal Investigator and his/her staff (together "Researchers"). Researchers may include staff of NYSPI, the New York State Office of Mental Health (OMH), Research Foundation for Mental Hygiene, Inc. (RFMH), and Columbia University (CU), provided such staff is a part of the study, and
- Providers of services for the Research at CU, NYSPI and/or RFMH, such as MRI or PET, or Central Reference Laboratories (NKI), if indicated in the consent form**.**

1. The Health Information that may be used and/or disclosed for this Research includes:

☑ All information collected during the Research as told to you in the Informed Consent Form.
☐ Health Information in your clinical research record which includes the results of physical exams, medical and psychiatric history, laboratory or diagnostic tests, or Health Information relating to a particular condition that is related to the Research.
☐ Additional information may include:

2. **The Health Information listed above may be disclosed to:**
☑ Researchers and their staff at the following organizations involved with this Research:
Nathan Kline Institute (where the laboratory specimens war analyzed)

☐ The Sponsor of the Research,

and its agents and contractors (together, "Sponsor"); and
☑ Representatives of regulatory and government agencies, institutional review boards, representatives of the Researchers and their institutions to the level needed to carry out their responsibilities related to the conduct of the research.
☐ Private laboratories and other persons and organizations that analyze your health information in connection with this study

☐ Other (family members or significant others, study buddies, outside agencies etc.) Specify:

3. By giving permission to release your Health Information as described above, you understand that your Health Information may be disclosed to individuals or entities which are not required to comply with the federal and state privacy laws which govern the use and disclosure of personal Health Information by NYSPI. This means that once your Health

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Information has been disclosed to a third party which does not have to follow these laws (e.g., a drug company or the Sponsor of the Research), it may no longer be protected under the HIPAA or NYS Mental Hygiene Law requirements but is subject to the terms of the consent form and may be subject to other state or federal privacy laws or regulations.

4. Please note that:

- You do not have to sign this Authorization form, but if you do not, you may not be able to participate in the study or receive study related care. You may change your mind at any time and for any reason. If you do so, you may no longer be allowed to participate in the study. If you withdraw this Authorization the research staff and the Sponsor, if this is sponsored research, may still use or disclose Health Information containing identifying information they already have collected about you as needed to maintain the reliability of the research. Any request to withdraw this Authorization must be made in writing to (enter name and contact information below):

  Jonathan W. Stewart, M.D.
  1051 Riverside Drive
  New York, New York 10032

- While the Research is going on, you may not be allowed to review the Health Information in your clinical research record that has been created or collected by NYSPI. When this research has been completed you may be allowed to see this information. If it is needed for your care, your Health Information will be given to you or your Doctor.

5. This Authorization does not have an end date.

6. You will be given a copy of this form after you have signed it.

I agree to the use and disclosure of Health Information about me as described above:

_____ _____

Signature of Participant/ Legal Representative Date

_____

Printed Name of Participant

_____

Relationship of Legal Representative to Participant (if applicable)

We also ask you or your legal representative to initial the statements below:

☐ **I have received a copy of the NYSPI/OMH Notice of Privacy Practices.**

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PATIENT ADHERENCE FORM

Patient ID _____

Date _____

Visit _____

---

1) Did patient complete self-report forms?

a) all

b) not all, but more than half

c) half or less

d) none

2) Did patient keep his/her appointment?

a) yes

b) if daily phone visits during interval, patient completed most

c) if daily phone visits during interval, patient completed half or fewer

d) no

3) Did patient follow assigned sleep times?

a) all the time

b) most of the time

c) half or less

d) not at all

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4) Did patient use bright lights at the assigned time?

a) all the time

b) most of the time

c) half or less

d) not at all

5) Did patient use bright lights for the assigned amount of time?

a) every use

b) most uses

c) half or less of the time

d) patient either did not use bright lights or rarely if at all at the right time

6) Did patient wear goggles at the assigned times?

a) every use

b) most uses

c) half or less of the time

d) patient either did not use goggles or rarely if at all

7) Did patient collect saliva at the assigned times?

a) patient collected saliva at all the assigned times

b) patient collected saliva at most of the assigned times

c) patient collected saliva at half or fewer of the assigned itmes

d) patient did not collect saliva or collected at the wrong times

e) no saliva was to be collected during this interval

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8) Did patient wear amber goggles during saliva collection?

a) always

b) during most of the collections

c) during half or less of the collections

d) patient did not wear goggles or wore the wrong goggles during saliva collections

e) no saliva was to be collected during this interval

Key

a = 0

b = 1

c = 2

d = 3

e = 0

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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.

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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

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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

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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?

- ❑ 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

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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: _____