Wake and light therapy for moderate-to-severe depression – a randomized controlled trial

Kragh M, Martiny K, Videbech P, Møller DN, Wilhborg CS, Lindhardt T, Larsen ER. Wake and light therapy for moderate-to-severe depression – a randomized controlled trial

Objective: To examine the efficacy of using wake and light therapy as a supplement to standard treatment of hospitalized patients with depression.

Method: In this randomized, controlled study, 64 patients with moderate-to-severe depression were allocated to standard treatment or to the intervention, which additionally consisted of three wake therapy sessions in one week, 30-min daily light treatment and sleep time stabilization over the entire nine-week study period.

Results: Patients in the wake therapy group had a significant decrease in depressive symptoms in week one as measured by HAM-D17, 17.39 (CI 15.6–19.2) vs. 20.19 (CI 18.3–22.09) (P = 0.04), whereas no statistically significant differences were found between the groups in weeks two to nine. At week nine, the wake therapy group had a significantly larger increase in general self-efficacy (P = 0.001), and waking up during nights was a significantly less frequent problem (1.9 times vs. 3.2) (P = 0.0008). In most weeks, significantly fewer patients in the wake therapy group slept during the daytime, and if they slept, their naps were shorter (week three: 66 min vs. 117 min P = 0.02).

Conclusion: The antidepressant effect initially achieved could not be maintained during the nine-week study period. However, sleep and general self-efficacy improved.

Significant outcomes

- The combined chronotherapeutic intervention had a fast-acting antidepressive effect measured by HAM-D17.
- In our population of treatment-resistant and highly medicated in-patients, the antidepressant effect of the intervention could not be maintained.
- Patients in the wake therapy group achieved higher general self-efficacy and, better sleep maintenance, and fewer of them slept during the daytime.

Limitations

- Drop-out rate from the study was relatively high.
- All sleep data were self-reported – additional objective measures would have been desirable.
- In both groups, type of medication and dose could be changed in the study period.

Introduction

There is a need for alternative, fast-acting and safe treatments for depression – both in combination with antidepressants and without. The treatment goal is to eliminate symptoms and re-establish psychosocial functioning (1). However, there are
several challenges to achieving this for patients hospitalized with depression. The therapeutic effect of antidepressants is often delayed, and for those patients who achieve remission, it takes 5–7 weeks on average (2). Furthermore, antidepressants have side-effects leading to discontinuation of treatment (3). Treatment resistance is another challenge, as despite multiple treatment attempts, up to 30% of patients fail to achieve remission (2). Psychotherapy is not always possible in the acute phase of depression and not recommended as monotherapy for patients with severe suicidality or psychotic symptoms (1). Electroconvulsive therapy is a fast-acting and effective treatment (4). However, due to the risk of cognitive side-effects, it is primarily recommended for severe depression (5).

Chronotherapeutic interventions may be useful adjunctive treatments. They are defined as a controlled exposure to environmental stimuli acting on biological rhythms (6). Sleep deprivation (wake therapy) where patients have prolonged times of wakefulness was the first chronotherapeutic intervention used in clinical practice and was demonstrated as an effective and fast-acting treatment for depression (7–9). However, the antidepressant effect was often brief, as most patients (80%) relapsed after the following recovery sleep (8). Combining wake therapy with pharmacotherapy seemed to sustain the effect (9–11). Additional combination with light therapy (12, 13) and sleep-phase advance therapy (14–17) or sleep time stabilization (18) further sustained the effect. The reported adverse effects of chronotherapeutic interventions are relatively few (6). However, for bipolar patients, there is a risk of switching into mania; the risk is approximately 6% for patients treated sufficiently with lithium (19). Furthermore, there is a risk of panic anxiety. In a recent study, 11% of the patients developed anxiety attacks related to wake therapy (18).

In pilot studies using combined chronotherapeutic interventions, a significant reduction in the patients' depressive symptoms was seen. The follow-up period spanned from 4 to 20 days (14–16). However, there was a lack of control groups in these studies. Two randomized controlled trials (RCTs) compared the efficacy of a combined chronotherapeutic intervention with pharmaceutical treatment (17) and exercise (18). Both studies showed a significantly larger reduction in depressive symptoms for patients in the combined chronotherapeutic groups. The follow-up periods in the studies were 7 weeks (17) and 9 weeks (18) and a further 20 weeks (20). However, the results are not unambiguous; a recent RCT with 62 juvenile in-patients with moderate-to-severe depressive symptoms found no benefits of adding wake therapy to light therapy. However, in that study, the majority of the patients (66%) did not receive any antidepressants (21).

In most studies, the effect of the combined chronotherapeutic interventions are described by a range of rating scales measuring degree of depression, level of functioning and quality of life (17, 18). However, because of the recurrent nature of depression, measures of the patient’s ability to cope with depressive symptoms could also be relevant. When describing coping, attention not only to patient’s skills is required but also to self-efficacy (22). Self-efficacy can be defined as a person’s judgement of their capability to accomplish a certain level of performance (23). Studies have shown that low depression coping self-efficacy was associated with reduced improvement in depressive symptoms (22, 24). In studies using a general self-efficacy scale, a similar association between low self-efficacy and depressive symptoms was found (25, 26). Self-efficacy may increase by performing a task successfully (23). Therefore, we decided to include general self-efficacy as an outcome measure as we hypothesized that it might increase after the chronotherapeutic intervention.

Previous combined chronotherapeutic studies included patients with unipolar (18) as well as bipolar depression (17). However, the patients in the studies were mainly out-patients admitted during the intervention and then discharged. The effect of combined chronotherapeutic interventions for hospitalized patients with depression is more sparsely described.

**Aim of the study**

The aim of the study was to examine the efficacy of a chronotherapeutic intervention combining wake and light therapy with the standard treatment of hospitalized patients with moderate-to-severe depression.

**Methods**

**Study design**

This randomized controlled study recruited patients from four wards at Aarhus University Hospital, Risskov, between February 2014 and May 2016. The inclusion criteria were as follows: a diagnosis of moderate-to-severe depression according to ICD10, a score of at least 18 on the Hamilton Depression Rating Scale, 17-item version (HAM-D17) (27), age 18–75, ability to speak and understand Danish and participation in adequate...
mood stabilizing therapy for at least one month at study entrance (if bipolar depression). Exclusion criteria were as follows: severe suicidal ideation (a score of 3 or above on the HAM-D17), psychic or somatic anxiety (a score of 3 or above on the HAM-D17), borderline personality disorder according to ICD10, drug or alcohol abuse, psychotic disorder, epilepsy, eye disorders, undergoing electroconvulsive therapy (ECT) and pregnancy. Patients from the affiliated out-patient clinic fulfilling the inclusion criteria but not the exclusion criteria were allowed to participate in the study and were offered admission for 2 weeks at participation. The possibility of including patients from the out-patient clinic was initiated due to slow recruitment of in-patients.

Procedures

The study follows the Consort criteria for reporting (28). In the recruitment period, all admitted patients were screened for eligibility. Patients meeting the study criteria were presented to the study by a project nurse. Patients from the out-patient clinic received the first information by the referring physician. Thereafter, both groups received further information about the project, orally and in writing. Informed consent was obtained and baseline data collected. The study period was 9 weeks, and, as a minimum, all patients were admitted for the first 9 days. Times of discharge were individual and decided by patients’ physicians. The patients from the out-patient clinic were discharged after 2 weeks.

Control group

The patients in the control group received the standard treatment. This involved individual pharmacologic treatment, milieu therapy, exercise, psychoeducation and in a few cases psychotherapy. The patients kept a sleep diary for the duration of the study in which they described their sleep onset, sleep offset, daytime sleep and sleep quality. At the weekly assessments, patients had supportive conversations with the project nurses focusing on individual themes preoccupying them and avoiding any psychoeducation on sleep.

Intervention group

In addition to the standard treatment, the intervention consisted of the following:

i) Wake therapy: Patients stayed awake for a total of 36 h three times during the first week of the study on Sunday, Tuesday and Thursday nights with recovery nights in-between, allowing them to sleep for 12 h. On the Monday, Wednesday and Friday, they were allowed to go to bed at 7 pm. They were encouraged to stay in the ward’s common room and to participate in as many activities as possible during the wake therapies. They could do puzzles, draw, play games, surf the Internet, perform physical activities or watch TV and movies. During the daytime, patients could go to the fitness centre and take long walks. At night, physical activities were limited to walks in the ward or in the atrium, or rides on the exercise bicycle. During the no-sleep nights, the patients were encouraged to stay in the wards’ living room or in a well-lit conference room, where different activities, snacks and drinks were available for the patients. Some patients stayed awake two and two together, others did it by themselves. However, the night shift staffs were instructed to check on them every half hour or hour depending of the patients’ need for support. If the patient and/or the staff had a concern about adherence to the protocol, the patient was accompanied by a medical student who helped to stay awake during the night. The project nurses had daily assessments with the patient during the first 9 days of the study.

ii) Daily light treatment: This consisted of 30 min every day of the entire 9-week project period using a daylight lamp with 10 000 lux white light (Uplift Technologies Inc, Dartmouth, NS, Canada). The patients were instructed to keep a 40 cm distance from the screen, and not to constantly stare into the lamp but glance at the screen a couple of times every minute. The dimension of the screen was 33.7 cm × 40.6 cm (13.25 in × 16 in). Timing of light therapy was based on the Morningness-eveningness questionnaire score (MEQ) (29), which was used to calculate the optimal timing for morning light therapy as advised by Terman and Terman (30). Depending on chronotype, patients started light therapy between 6 am (for morning types) and 8 am (for evening types). On recovery nights, the time for light therapy could be postponed until 8 am for all patients regardless of chronotype. The patients started light therapy the morning after the first wake therapy and over the following 9 weeks. After discharge, patients received light therapy at home.

iii) Sleep time stabilization: Patients kept a sleep diary for 9 weeks describing sleep onset, sleep offset, daytime sleep and sleep quality.
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In the weekly assessments with the project nurse, the focus was on psychoeducation regarding good sleep hygiene and maintaining a stable diurnal rhythm. The psychoeducation was based on the records in the diaries. The patients were requested to go to bed before midnight and to get up before 8 am, and to avoid sleep during daytime. If necessary, they could take a 30-min power nap in the afternoon.

Assessment

Each patient’s physician made the diagnostic assessment, and patients were included in the study based on the recorded diagnosis in their medical file. For each patient, sociodemographic variables were obtained at baseline. The severity of depression was assessed using the interview-based 17-item Hamilton Depression Rating Scale (27). Five trained assessors, who regularly participated in co-ratings, performed the Hamilton ratings and the other assessments. The Social and Occupational Functional Assessment Scale (GAF) (31) and Bech-Rafaelsen Mania Scale (MAS) (32) were also used. Additionally, to calculate a score of treatment resistance, we used the Maudsley Staging Method (33), which was based on episode duration, baseline symptom severity and treatment failure. For patient-reported outcome measures, we used the Major Depression Inventory (MDI) (34), the World Health Organization (WHO)-5 Well-Being Index (WHO-5) (35), Morningness-Eveningness Questionnaire (29) and the General Self-Efficacy Scale (36), a 10-item psychometric scale designed to assess optimistic self-beliefs in coping with a variety of demands in life. The range is from 10 to 40 points.

Outcomes

Primary outcome criteria were the response and remission rate in week 2. Response was defined as a 50% reduction or more from baseline score on the HAM-D17. Remission was defined as a score of <8 in HAM-D17. Secondary outcomes were the length of admission and the percentage of patients with response and remission in week 9 as well as the percentage of patients excluded due to the initiation of ECT. Additional secondary outcomes were HAM-D6, GAF, MDI, WHO-5, General Self-Efficacy and sleeping variables such as sleep onset, sleep offset, sleep duration, sleep quality, percentage of patients sleeping during daytime and length of naps.

Randomization

The patients were randomized to the two groups in a 1:1 ratio using the following method: sealed, opaque, sequentially numbered envelopes with block randomization in varying block size (37). A project nurse opened the envelopes and informed the patients about their allocation.

Sample size

Response rates after two weeks were expected to be 41% in the intervention group and 13% in the control group (18). A power analysis based on these rates showed that if α = 0.05 and β = 0.80, 37, patients should be included in each group, 74 in total.

Blinding

Due to the nature of the intervention, the patients, project nurses and medical staff in the two wards involved could not be blinded. However, the assessors for weekly HAM-D17 assessments were blinded to patient allocations. Prior to every assessment, the patients were reminded that they should not reveal their allocation. The assessment in the first week of the study was not always blinded, as the allocation of the patient was sometimes visible for the assessor, due to the profound tiredness of the patients in the intervention group.

Statistical methods

Sociodemographic variables were compared using two-sample Mann-Whitney-Wilcoxon test or Fisher’s exact test. In the drop-out analysis, the same methods were used. Treatment effect (response and remission) between groups were analysed with Fisher’s exact test. An 'intention-to-treat' analysis principle was applied. The outcome variables were measured weekly or daily for each patient for 9 weeks, and the data were analysed using repeated-measures ANOVA, or precisely using a mixed model by adjusting for gender, age and degree of resistance. The correlation between MEQ score and HAM-D17 was tested in a linear regression analysis including the variables HAM-D17, period and baseline MEQ score. Analysis was performed using STATA software version 13. The level of statistical significance was set at 5%.

Ethics

The study was carried out according to the Helsinki Declaration. The Danish Central Region
Committee of Health Research Ethics (1-10-72-254-13) and the Danish Data Protection Agency (1-16-02-209-13) have approved the study. Furthermore, the study was registered at Clinical Trials.gov (NCT02047968).

Results

Patient flow

In total, 2,335 admissions were screened between February 2014 and May 2016, and 163 patients fulfilled the inclusion and exclusion criteria. They were informed about the study, and 99 declined to participate. Common reasons for declining were lack of motivation or fear of prolonged hospitalization. In total, 64 patients were included in the study with 32 randomized to the wake therapy group and 32 to the control group. Twenty-four patients were excluded or lost to follow-up in the study period of whom 10 were in the wake therapy group (n = 10) and 14 in the control group (n = 14). Reasons for drop-out were referral to ECT or because patients were not able to stay in the study for various reasons (Fig. 1). Five patients from the out-patient clinic were included in the study. Of those, two were randomized to the wake therapy group and both completed the 9-week study period. However, all three patients randomized to the control group withdrew from the study within the first few days.

Table 1 shows the sociodemographic variables, somatic conditions, depression state, self-efficacy and social function. We found no significant differences except smoking status. The majority of the patients suffered from unipolar depression (n = 29) in the wake therapy group and (n = 27) in the control group. All patients had some degree of treatment resistance, 27 patients to a mild degree (score 3–6) and 31 to a moderate degree (score 7–10), and six had severe treatment resistance (score 11–15). The mean score was 7.05 (SD = 2.2). Except for smoking status (data not presented), patients who completed the study and those who were excluded or lost to follow-up were not significantly different at baseline regarding the variables shown in Table 1. At drop-out, HAM-D17 was 19.4 in the wake therapy group and 20.1 in the control group (P = 0.71). Table 2 shows the mean daily dosages of psychoactive medications by treatment group.

Clinical outcome measures

Post hoc analysis showed that response rates were higher in the wake therapy group than in the control group in week one, 9.4% vs. 0% (P = 0.08); eight, 21.9% vs. 15.6% (P = 0.64); and nine, 34.4% vs. 18.75% (P = 0.16), although the differences were non-significant (NS). In weeks three, four, five, six and seven, the response rates in the two groups were similar or marginally higher in the control group (NS). The remission rates were low in both groups, and no statistically significant differences between the groups were found. In the wake therapy group, three patients (9%) were excluded because they started ECT within the 9-week study period. In the control group, the number starting ECT was six (18%) (P = 0.13).

Median length of admission in the wake therapy group was 48 days (range 15–198) and in the control group 30 days (range 15–141) (P = 0.15). From study entry and until discharge or end of study period, the median length was 36 days (range 9–63) in the wake therapy group and 21 days (range 3–63) in the control group (P = 0.09). The five out-patients were excluded in this analysis.

Statistically significant reductions in HAM-D17 from baseline to week nine were seen in both groups. The improvement in week one for the wake therapy group was significantly higher than that in the control group measured on HAM-D17 scale, 17.39 (CI 15.6–19.2) vs. 20.19 (CI 18.3–22.09) (P = 0.04), whereas no significant difference was found between the groups in weeks two to nine (Fig. 2). Using the HAM-D17 scale as measurement tool, no significant differences between the groups were found. At baseline, the wake therapy group had a mean score on the HAM-D17 scale of 11.2 (CI 10.2–12.1) vs. 10.9 (CI 9.9–11.8) (P = 0.68) in the control group. In week one, the scores were 8.5 (CI 7.5–9.5) vs. 9.2 (8.2–10.2) (P = 0.36); in week two, 9.1 (8.1–10.1) vs. 8.8 (7.8–9.2) (P = 0.19); and in week nine, 6.5 (5.4–7.6) vs. 6.3 (5.0–7.5) (P = 0.8). No statistically significant differences between groups were found in the estimated post hoc analysis on the WHO-5 and MDI scale. In both groups, increases in WHO-5 were seen. The score in the wake therapy group in week zero was 14.4 (CI 8.7–19.7) and in week nine 33.99 (CI 27.4–40.5). In the control group, the score was 15.5 (CI 9.9–21.5) and 35.18 (27.8–42.5). The MDI score decreased in both groups from week zero to week nine. In the wake therapy group, the score in week zero was 38.55 (CI 35.52–41.56) and in week nine 22.94 (CI 19.41–26.46). In the control group, the score was 37.48 (CI 34.45–40.51) in week zero and 21.54 (CI 17.61–25.46) in week nine.

Mean general self-efficacy in the wake therapy group was 17.3 (SD 5.5) at baseline and estimated to be 22.2 (CI 19.8–24.9) at week nine, and in the control group, 17.4 (SD 4.8) and 18.8 (CI 16.5–
21.5). There was a significantly higher increase in general self-efficacy score from baseline to week nine in the wake therapy group compared to the control group ($P = 0.001$). The mean GAF score increased in both groups from baseline to week nine; in the wake therapy group, it increased from 57.1 (SD 10.2) to estimated 60 (CI 56.6–63.5) and in the control group from 57.9 (SD 10.1) to 63.6 (CI 60–67). No significant difference between the groups was seen.

Estimated mean sleep onset in the wake therapy group was 20:32 pm (CI 20:10–20:53) in week one and 23.59 (CI 23:35–00:25) in week nine. In the control group, it was 00:04 (CI 23:53–00:25) and 23:40 (CI 23:11–00:08). Between groups, the mean sleep onset was significantly different in week one ($P = 0.0001$), whereas no significant differences were found in weeks two to nine. Estimated mean sleep offset in the wake therapy group was 07:30 am (CI 07:01–08:00) in week one and 07:24 (CI 06:56–07:57) in week nine. In the control group, it was 07:25 (CI 06:51–07:58) and 07:53 (CI 07:17–08:26). No significant differences were found between the groups in any week. The estimated highest mean sleep quality, on a 0–10 scale, was found in the wake therapy group in week one: 6.8 (CI 6.3–7.3). In this week, the sleep quality in the control group was significantly lower: 5.4 (CI 4.9–5.8) ($P = 0.0001$). In weeks two to nine, no significant differences in mean sleep quality were seen.
Table 1. Baseline characteristics by treatment groups (n = 64)

<table>
<thead>
<tr>
<th>Sociodemographics</th>
<th>Wake therapy</th>
<th>Control group</th>
</tr>
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<tbody>
<tr>
<td>Age, years, mean (SD) [range]</td>
<td>38.4 (12) [19–67]</td>
<td>40.3 (11.5) [25–68]</td>
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<tr>
<td>Gender: female, number (%)</td>
<td>16 (50)</td>
<td>12 (38)</td>
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<tr>
<td>Married/live together, number (%)</td>
<td>13 (41)</td>
<td>12 (38)</td>
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<tr>
<td>Clinical measures</td>
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<tr>
<td>HAM-D score, mean (SD) [range]</td>
<td>22.9 (3.5) [18–30]</td>
<td>22.5 (3.0) [16–28]</td>
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<td>MDI score, mean (SD) [range]</td>
<td>28.3 (6.8) [24–50]</td>
<td>27.9 (5.1) [22–41]</td>
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<tr>
<td>WHOD-5 score, mean (SD) [range]</td>
<td>14.9 (6.8) [9–26]</td>
<td>14.8 (12.3) [6–44]</td>
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<tr>
<td>GAF score, mean (SD) [range]</td>
<td>57.1 (10.2) [33–76]</td>
<td>57.9 (10.1) [33–76]</td>
</tr>
<tr>
<td>Self-efficacy score, mean (SD) [range]</td>
<td>17.3 (5.5) [10–17]</td>
<td>17.4 (4.8) [10–27]</td>
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<td>No. of previous admissions, mean (SD) [range]</td>
<td>2.5 (2.3) [1–6]</td>
<td>3.7 (2.6) [1–10]</td>
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<tr>
<td>Diagnosis</td>
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<tr>
<td>Bipolar disorder, number (%)</td>
<td>3 (9.4)</td>
<td>5 (16)</td>
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<tr>
<td>MDE*, moderate, number (%)</td>
<td>14 (44)</td>
<td>17 (53)</td>
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<tr>
<td>MDE*, severe, number (%)</td>
<td>15 (47)</td>
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<td>Treatment resistance**</td>
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<td>Treatment resistance, mean (SD) [range]</td>
<td>6.9 (0.4) [4–13]</td>
<td>7.2 (0.3) [4–12]</td>
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<td>Mild score (3–6), number (%)</td>
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<td>11 (34)</td>
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<td>Moderate score (7–10), number (%)</td>
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<td>19 (59)</td>
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<tr>
<td>Severe score (11–15), number (%)</td>
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<td>Somatic conditions</td>
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<td>BMI, mean (SD) [range]</td>
<td>25.5 (4.3) [20–40]</td>
<td>26.7 (5.3) [18–38]</td>
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<td>Smoker***, number (%)</td>
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<td>30 min, number (%)</td>
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<td>Primary and lower secondary school, number (%)</td>
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<td>Technical college, number (%)</td>
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<td>Short education</td>
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<td>1–2 years</td>
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<td>Bachelor level, number (%)</td>
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<td>College level or higher, number (%)</td>
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<td>Employment status</td>
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<td>Unemployed, number (%)</td>
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<td>Student, number (%)</td>
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<td>On sick leave, number (%)</td>
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<td>Disabled (pension), number (%)</td>
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<td>4 (13)</td>
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<td>Employed part time or part time for full-time, number (%)</td>
<td>2 (6.3)</td>
<td>2 (6.3)</td>
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*Major depressive disorder (MDE).
**The Maudsley Staging Method.
***Smoking status at baseline was statistically different in the two groups (P=0.0048). For the remaining variables, no other significant differences were found.

between groups. The mean duration of sleep in the wake therapy group in week one was 5.9 h (SD 5.2), whereas it was 6.6 h in the control group (SD 0.18). In week nine, the estimated mean duration of sleep was 7.09 h (CI 6.39–7.42) and 7.32 h (CI 6.54–8.06) respectively. Mean duration of sleep was not significantly different between the groups in any study week. In all weeks, the wake therapy group had an estimated lower number of awakenings during the night than did the control group. In week nine, the difference between the groups was statistically significant, 1.9 (CI 1.3–2.5), compared with the control group, 3.3 (CI 2.6–3.9) (Fig. 3).

We found that significantly more patients in the wake therapy group avoided sleep during daytime: in week one: 33.3% vs. 13% (P = 0.04), week two: 28% vs. 6.3% (P = 0.02), week three: 25% vs. 3% (P = 0.01), week four: 28% vs. 3% (P = 0.02), week five: 31% vs. 13% (P = 0.07), week six: 31% vs. 13% (P = 0.07), week seven: 31% vs. 22% (P = 0.39), week eight: 38% vs. 16% (P = 0.05) and week nine: 13% vs. 6% (P = 0.39). The patients from the wake therapy group who did sleep during daytime took shorter naps than the
control group. A significant difference in length of daytime sleep was seen in week three: 66 min. (CI 34.9–97.4) in the wake therapy group vs. 117 min (CI 89.4–143.7) in the control group \( (P = 0.02) \), and in week six: 70 min. (CI 34.4–106.7) vs. 119 min. (CI 86.6–151.8) \( (P = 0.05) \).

The mean Morningness–eveningness questionnaire score in the wake therapy group was 48.9 (SD 1.96) at baseline and 51.6 (SD 2.1) in week nine. There was as indication of a shift in the direction of becoming more morning types. However, the increase was not significant. In all weeks, we found a significant negative correlation between the MEQ score at baseline and HAM-D17 score, patients with lower MEQ score (evening types) having a larger decrease in HAM-D17 score. Light therapy was used with a mean duration of 32 min (mean of SD 7.49). The mean time of daily start was 7.54 am (mean of SD 00.57). Compliance with light therapy was 93%.

Complications and adverse effects

We had to exclude two patients randomized to the intervention group during the 2- to 6-day period from inclusion until start of wake and light therapy, one because of hypomanic symptoms and one due to self-harm. During wake therapy, one patient felt an increase in anxiety and withdrew from the study. A patient in the wake therapy
group had an incidence of self-harm in the second week of the study (drank alcohol despite being treated with Antabuse) - due to disappointment because he did not experience any effect of wake therapy. No patients developed manic or hypomanic symptoms in the intervention period, and the highest measured MAS score was 4. Adverse effects in the week of the wake therapies were measured on a modified side-effect rating scale (38). The most frequently reported symptoms were tiredness (55%), restlessness (52%), sensitivity (80%), concentration difficulties (74%), memory difficulties (70%) and headache (80%).

Discussion

The aim of this RCT was to assess whether standard treatment supplemented with a chronotherapeutic intervention was more effective than standard treatment alone. In the first week, the wake therapy group had a significantly larger reduction in depressive symptoms on HAM-D17 than the control group, whereas no statistically significant differences between groups in response and remission rates were seen at any time during the trial. Compared with the control group, general self-efficacy increased significantly more in the wake therapy group, awakening during nights was a significantly less frequent problem, and fewer slept during the daytime. If they did sleep, it was for significantly shorter times.

We found no statistically significant differences between groups in response and remission rates – a finding that differs from a study by Martiny et al. showing a significant difference in response and remission rates over a nine-week period after a similar chronotherapeutic intervention (18). However, we found a significant reduction in depressive symptoms in week one, which is in accordance with several studies which demonstrate that wake therapy is a fast-acting treatment (7-9, 17, 18). However, in our study, the difference in HAM-D17 between groups diminished as early as the second week and using HAM-D6, we found no difference at any time. The difference between results measured with HAM-D17 and HAM-D6, respectively, can be explained by the positive effects that the intervention has on sleep items. These items are included in the 17-item version but not in the six-item version. Our finding differs from two other trials using combined chronotherapeutic interventions in which the antidepressant effect was maintained over seven and nine weeks (17, 18) respectively. The patients in our study differ from the participants in those studies, and this might have caused the diverse results. In the study by Wu et al., the participants all had bipolar depression, in contrast to only eight such patients in our study. Bipolar patients tend to respond better to wake therapy than those with unipolar depression (39). In the study by Martiny et al., the participants were more comparable to ours as the majority had unipolar depression. However, in our study, all patients were treatment resistant compared with 63.3% in theirs (18). Patients who have previously responded to antidepressants tend to respond better to wake therapy (6). In our study, nearly all of the participants were in-patients, whereas the majority in Martiny et al.'s study, and all participants in the study of Wu et al., were outpatients, only hospitalized due to participation in the studies (17, 18). Another difference between the studies was the more extensive use of psychoactive drugs among patients in our study. In our study, fourteen patients in the wake therapy group received quetiapine with a mean daily dose of 156 mg during the nine-week period. In comparison, one received quetiapine with a mean dose of 5.6 mg in Martiny et al.'s study (18). Research has suggested that antipsychotic drugs could impair or abolish the effect of wake therapy (40).

Furthermore, attention should also be drawn to our control group; the outcomes in this group may not entirely represent standard treatment. The control group also filled out sleep diaries and had assessments with the project nurses on a weekly basis. Although the nurses were instructed not to focus on sleep in their conversations with the patients, it may well be that control patients obtained knowledge or awareness related to sleep patterns during the process. Thus, potentially the control group achieved better outcomes than patients receiving standard treatment, resulting in a diminished difference between the wake therapy and control groups.

General self-efficacy increased significantly more in the wake therapy group than in the control group. The theory of self-efficacy is a part of Albert Banduras’ Social Cognitive Theory, and self-efficacy can be defined as a person’s judgement of their capability to accomplish a certain level of performance (23). Performing a task successfully may increase self-efficacy (23), and this might explain why self-efficacy increased significantly more in the wake therapy group. This agrees with our previous findings (Krath et al. 2016) in the qualitative study of depressive patients’ experience of combined wake and light therapy, where it was described as a personal victory to have completed the intervention (41). The combination of wake therapy, light therapy and sleep time stabilization seems to have a positive impact on patients’ sleep.
This is in line with the study of Martiny et al. (2013), who found that the wake therapy patients slept significantly longer and they found a significant advance of the sleep-wake cycle, indicating that patients had fewer problems falling asleep. In addition, they found better sleep maintenance (20). In a study examining patients’ experience of the combined chronotherapeutic intervention, they were asked whether they would try wake and light therapy again. Some answered that they would not choose the treatment if they became depressed again. However, they would consider chronotherapeutic intervention if they again experienced severe sleep problems (41).

One limitation in this study is the high rate of drop-out and excluded patients. However, a drop-out analysis revealed that those lost to follow-up were not significantly different from the completers in the measured variables at baseline, except for smoking status. At drop-out, their degree of depression was not significantly different. However, they could have differed in unmeasured variables, which could have introduced bias. Another limitation is that medication could be added and doses changed during the study period, thereby possibly influencing the results. We chose this naturalistic design to ensure as high follow-up rates as possible. An additional limitation is related to the sleep data. We used subjective data from the patients’ sleep diaries, but no objective measures. The gold standard in measurement of many of the sleep parameters is considered to be polysomnography (PSG). However, the use of PSG in long-term sleep monitoring is limited because of cost and inconvenience for the patients, which is also the rationale behind our decision to use sleep diaries. Nonetheless, it could have strengthened our study if we also had used actigraphs, as their measurements of sleep are more closely approximated to those of polysomnography than to sleep diaries (42, 43). However, the weaknesses in our sleep data are similar in the two groups and should not influence the difference between the groups. Due to time constraints, we stopped inclusion at 64 patients and so did not reach the expected inclusion. Therefore, we cannot rule out that our study was insufficiently powered to show a difference in HAM-D17.

Another potential limitation is the non-constant observation of patients during the 36 h of wakefulness, an approach we chose to examine the feasibility of the chronotherapeutic intervention with the existing staffing. However, we cannot rule out that some patients took brief naps without reporting it, and previous research has shown that naps during wake therapy sessions can influence the effect negatively (43, 44). Yet, to minimize the risk of non-adherence, we regularly assessed patients’ motivation for and capability to adhere with the protocol and offered them individualized support when necessary (e.g. company by a medical student during the no-sleep/wake nights).

A general strength is the study design as the randomized design minimizes the risk of confounding and selection bias. Furthermore, the assessors in our study were blinded, however, only partly so in week one. An additional strength is the high external validity as we screened all patients hospitalized at our department during the two-year and three-month inclusion period and included the relevant in-patients consecutively.

Our results suggest that for treatment-resistant and highly medicated in-patients, the combined chronotherapeutic intervention as an adjunctive antidepressant treatment seems less useful. However, previous studies have demonstrated positive effects in selected patient groups, and further research aiming at identifying predictors of good response is desirable. Thereby, selected in-patients with a high chance of positive outcome could be offered the treatment. Our finding related to improved self-efficacy indicates that involving patients in their own treatment is beneficial. The improvement in patients’ sleep is a promising finding worth investigating in future studies.

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