A 9-Week Randomized Trial Comparing a Chronotherapeutic Intervention (Wake and Light Therapy) to Exercise in Major Depressive Disorder Patients Treated With Duloxetine

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ABSTRACT

Objective: The onset of action of antidepressants often takes 4 to 6 weeks. The antidepressant effect of wake therapy (sleep deprivation) comes within hours but carries a risk of relapse. The objective of this study was to investigate whether a new chronotherapeutic intervention combining wake therapy with bright light therapy and sleep time stabilization could induce a rapid and sustained augmentation of response and remission in major depressive disorder.

Method: 75 adult patients with *DSM-IV* major depressive disorder, recruited from psychiatric wards, psychiatric specialist practices, or general medical practices between September 2005 and August 2008, were randomly assigned to a 9-week chronotherapeutic intervention using wake therapy, bright light therapy, and sleep time stabilization (n = 37) *or* a 9-week intervention using daily exercise (n = 38). Patients were evaluated at a psychiatric research unit. The study period had a 1-week run-in phase in which all patients began treatment with duloxetine. This phase was followed by a 1-week intervention phase in which patients in the wake therapy group did 3 wake therapies in combination with daily morning light therapy and sleep time stabilization and patients in the exercise group began daily exercise. This phase was followed by a 7-week continuation phase with daily light therapy and sleep time stabilization *or* daily exercise. The 17-item Hamilton Depression Rating Scale was the primary outcome measure, and the assessors were blinded to patients' treatment allocation.

Results: Both groups responded well to treatment. Patients in the wake therapy group did, however, have immediate and clinically significantly better response and remission compared to the exercise group. Thus, immediately after the intervention phase (week 2), response was obtained in 41.4% of wake therapy patients versus 12.8% of exercise patients (odds ratio [OR] = 4.8; 95% CI, 1.7–13.4; *P* = .003), and remission was obtained in 23.9% of wake therapy patients versus 5.4% of exercise patients (OR = 5.5; 95% CI, 1.7–17.8; *P* = .004). These superior response and remission rates obtained by the wake therapy patients were sustained for the whole study period. At week 9, response was obtained in 71.4% of wake therapy patients versus 47.3% of exercise patients (OR = 2.8; 95% CI, 1.1–7.3; *P* = .04), and remission was obtained in 45.6% of wake therapy patients and 23.1% of exercise patients (OR = 2.8; 95% CI, 1.1–7.3, *P* = .04). All treatment elements were well tolerated.

Conclusions: Patients treated with wake therapy in combination with bright light therapy and sleep time stabilization had an augmented and sustained antidepressant response and remission compared to patients treated with exercise, who also had a clinically relevant antidepressant response.

Trial Registration: ClinicalTrials.gov identifier: NCT00149110

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The onset of action of antidepressants in patients with major depressive disorder is often delayed by 4 to 6 weeks. Strategies to minimize this latency period are, therefore, an important area of research.[1] The objective of this study was to investigate whether a new combination of chronotherapeutic interventions using wake therapy (sleep deprivation), bright light therapy, and sleep time stabilization could induce a rapid and sustained augmentation of response and remission in depressed patients receiving antidepressant drug treatment.

Pflug and Tölle[2–4] were the first to establish clinical evidence for an acute antidepressant effect of wake therapy, according to a case report from Schulte.[5] Research results from Kuhs and Tölle,[6] Wu and Bunney,[7] and Wirz-Justice and Van den Hoofdakker,[8] among others, have confirmed the acute antidepressant effect of wake therapy. However, in the study by Holsboer-Trachsler et al,[9] wake therapy did not increase response rate in depressed patients treated with trimipramine. Thus, some differential effects of wake therapy are probably due to different classes of antidepressant medication. The tolerability and safety of wake therapy are, in general, good. Tiredness during the night awake is inherent, but depressed patients do not get as tired as nondepressed persons who stay up all night. Importantly, Colombo et al[10] found no indication of an increased switch rate in bipolar patients treated with wake therapy, provided patients are on prophylactic medication. Benedetti et al[11] reported a trial with 5 consecutive patients with delusional depression, all of whom worsened after wake therapy, and Roy-Byrne et al[12] found that some patients with panic disorder developed panic attacks after 1 night of wake therapy. Thus, care has to be taken when using wake therapy in patients with comorbid panic disorder or psychotic depression.

Wirz-Justice et al[13] argued that wake therapy has not been incorporated into standard clinical practice probably because patients and physicians think it is too cumbersome but also because of the usual (partial) relapse following recovery sleep. The important development in past years has been to test new chronobiological principles to sustain the acute effect. These regimens, including the use of bright light therapy, sleep-phase advance, and sleep hygiene measures in combination with pharmacotherapy,

Clinical Points

- Combining wake therapy, light therapy, and sleep time stabilization with duloxetine treatment induced a very rapid and sustained increase in antidepressant response in patients with treatment resistance; this method offers an alternative to polypharmacy treatment.
- Exercise in combination with duloxetine also induced a clinically meaningful antidepressant response, but less than the wake therapy, light therapy, and sleep time stabilization combined with duloxetine.
- We found that the individually tailored exercise program was easy to implement and that patients were highly compliant and had very few side effects. We believe that the weekly assessment and guidance by a physiotherapist was very important in obtaining this high level of compliance.
- Wake therapy was well tolerated, with a high level of compliance. Patients experienced only a moderate degree of sleepiness during the wake nights. Light therapy was also well tolerated, with a high degree of compliance. The sleep diary was found to be a helpful tool in stabilizing the sleep-wake cycle.

have been investigated by Wirz-Justice et al,[14] Wu et al,[15] Colombo et al,[16] and Smeraldi et al.[17]

Studies investigating mechanisms underlying the rapid antidepressant effect have found changes within hours that parallel the changes within weeks for antidepressant pharmacotherapy. These findings suggest important similarities in neurobiological substrate, with important differences in the time course: serotonergic neurotransmission, as found by Prévot et al[18]; glutaminergic system (using magnetic resonance spectroscopy), as found by Benedetti et al[19]; brain glucose metabolism (using positron emission tomography), as found by Wu et al[20]; and brain-derived neurotrophic factor, as demonstrated by Gorgulu and Caliyurt.[21]

Rosenthal et al[22] introduced bright light therapy into psychiatry in the early 1980s following the description of seasonal affective disorder. Many studies have shown that a morning light pulse of about 30 minutes is sufficient and yields a positive effect within a few days of treatment. Bright light therapy is an accepted treatment for both seasonal and nonseasonal depression as shown by Tuunainen et al,[23] Golden et al,[24] and Martiny et al.[25] Terman and Terman[26] found side effects to be mild.

Sleep time stabilization is used as an instrument to prevent morning oversleeping and to maintain a regular sleep-wake cycle. The evidence for a therapeutic effect of sleep time stabilization is based on patients who experienced worsening of mood when sleeping irregularly or late in the morning, as described by Pflug and Tölle.[2]

The interventions used in this study cannot be blinded, and, to balance treatment expectation, we opted for the use of exercise as an active comparator. Exercise is well tolerated, is often favored by patients, and has a long list of beneficial health effects. The efficacy of exercise in major depressive disorder is, however, still inconclusive, with both positive and negative study results, as shown in the Cochrane review by Mead et al[27] and the review by Krogh et al.[28] In this study, we did not a priori rule out that exercise might have an antidepressant effect, but we expected this effect to come more slowly than the antidepressant effect of wake therapy.

For antidepressant medication, we chose the noradrenergic and serotonin reuptake inhibitor duloxetine on the basis of its dual action and lack of sedation.

In this article, and in communication with patients, the term *wake therapy* is preferred to *sleep deprivation*. When used as in our protocol, wake therapy is more a reallocation of sleep than a deprivation of sleep, as patients catch up on sleep loss during recovery nights.

METHOD

Patients

This study, registered at ClinicalTrials.gov (identifier: NCT00149110), was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonisation-Good Clinical Practice guidelines, as laid out by the European Medicines Agency.[29] The Danish Committee on Biomedical Research Ethics, the Danish Medicines Agency, and the Danish Central Data Register approved the study. The Copenhagen Good Clinical Practice (GCP) unit monitored the study.

Patients with *DSM-IV* major depressive disorder were recruited from general medical practices, psychiatric practices, and psychiatric wards, and, for this study, patients were seen at a psychiatric research unit located in the Greater Copenhagen area. Written study information and oral description of the study were given to the patients before written informed consent was obtained. Inclusion criteria were age ≥18 years, current *DSM-IV* major depressive episode, and a score ≥13 on the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$)[30]; in addition, bipolar disorder patients had to be currently receiving mood stabilizing treatment for at least 1 month at a recommended dosage. Exclusion criteria were psychotic disorder, organic brain disorder, mental retardation, alcohol or drug abuse, pregnancy or insufficient contraception, light-induced migraines or epilepsy, retinal blindness or severe cataract, glaucoma, retinal diseases, antipsychotic drug treatment, marked suicidal ideation, and severe agitation.

Study Design

The trial covered a period of 9 weeks, during which a fixed dosage of duloxetine was used, followed by a 20-week follow-up period in which medication could be changed. The first 9 weeks of therapy are reported here. The design aimed at equal contact of investigators and staff with the 2

groups. The wake therapy group was expected a priori to experience more efficacious results in relieving depressive symptoms. Three study periods were distinguished:

1. A 1-week run-in phase in which randomization to groups was performed and all patients were started on duloxetine.
2. A subsequent 1-week intervention phase in which all patients were admitted to an inpatient ward; the wake therapy group carried out wake therapies, daily morning bright light therapy, and sleep time stabilization; and the exercise group started a daily exercise program. Patients were all discharged at the end of the intervention phase.
3. A subsequent 7-week continuation phase in which patients in the wake therapy group continued with daily bright light therapy and sleep time stabilization and patients in the exercise group continued with daily exercise and weekly training sessions with physiotherapists.

Detailed description of the different types of interventions is given below.

Wake Therapy Procedures

Wake therapy nights were scheduled for Monday, Wednesday, and Friday. Patients were instructed to stay up the entire night and to not sleep on the following day until 8:00 PM. Patients filled in the Stanford Sleepiness Scale[31] (evaluated by MacLean et al[32]) for each hour on wake therapy nights. Patients were, during the time awake, allowed to walk freely inside and outside the ward and to use the facilities, and they were instructed to avoid darkness. The light intensity during the wake therapy was thus ambient level. The ward staff was instructed not to press patients to stay awake, and patients were informed that no substantial help could be expected from ward personnel to stay awake. On Tuesday, Thursday, and Saturday nights, patients were scheduled to go to sleep at 8:00 PM and to wake up no later than 8:00 AM (a milder version of a sleep phase advance). Patients were allowed to take a maximum of 2 additional separate wake therapies during weeks 4 to 7 if they had not attained an adequate response ($HDRS_{17}$ score ≤ 7).

Light Therapy

Patients received 30 minutes of light therapy at 4:00 AM on wake therapy nights to alleviate tiredness. Daily morning light therapy was then started on the morning after the first wake therapy night. Light therapy was done each morning in the ward and continued for the remaining study period (at home). Light was administered using a Smifa Bio Lamp (Smifa Health Care; Solrød Strand, Denmark) with a color temperature of 5,500 K and with 10,000 lux white light at a 40-cm distance from the screen; duration of treatment was 30 minutes. Timing of light therapy was scheduled from an algorithm based on the Morningness-Eveningness Questionnaire[33] score, with 7:00 AM as the earliest, as devised by Terman and Terman.[34] The same lamp was used for light on wake therapy nights and for daily light therapy.

Sleep Time Stabilization

Sleep logs were used to guide patients to keep a stable sleep-wake cycle and prevent oversleeping. Patients were encouraged not to go to sleep later than midnight.

Exercise

After admittance to the psychiatric ward, each participant in the exercise group planned an individually tailored daily exercise program of 30 minutes' minimum duration with the physiotherapist. Patients in this group followed the ordinary bedtime and sleep-length regimen in the open ward. At the hospital, exercise was done between 9:00 AM and 4:00 PM. At home, patients could start exercise in the morning as early as they wished but were advised not to exercise later than 8:00 PM due to the risk of insomnia. Patients were seen weekly during the 7-week continuation phase for group training or individual instruction. At each visit, the physiotherapists evaluated each patient's exercise performance. The evaluation was done by inspecting the daily entries in the exercise logs and through a questionnaire that measured for the preceding week the degree of compliance with the training program (0 = none, 100 = complete compliance, and > 100 = more than expected) and the need for support (ranging from minimal to maximal, with a score from 1 to 6). The duration and type of exercise could be adjusted at all visits according to the individual patient's motivation. Patients were also allowed extra sessions with the physiotherapist if needed. Training was for 1 hour in a group of 3 to 5 patients or individually.

Medication

Study medication was a 60-mg fixed dosage of duloxetine. Upon patients' inclusion in the study, all other antidepressant drugs were discontinued, other psychopharmacologic treatment was maintained at the same dosage, and anxiolytics and hypnotics could be prescribed.

Sample Size

With an expected reduction in mean $HDRS_{17}$ score of 14 points (from 24 points to 10 points) in the wake therapy group and of 11 points (from 24 points to 13 points) in the exercise group, with a standard deviation (SD) of 6 points and a power of 80% to detect a significant difference ($P = .05$, 2-sided), 64 patients were needed in each group. This number corresponds to an effect size of 0.50 (difference between groups/pooled SD).

Randomization

An external statistician created a computer-generated random list with a block size of 4 (block size was blinded). A GCP-qualified research coordinator labeled envelopes with consecutive numbers and inserted group-specific instruction letters according to the randomization list (which was kept locked up). An envelope was handed to each patient after the patient signed the informed consent form.

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Blinding

Raters for the HDRS were blinded to treatment assignment. Patients were instructed not to reveal any information on group allocation to HDRS interviewers or fellow patients.

Assessments

Diagnostic assessments were made using the Mini-International Neuropsychiatric Interview (MINI)[35] and the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders (SCID-II).[36] Patients were assessed at 10 weekly visits during the 9 weeks (including the baseline visit). For interview-based outcome measures, we used the $HDRS_{17}$, the 6-item subscale of the HDRS ($HDRS_6$) as described by Bech[37(pp141–144)] and O'Sullivan et al,[38] the Melancholia Scale,[39] and the Bech-Rafaelsen Mania Scale (score range of 0 to 44).[40] *Response* was defined as a reduction from baseline score of 50% or more on the $HDRS_{17}$, and *remission* was defined as a score < 8 on the $HDRS_{17}$. To assess treatment resistance, we adopted the Maudsley Staging Method based on criteria from Fekadu et al,[41] using episode duration, baseline symptom severity, and treatment failures. The score range for the Maudsley Staging Method is from 3 to 15: scores from 3 to 6 signify mild treatment resistance, scores from 7 to 10 indicate moderate treatment resistance, and scores above 11 indicate severe treatment resistance. For patient-reported outcome measures, we used the Major Depression Inventory (MDI),[42] the World Health Organization (WHO)-5 Well-Being Index (WHO-5),[43] and the Symptom Checklist-90 and Symptom Checklist-90R (SCL-92).[44] Patients were asked, after being informed of treatment assignment and procedures, about their expectation regarding outcome (0 = no improvement; 10 = without depression). Global functioning and symptom burden were assessed using the Social and Occupational Functioning Assessment Scale[45(p818)] and the Global Assessment of Functioning,[45(p34)] both in the *DSM-IV-TR*. The Seasonal Pattern Assessment Questionnaire by Rosenthal et al[46] and the seasonal pattern specifier from *DSM-IV-TR*[45(p427)] were used to evaluate seasonality.

Patients in the wake therapy group filled in daily light therapy logs and the Stanford Sleepiness Scale on wake therapy nights. Patients in the exercise group filled in daily exercise logs and the Borg Scale of Perceived Exertion.[47] All patients filled in daily sleep logs. Interviewers completed medication compliance logs. Side effects were measured at all visits using the UKU Side Effect Rating Scale (UKU).[48]

Outcomes

The primary efficacy parameters were response and remission rates at weeks 2 and 9, and all other end points were secondary. Raters for the HDRS were certified for good interrater and test-retest reliability.

Data Analysis

The intention-to-treat principle was applied. Sociodemographics were compared using the Fisher exact test or the 2-sample *t* test. Continuous scale scores were analyzed in a regression model for repeated measurements (RRM), specifying an autoregressive correlation structure over time. The model was parametrized to allow for separate evaluation of the treatment effects in the 3 study periods. Baseline values were included as covariate values to adjust for (small) chance differences in the treatment groups. Response and remission were analyzed in a logistic regression model for repeated measurements, using a generalized estimation equation (GEE) to allow for autocorrelation over time. Baseline $HDRS_{17}$ scores were used as a covariate, but the parametrization was a simple 2-way analysis of variance in time and treatment, with possible interaction. Treatment effect (between groups) was presented as odds ratios (for response and remission) and score differences with 95% confidence intervals (CIs) and *P* values. To facilitate comparisons with other studies, the unbiased Cohen effect size was calculated, as described by Hedges and Olkin.[49] For the Cohen effect size and the UKU, we used the method of last observation carried forward, whereas the RRM and GEE used available data. Student *t* tests were used for comparison between groups. All time points are shown in the format of hour:minutes. Analyses were performed using SAS software, version 9.2 (SAS Institute Inc, Cary, North Carolina). The level of statistical significance was set at 5% (2-sided).

RESULTS

Patients were recruited from September 2005 to August 2008, and the last patient's last visit was in March 2009. In all, 100 patients were screened and 75 patients were included, with 37 patients randomized to the wake therapy group and 38 to the exercise group. Inclusion was stopped at 75 patients due to time constraints and funding limits.

Table 1 shows sociodemographics, somatic conditions, antidepressant status, and social function. All variables were balanced between groups except for sick leave at inclusion.

Results from the MINI and the SCID-II showed that the majority of patients were suffering from recurrent major depressive disorder with melancholic features. There were 3 patients with bipolar I disorder and 3 patients with bipolar II disorder in each group. The most prevalent comorbid disorders were generalized anxiety disorder, panic disorder, and social phobia. The most prevalent personality disorders were avoidant, obsessive-compulsive, and depressive (research criteria) personality disorders.

Table 2 shows mean daily dosages of duloxetine and concomitant psychoactive medications. The most frequently used medications were zopiclone, clonazepam, and oxazepam, with clonazepam more frequently used in the wake therapy group (statistically insignificant). Analyses of the subset of patients treated with clonazepam showed a lesser depression score separation between treatment groups than for the whole sample.

Side effects as measured with the UKU were moderate. Four patients developed anxiety attacks related to wake therapy and received benzodiazepines to treat anxiety, 1 diabetic patient experienced hypoglycemia during a wake therapy night, and 1 patient had running eyes due to the light

Table 1. Baseline Clinical and Demographic Characteristics by Treatment Group (N = 75)

	Wake Therapy (n = 37)		Exercise (n = 38)	
Characteristic	Mean (SD)	Range	Mean (SD)	Range
Age, y	46.9 (12.6)	21–70	48.5 (11.2)	23–69
Age at first MDE, y	32.7 (15.9)	10–66	32.6 (14.0)	9–68
No. of past MDEs	8.7 (11.0)	0–40	6.2 (7.5)	0–30
Duration of current MDE, mo	24.6 (29.0)	1–120	21.3 (54.3)	1–288
Time spent depressed in past 5 years, mo	32.8 (20.3)	3–60	24.6 (20.3)	1–60
Time spent manic in past 5 years, mo	1.2 (5.1)	0–27	0.5 (1.6)	0–7
Time spent euthymic in past 5 years, mo	25.9 (20.7)	0–57	34.7 (20.0)	0–59
Global seasonality score	9.2 (4.7)	0–20	8.0 (5.2)	0–19
GAF score	49.5 (5.7)	35–58	49.8 (7.0)	35–65
SOFAS score	50.7 (10.2)	32–75	51.6 (10.0)	32–72
	n (%)		n (%)	
Sex, female	24 (64.9)		20 (52.6)	
Diabetes	3 (8.1)		2 (5.3)	
Past cerebral insults	0 (0.0)		1 (2.6)	
Hypertension or ischemic heart disease	6 (16.2)		6 (15.8)	
Treated with antidepressants at study inclusion	31 (83.8)		32 (84.2)	
Previously treated with antidepressants for MDE	21 (56.8)		21 (55.3)	
On sick leave at study inclusion[a]	24 (85.7)*		19 (61.3)	
Employment status				
Employed	17 (46.0)		26 (68.4)	
Unemployed	11 (29.7)		5 (13.2)	
Retired	5 (13.5)		3 (7.9)	
Disabled (pension)	4 (10.8)		4 (10.5)	

[a]Retired and pensioned patients excluded; n = 28 for wake therapy and n = 31 for exercise.
*$P = .03$.
Abbreviations: GAF = Global Assessment of Functioning, MDE = major depressive episode, SOFAS = Social and Occupational Functioning Assessment Scale.

Table 2. Mean Doses of Concomitant Psychoactive Medications by Treatment Group (N = 75)

	Wake Therapy (n = 37)		Exercise (n = 38)	
Drug	Mean (SD)	n	Mean (SD)	n
Duloxetine, mg/d	60.0 (7.1)	37	59.6 (4.4)	38
Zopiclone, mg/d	7.4 (2.9)	14	5.4 (4.2)	17
Clonazepam, mg/d	0.55 (0.62)	14	0.43 (0.43)	7
Oxazepam, mg/d	8.3 (11.8)	6	14.7 (13.6)	8
Mianserin, mg/d	2.2 (5.5)	2	2.2 (4.4)	1
Lamotrigine, mg/d	115.3 (42.1)	3	166.7 (38.3)	2
Melatonin, mg/d	1.7 (1.6)	1	1.7 (1.5)	2
Bromazepam, mg/d	0.0 (0.0)	0	6.0 (0.0)	1
Zolpidem, mg/d	0.0 (0.0)	0	8.9 (3.3)	1
Quetiapine, mg/d	5.6 (16.7)	1	0.0 (0.0)	0
Lithium, mmol/d	27.0 (0.0)	1	27.5 (6.2)	2

therapy. In the exercise group, 1 patient reported substantial pain in the Achilles tendons.

Table 3 shows that baseline-adjusted estimated mean response and remission rates in the wake therapy group were superior to the exercise group immediately after the intervention phase and were maintained for the whole of the continuation phase, with response rates at 9 weeks of 71.4% and 47.3%, respectively (OR = 2.8; 95% CI, 1.1–7.3; $P = .04$), and remission rates at 9 weeks of 45.6% and 23.1%, respectively (OR = 2.8; 95% CI, 1.1–7.3; $P = .04$). Post hoc analysis showed a statistically significantly better improvement in the wake therapy group compared to the exercise group at all weekly assessments (see Table 3). No patients obtained response or remission before the intervention phase.

Table 4 shows baseline-adjusted estimated mean scores on the $HDRS_{17}$ by study week. A statistically significantly larger reduction in scores in the wake therapy group as compared to the exercise group was seen in the whole of the continuation phase ($F_{529} = 12.75$; $P = .0004$). Post hoc analysis showed a continued statistically significantly better outcome in the wake therapy group at all postintervention weekly assessments. The estimated mean score difference between groups on the $HDRS_{17}$ was 3.9 (95% CI, 1.8–6.0; $P = .0004$) at week 2, with a gradual decrease to 3.0 (95% CI, 0.8–5.3; $P = .008$) at end point. Scores from the $HDRS_6$ and Melancholia Scale showed comparable results. The Cohen unbiased effect size, using the $HDRS_{17}$, was 0.69 at week 2 (95% CI, 0.22–1.15), 0.67 at week 3 (95% CI, 0.21–1.14), 0.36 at week 4 (95% CI, −0.09 to 0.82), 0.55 at week 5 (95% CI, 0.09–1.01), 0.50 at week 6 (95% CI, 0.04–0.96), 0.29 at week 7 (95% CI, −0.17 to 0.74), 0.24 at week 8 (95% CI, −0.22 to 0.69), and 0.39 at week 9 (95% CI, −0.07 to 0.84). On the $HDRS_6$ and Melancholia Scale, the effect sizes were 0.63 (95% CI, 0.17–1.10) and 0.72 (95% CI, 0.25–1.18), respectively, at week 2 and 0.45 (95% CI, −0.01 to 0.91) and 0.49 (95% CI, 0.03–0.94), respectively, at week 9. With the obtained results, a power above 80% was achieved with the included 75 patients on the basis of $HDRS_{17}$ scores. Subgroup analyses showed that results from the $HDRS_{17}$ were similar when patients with bipolar depression were excluded. In all, 12% of patients had an $HDRS_{17}$ score of 13 through 17, signifying mild depression; 46.7% had an $HDRS_{17}$ score of 18 through 24, signifying moderate depression; and 41.3% had an $HDRS_{17}$ score ≥ 25, signifying moderate-severe depression.

Treatment resistance was found in 62.3% of patients (43 of 69; data were missing for 6). In all, 27 patients had a mild degree of treatment resistance (score, 3–6), and 16 had a moderate degree of treatment resistance (score, 7–10). No patients were severely treatment-resistant. The mean score for treatment resistance was 6.2 (SD = 1.5; range, 3–9), with a score of 6.4 (SD = 1.6; range, 3–9) in the wake therapy group and a score of 6.1 (SD = 1.4; range, 3–9) in the exercise group ($P = .48$). The mean $HDRS_{17}$ scores for patients with treatment resistance scores above 6 (8 patients in each group) were reduced from 21.7 (SD = 1.79) at baseline to 11.3 (SD = 1.7) at end point in the exercise group compared to a reduction from 20.6 (SD = 1.9) to 8.9 (SD = 2.0) in the wake therapy group. The level of treatment resistance had a small, statistically insignificant effect on depression scores in both groups ($P = .77$).

Figure 1 shows estimated mean $HDRS_{17}$ depression scores with standard errors for the 2 treatment groups. Supplementary eFigure 1 shows the flow of the study design with the run-in, intervention, and continuation phases. Supplementary eFigure 2 shows estimated mean WHO-5 well-being

Table 3. Estimated Postintervention Response[a] and Remission[b] Rates for Each Treatment Group by Week[c]

	Response					Remission				
Week	Wake Therapy (n = 37), %	Exercise (n = 38), %	Odds Ratio	95% CI	*P* Value	Wake Therapy (n = 37), %	Exercise (n = 38), %	Odds Ratio	95% CI	*P* Value
2	41.4	12.8	4.8	1.7–13.4	.003	23.9	5.4	5.5	1.7–17.8	.004
3	45.8	15.9	4.5	1.8–11.1	.001	26.6	6.7	5.0	1.8–14.0	.002
4	50.3	19.7	4.1	1.8–9.3	.0007	29.4	8.4	4.5	1.8–11.3	.001
5	54.8	24.1	3.8	1.8–8.2	.0006	32.4	10.4	4.1	1.8–9.4	.0008
6	59.2	29.2	3.5	1.7–7.5	.001	35.5	12.8	3.7	1.7–8.2	.001
7	63.5	34.9	3.3	1.5–7.2	.004	38.8	15.7	3.4	1.5–7.6	.003
8	67.6	41.0	3.0	1.3–7.1	.01	42.1	19.1	3.1	1.3–7.3	.01
9	71.4	47.3	2.8	1.1–7.3	.04	45.6	23.1	2.8	1.1–7.3	.04

[a]*Response* was defined as a 50% or greater reduction in $HDRS_{17}$ baseline score.
[b]*Remission* was defined as an $HDRS_{17}$ score < 8.
[c]No patients obtained response or remission before the intervention phase.
Abbreviation: $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale.

Table 4. Estimated Mean Postbaseline $HDRS_{17}$ Depression Scores for Each Treatment Group by Week

	Wake Therapy (n = 37),	Exercise (n = 38),	Difference Between Groups		
Week	Mean (SE)	Mean (SE)	*df*	*t*	*P* Value
0	23.9 (0.71)	22.3 (0.62)	NA	NA	NA
1	20.7 (0.82)	20.9 (0.80)	71	0.14	.89
2	12.6 (0.79)	16.5 (0.75)	529	3.59	.0004
3	12.1 (0.67)	15.9 (0.64)	529	4.07	< .0001
4	11.6 (0.58)	15.2 (0.55)	529	4.52	< .0001
5	11.0 (0.54)	14.6 (0.51)	529	4.73	< .0001
6	10.5 (0.55)	13.9 (0.51)	529	4.50	< .0001
7	10.0 (0.61)	13.3 (0.57)	529	3.91	.0001
8	9.5 (0.71)	12.6 (0.66)	529	3.24	.001
9	9.0 (0.83)	12.0 (0.78)	529	2.65	.008

Abbreviations: $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, NA = not applicable, SE = standard error.

scores for the 2 treatment groups with the national norm level inserted. Supplementary eFigure 3 shows the Consolidated Standards of Reporting Trials (CONSORT) flow diagram. (See Supplementary eFigures 1–3 at PSYCHIATRIST.COM.)

The mean mania scale scores were 0.2 (SD = 1.1) and 0.2 (SD = 0.9) for the wake therapy group and exercise group, respectively. No patients developed manic symptoms, but 1 patient in each group developed hypomania, with a score of 9. No patients were excluded due to manic symptoms.

Baseline-adjusted estimated mean scores on the WHO-5, MDI, and SCL-92 scales were statistically significantly improved in the wake therapy group compared to the exercise group after the intervention phase (WHO-5: $F_{71} = 6.49$, $P = .01$; MDI: $F_{516} = 4.83$, $P = .03$; SCL-92: $F_{531} = 9.73$, $P = .002$). Post hoc analysis of postintervention weeks showed a statistically significantly better outcome in the wake therapy group for the WHO-5, MDI, and SCL-92 scales—for the WHO-5 from week 2 ($t_{533} = 2.86$, $P = .004$) until week 6 ($t_{533} = 2.36$, $P = .02$), for the MDI from week 2 ($t_{516} = 2.69$, $P = .007$) until week 6 ($t_{516} = 2.49$, $P = .01$), and for the SCL-92 from week 2 ($t_{531} = 3.26$, $P = .001$) until week 7 ($t_{531} = 2.48$, $P = .01$).

Mean outcome expectation scores were 8.4 (SD = 1.8; range, 2–10) and 8.6 (SD = 1.5; range, 5–10) for the wake therapy and exercise groups, respectively. Mean daily dosages of duloxetine were 60.0 mg (SD = 7.1 mg) and 59.6 mg (SD = 4.4 mg) for the wake therapy and exercise groups, respectively. Mean systolic and diastolic blood pressures were 142/90 mm Hg (SD = 21/13 mm Hg) and 140/89 mm Hg (SD = 19/12 mm Hg) for baseline and end point, respectively (for completers), and mean weight was 84.1 kg (SD = 19.7 kg) and 84.6 kg (SD = 19.9 kg) for baseline and end point, respectively (for completers).

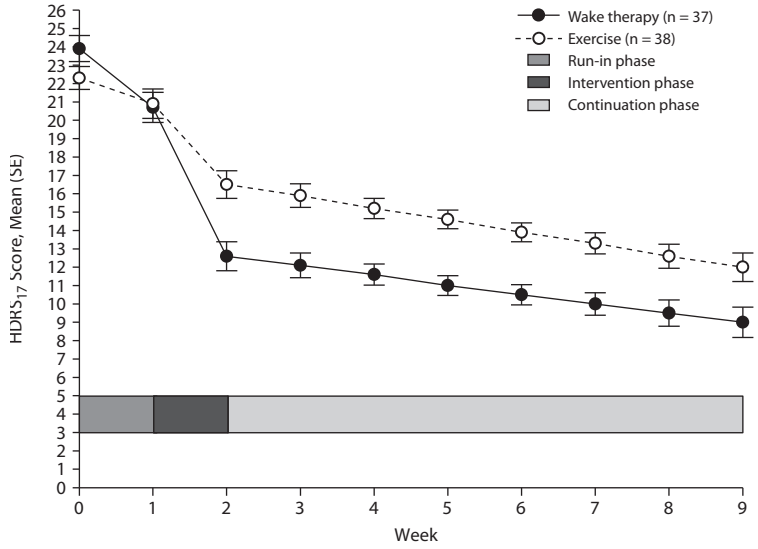
Compliance with light therapy was 94.1%, with a mean duration of 29.5 min/d (SD = 10.2 min/d). The mean hour of daily start of light therapy was 8:00 AM (SD = 1:40). No relation was found between the daily time of light therapy and response to treatment.

In all, 27.0% of patients (n = 10) in the wake therapy group used extra wake therapies. The mean number of performed wake therapies was 3.3 (SD = 0.9; range, 2–5), and the self-estimated percentage of sleep during the wake therapy was below 5%. When we analyzed depression outcome on the $HDRS_{17}$, excluding patients with extra wake therapies, we found a score difference at end point between the wake therapy and exercise groups of 3.5 points, compared to 3.0 points for the whole group. The mean score on the Stanford Sleepiness Scale was 3.2 (SD = 1.0; range, 1.2–6.2), indicating mild to moderate sleepiness.

In the exercise group, compliance was 82.2% for the planned daily exercises, with a mean exercise duration of 63.0 min/d (SD = 55.3 min/d). The mean score on the Borg Scale of Perceived Exertion was 12.4 (SD = 3.1), corresponding to moderate exertion. Outdoor daily exercise time was calculated to be 34.7% of the total daily exercise time. Mean compliance score for the training program, as estimated weekly by the physiotherapists, was 95 (SD = 25.8) (100 signifies full compliance). The patient's individualized exercise program was intensified in 44.8% of patients (n = 17) and was reduced in 2.6% (n = 1). The need for support of physiotherapists was estimated as a score of 2.2 (SD = 1.2), signifying a moderate need.

The mean global seasonality score was 8.6 (SD = 5.0). Seasonal affective disorder and subsyndromal seasonal affective disorder were present in 23.8% and 14.3%, respectively, of the total sample. There was no relation between global seasonality score and response to treatment. The seasonal pattern specifier from the *DSM-IV-TR* was fulfilled in 3 patients. In all, 28.0% of patients were treated in the spring, 22.7% in summer, 25.3% in autumn, and 24.0% in the winter.

Figure 1. Baseline-Adjusted Estimated Mean $HDRS_{17}$ Scores by Treatment Group



Abbreviations: $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, SE = standard error.

The mean Morningness-Eveningness Questionnaire score was 49.8 (SD = 12.6; range, 24–76).

Mean sleep onset in the wake therapy and exercise groups was 11:43 PM (SD = 1:53) and 11:46 PM (SD = 1:60), respectively, at baseline and 10:55 PM (SD = 1:20) and 11:53 PM (SD = 1:30), respectively, at week 9 ($P < .001$ for the wake therapy group and $P = .68$ for the exercise group). Mean sleep offset in the wake therapy and exercise groups was 7:28 AM (SD = 1:53) and 7:28 AM (SD = 1:49), respectively, at baseline and 7:14 AM (SD = 1:17) and 7:45 AM (SD = 1:48), respectively, at week 9 ($P = .02$ for the wake therapy group and $P = .09$ for the exercise group). Mean sleep duration in the wake therapy and exercise groups was 7:44 (SD = 1:60) and 7:42 (SD = 1:37), respectively, at baseline and 8:19 (SD = 1:17) and 7:53 (SD = 1:60), respectively, at week 9 ($P < .001$ for the wake therapy group and $P = .008$ for the exercise group). Sleep midpoint in the wake therapy and exercise groups was 3:34 AM (SD = 1:41) and 3:28 AM (SD = 1:51), respectively, at baseline and 3:02 AM (SD = 1:06) and 3:43 AM (SD = 1:47), respectively, at week 9 ($P < .001$ for the wake therapy group and $P = .08$ for the exercise group).

These data show an advance of sleep in the wake therapy group, a minor sleep delay in the exercise group, and an increase of sleep duration in the wake therapy group. There was no relation between time of sleep onset and change in depression scores in any of the groups. The relation between sleep offset and depression scores showed that patients who were in remission at end point had an earlier sleep offset time. Thus, patients in remission woke up at 6:55 AM (SD = 1:19) as compared to patients not in remission, who woke up at 7:30 AM (SD = 1:50). This difference in wake-up time was statistically significant, however, only for the exercise group ($P < .001$). Furthermore, at end point, the day-to-day variation of sleep onset, sleep offset, sleep duration, and sleep midpoint, as measured by the variance, was consistently and statistically significantly smaller in the wake therapy group than in the exercise group. For sleep midpoint, the variance ratio was 11.4/4.4, giving an F value of 2.6 ($P < .01$).

DISCUSSION

The results of this study (for which emphasis has been placed on balancing expectations and flexibility in the 2 groups) show that the usual response and remission rates after beginning a new antidepressant drug can be augmented, and without relapse, by use of a set of chronotherapeutic techniques. This finding does not, however, rule out that exercise in this study had an antidepressant effect on its own.

The effect sizes for the 3 clinician-rated scales were moderate, with values between 0.72 and 0.69 at week 2 and between 0.39 and 0.49 at week 9. The depression score difference between groups thus diminished somewhat during the study period. It is uncertain whether this diminishing difference was due to an antidepressant effect of exercise or due to a gradually reduced effect of the chronointervention, or both. The finding does emphasize, however, that we should continue to search for methods that will facilitate a full response after wake therapy—whether they be another class of antidepressants or lithium or other combinations of exercise, light, and drugs.

The majority of the patients in our study were suffering from recurrent, unipolar, long-standing melancholic depression and were receiving antidepressant treatment at inclusion, and, as expected, most of the patients could be classified as treatment-resistant. Furthermore, most of the patients were on sick leave and clearly had impaired social function and a substantial symptom burden. It is against this background that the results should be interpreted. The most significant finding is that, in this mainly unipolar sample of patients, the effect of wake therapy was apparent immediately following the intervention phase.

It is also significant that patients in the exercise group had a clinically large, albeit more slowly evolving, response when considering that the majority of these patients were already receiving antidepressant drug therapy at inclusion. The finding that the 8 most treatment-resistant patients in this group had a 47.9% reduction in depression scores over the 9 weeks of therapy also supports the effect of exercise. Patients in the exercise group had a high degree of compliance and only a moderate need for support, and they even intensified their program. The applicability of exercise was thus very good in this patient group. This fact gives hope that exercise could have a role in treatment-resistant depression and this possibility should be investigated in future studies.

Patients in the exercise group performed some of their activity outdoors and thereby received outdoor light

exposure that might have added to the antidepressant effect.

The timing of light therapy in the wake therapy group was not found to be related to antidepressant response to treatment, probably because light timing was already working optimally through the algorithm linking the Morningness-Eveningness Questionnaire scores to light therapy timing.

The subsample of bipolar patients had a similar reduction in depression scores as compared with the unipolar patients, pointing to a general effect of wake therapy across the unipolar-bipolar dimension. The level of seasonality was moderate and had no impact on depression outcome.

To ensure safety, we chose to carry out the acute intervention as an inpatient procedure. As no serious adverse effects were reported due to wake therapy, these procedures might be carried out on an outpatient basis in a defined environment or, after successful application, perhaps even at home. A few patients without preexisting panic disorder but with higher anxiety scores on the $HDRS_{17}$ suffered panic attacks in relation to wake therapy. Roy-Byrne et al[12] reported this phenomenon. We believe that special attention should be given to patients with high anxiety, a condition for which wake therapy might be a relative counterindication. If wake therapy is performed with anxious patients, they should have access to an anxiolytic drug.

The moderate sample size is a limitation of our study. Although reasonable in comparison with existing studies, our sample size does not allow for extensive subgroup analyses. Another limitation is that, due to the inclusion of mainly treatment-resistant patients, we cannot generalize results to the larger group of non–treatment-resistant patients. Furthermore, the use of light therapy during the wake therapy nights might have caused a phase delay, counteracting the effect of wake therapy.

The observed phase advance of the sleep-wake cycle in the wake therapy group might have had an antidepressant effect on its own as sleep phase advance has been shown to be an antidepressant.[50] The observed smaller day-to-day variation in the sleep-wake cycle points to a stabilizing effect of the chronointervention, an effect that we normally try to accomplish by using psychoeducation in these patients.

The main finding of this study is in line with the few other studies using comparable chronotherapeutic methods.[15–17] The response and remission rates seen in the exercise group are within the range of results obtained in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,[51] but, given that patients in this study were predominantly treatment-resistant, response in the exercise group is higher than expected and, again, points to the possibility that exercise might have had an antidepressant effect.

In summary, this study adds to the accumulating evidence not only for the rapid antidepressant efficacy of chronobiological interventions but also for a possible effect of exercise. Regarding the chronobiological intervention, this therapy could probably be used more widely on its own, as demonstrated by Wirz-Justice et al.[52]

Drug names: clonazepam (Klonopin and others), duloxetine (Cymbalta), lamotrigine (Lamictal and others), lithium (Lithobid and others), quetiapine (Seroquel and others), trimipramine (Surmontil and others), zolpidem (Ambien, Edluar, and others).
Author affiliations: Department of Psychiatry, University Hospital of Copenhagen, Rigshospitalet, Copenhagen (Dr Martiny); Psychiatric Research Unit, Mental Health Centre North Zealand, Hillerød (Mss Refsgaard, Lund, Lunde, Sørensen, and Lindberg and Dr Bech); and Child and Adolescent Psychiatric Center Bispebjerg, Copenhagen (Ms Thougaard), Denmark.
Potential conflicts of interest: **Dr Martiny** has served as a speaker for pharmaceutical companies with an interest in the drug treatment of affective disorders (Servier and Eli Lilly). **Dr Bech**, until August 2008, received funding from and was a speaker or member of advisory boards for pharmaceutical companies with an interest in the drug treatment of affective disorders (AstraZeneca, Eli Lilly, Lundbeck, and Organon). **Mss Refsgaard**, **Lund**, **Lunde**, **Sørensen**, **Thougaard**, and **Lindberg** report no conflicting financial relationships with commercial interests.
Funding/support: Material support (duloxetine medication) was provided by Eli Lilly, Copenhagen, Denmark; the company had no role in the design or conduct of the study or in the analysis of the data. Financial support was provided by the Danish Agency for Science, Technology and Innovation, Copenhagen, Denmark; Eli Lilly, Copenhagen, Denmark (funding for part of Dr Martiny's and part of Ms Refsgaard's salaries; the company had no role in the design or conduct of the study or in the analysis of the data); The Region 3 Foundation, Copenhagen, Denmark; the Olga Bryde Nielsen Foundation, Hillerød, Denmark; Frederiksborg General Hospital, Hillerød, Denmark (in addition to a research grant to Dr Martiny, the hospital provided management of open ward facilities for the study); and AstraZeneca, Copenhagen, Denmark (travel award to Dr Martiny).
Previous presentations: Study data were partly presented in oral symposia presentations at the ▪ World Psychiatric Association International Congress; April 1–4, 2009; Florence, Italy ▪ 21st Annual Meeting of the Society for Light Treatment and Biological Rhythms; June 24–27, 2009; Berlin, Germany ▪ 9th World Congress of Biological Psychiatry, World Federation of Societies of Biological Psychiatry; June 28–July 2, 2009; Paris, France ▪ 19th European Congress of Psychiatry, European Psychiatric Association; March 12–15, 2011; Vienna, Austria.
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Supplementary material: Supplementary eFigures 1–3 are available at PSYCHIATRIST.COM.

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See supplementary material for this article at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: A 9-Week Randomized Trial Comparing a Chronotherapeutic Intervention (Wake and Light Therapy) to Exercise in Major Depressive Disorder Patients Treated With Duloxetine

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List of Supplementary Material for the article

1. eFigure 1 Design Flowchart Showing the Run-In, Intervention, and Continuation Phases
2. eFigure 2 Estimated Mean WHO-5 Well-Being Scores Shown for Each Treatment Group and With Danish National Norm Inserted
3. eFigure 3 CONSORT 2010 Flow Diagram

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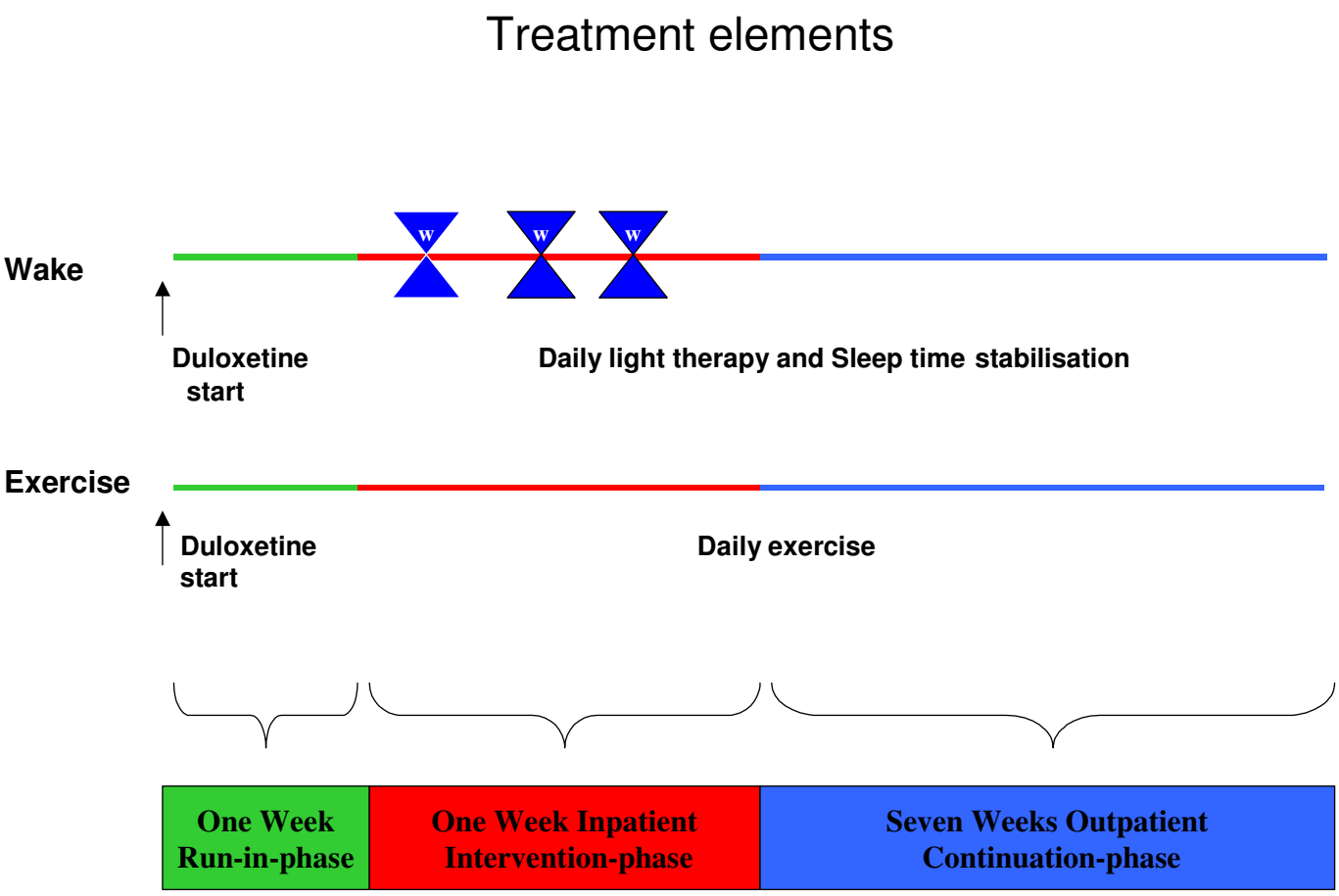
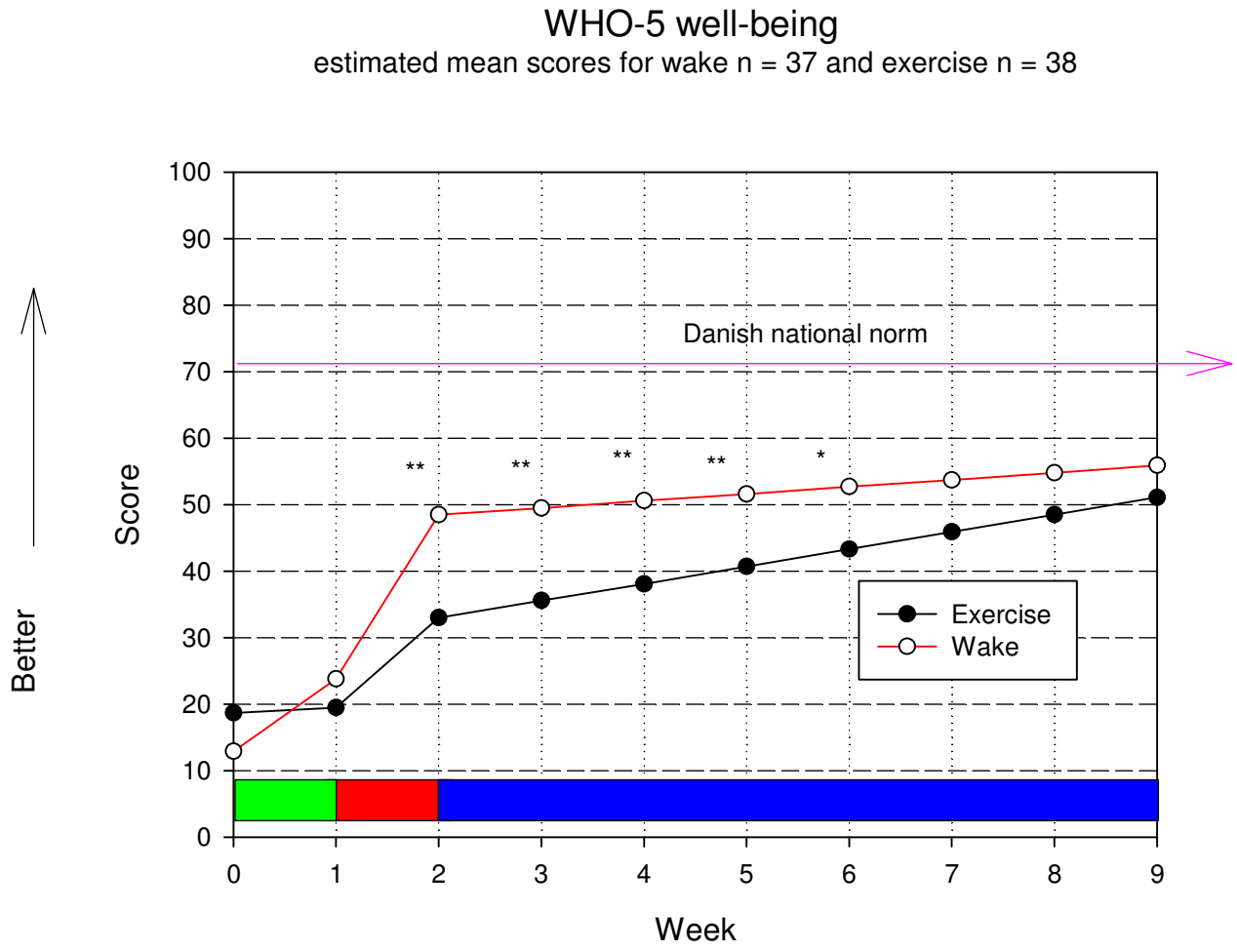
Supplementary eFigure 1. (Design Flow Chart Showing the Run-in, Intervention and Continuation-phases. W signifies individual wake night)



Supplementary eFigure 2. (Estimated mean WHO-5 well-being scores shown for each treatment Group and with Danish national norm inserted. Green bar indicates run-in-phase, red bar intervention-phase and blue bar continuation-phase)



Random-effects Regression Model (RRM) ** p< 0.01 post hoc analysis, * p< 0.05

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Klaus Martiny

Supplementary eFigure 3. (CONSORT 2010 Flow Diagram)