

# Randomized Clinical Trial on the Effect of a Single Nights' Wake Followed by Bright Light Therapy on Depression

Degree Project Thesis in Medicine

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## Abstract

**Introduction:** Wake-therapy (or "Sleep deprivation") has the potential of providing a fast anti-depressive response, however, the effect tends to fade after subsequent sleeping. Bright light therapy has the ability of maintaining the positive effect. Agitation among patients suffering from mood disorders has been scarcely investigated and no study has yet measured the possibility of increased agitation when undergoing wake-therapy.

**Objectives:** To determine the effect of combined wake- and bright light therapy as an enhancement of existing conventional anti-depressive treatment.

**Methods:** Patients suffering from a depressive episode were randomized to either wake-therapy combined with bright light therapy in addition to treatment as usual (TAU) or to the control group (psycho education on sleep hygiene in addition to TAU). On day 1, before wake-therapy or psycho education, patients filled out Montgomery-Åsberg Depression Rating Scale (MADRS-S) and Insomnia Severity Index (ISI). Agitation was assessed using Positive And Negative Symptoms of Schizophrenia (PANSS-EC) on day 1 and 2. On day 7 all patients again filled out MADRS-S and ISI.

**Results:** This ongoing randomized clinical trial will consist of 50 patients in total. In this thesis, the results from the first 8 patients is presented. Wake-therapy combined with bright light therapy in addition to TAU reduced the median MADRS-S score non-significantly by 6 points, compared to 4 points in the control group ( $p=0.73$ ). Median ISI score was reduced non-significantly by 2 and 4 points, respectively ( $p=0.71$ ). Agitation level among patients undergoing wake-therapy was not significantly raised ( $p=0.22$ ).

**Conclusion:** So far a non-significant reduction in MADRS-S and ISI has been observed using combined wake- and bright light therapy, whilst agitation levels have not been significantly raised. Pending the final results from this randomized controlled trial, this approach could

become a valuable addition to conventional anti-depressive treatment, without significantly adding to harmful effects.

**Key words:** Depressive disorders, chronobiology, sleep deprivation, phototherapy, psychomotor agitation (Mesh-terms).

## **Introduction**

### **Depression**

During the last 50 years, the rate of diagnosed depression has become more prevalent in our society, at least for the mild and modest depressive states whilst prevalence of severe depression remains largely unchanged. Depressive disorders are among the diseases that in the whole world accounts for the greatest part of illness, loss of productivity and inability to work. In Sweden the point prevalence of depression is between 4 to 10% of the population and the risk of developing a depression during an individual's lifespan has been estimated to be approximately 27% for men and 45% for women (1).

### **Sleep disturbances in depressed patients**

A symptom of depression is sleep disturbances. Sleep patterns for depressed patients vary widely, from clinical insomnia to hypersomnia. Sleep disturbances and insomnia in depressed patients has been reported to afflict as many as two out of three patients (2). The prevalence of suicidal tendencies for patients suffering from sleep disturbances are significantly elevated (3) adding to the health risks of depressed patients. Furthermore, reports indicate that inferior response from psychological and psychopharmacological treatment in depressed patients with poor sleep quality is achieved (4, 5).

### **Wake-Therapy**

Wake-therapy has long been a recognized method in psychiatry, mainly used as a way of initiating a fast response and remission when treating patients with depressive symptoms of various character. More often wake-therapy is called "sleep deprivation", however this denomination has somewhat a negative sound and therefore the term wake-therapy will be used in this article concerning the therapeutic approach of keeping patients awake during the whole night, which often is termed total sleep deprivation (TSD) in scientific literature.

The positive anti-depressive effect of wake-therapy usually occurs during the second half of the night or on the next day after wake-therapy, this happens in approximately 60 % of patients (6). However this effect fades after sleep on the night after wake-therapy and therefore duration of the positive effect is short, diminishing in a matter of days (7). Although, numerous clinical trials have shown considerable effect of wake-therapy on the depressive state of severely ill patients, both in the shorter and longer perspective (8-10).

### **Bright Light Therapy**

The role of bright light therapy during treatment of depression was first established in the early 80's and in 2005 APA (American Psychiatric Association) determined that it could be used in treating depression. Either as an alternative to or as an adjunct therapy to antidepressants. Later studies has shown that for non-seasonal depression the effect of light-therapy is enhanced by as much as 30% when combined with antidepressant drugs (11, 12). When combining these two modalities with antidepressants the therapeutic response is fast, within hours and is estimated to last for weeks to months (13).

### **Potential Side Effects of Wake-Therapy**

However it is also important to rule out any possible side effect that could be potentially harmful for patients and staff. Agitation among patients suffering from mood disorders has been scarcely investigated. Earlier clinical trials using wake-therapy has sporadically reported on side effects such as hypomania and irritability which relates to agitation (9). To our knowledge no study has yet measured the possibility of increased agitation when undergoing wake-therapy. Recent research on the Swedish population found that patients suffering from depression has a significantly increased risk of performing violent crimes (14), indicating that a depressed patient may have a higher risk of becoming agitated or aggressive. Agitation can be considered as a potential security risk not only for the patient undergoing treatment but also for other admitted patients and for the staff. Furthermore, agitation increases the length of

stay, leads to more frequent re-admission to psychiatric wards and moreover, agitated patients have a tendency to require a larger amount of medication while admitted (15). In turn this causes higher health costs overall when treating agitated patients.

### **Necessity of additional interventional strategies in the treatment of depression**

Antidepressant drugs generate an antidepressant effect after 4 to 6 weeks (16), which might seem like a short duration from initiation of therapy and onset of effect when comparing many other pharmaceuticals. Considering the severe risks that a depressed patient faces in terms of suicide and suffering, this delay of effect could mean the difference between life and death for some patients. A more rapid, and at the same time safe, therapy should be available for inpatients suffering from severe depressive disorders in order to ensure their wellbeing. Wake therapy has yet not become general practice in psychiatric wards but has the potential of providing superior response of conventional anti-depressive treatment without adding to harmful effects. Prior to this randomized clinical trial, a pilot study comprising 10 patients was executed in 2014 that indicated positive effects from wake- and bright light therapy with remission from depression in 30 % of subjects whilst reported side effects were insignificant (17). The need for further studies on chronotherapeutic approaches when treating patients suffering from depressive episodes is still great and in order to be able to use wake-therapy and light therapy as a routine in psychiatric wards the need for more conclusive evidence is still sought for.

## Aim

This randomized clinical trial is aimed at determining the effect of combined wake- and bright light therapy as an enhancement of existing conventional anti-depressive treatment of various categories. Primary effect outcome is self-assessed alteration in depression after one week of treatment, reflecting a patient oriented view concerning improvement of remission during a depressive episode.

Furthermore, level of agitation was recorded among patients included in the clinical trial. We hypothesize that agitation may be a potential side effect to wake-therapy and therefore agitation was assessed and measured.



## Material and Methods

### Inclusion and Exclusion

Patients admitted to a closed psychiatric ward at Östra/Sahlgrenska University Hospital due to a depressive episode were screened for eligibility. The primary inclusion criteria were depressive episode, whether it may be of the unipolar, bipolar or chronic type. Multiple psychiatric diagnoses were included, however, a list of exclusion criteria was applied for ethical and safety reasons:

- Pregnant women
- Manic/hypomanic state or a diagnosis of bipolar disorder without mood-stabilizing treatment
- Epilepsy
- Age <18 or >65 years
- Ongoing psychosis
- Ongoing alcohol- or drug use disorder
- Ongoing compulsory psychiatric care
- Retinal dystrophies or age-related macular degeneration
- Porphyria, systemic/discoid lupus, chronic actinic dermatitis or solar urticaria

Reasons for exclusion are directly related to potentially harmful effects of either wake-therapy or bright light therapy (6). Pregnant women were mainly excluded due to ethical considerations. Alcohol or drug misuse would be a profoundly confounding factor when interpreting our results and therefore these patients were excluded. An anonymous list of all patients excluded after screening was archived including diagnosis, gender and age.

## **Screening**

Screening included several questionnaires and diagnostic tools in order to determine if patients were eligible.

Mini International Neuropsychiatric Interview (MINI) was used to establish the diagnosis of a depressive episode, a widely used standardized interviewing method with good diagnostic properties (18) aimed at examining and detecting certain symptoms indicating specific psychopathological conditions. For this study parts A, B and C of the MINI were used as these are aimed at Major Depressive episode (A), Suicidality (B) and Bipolar Syndrome (C) in order to strengthen clinical diagnosis of a depressive episode which is the main inclusion criteria.

Alcohol Use Disorders Identification Test (AUDIT) and Drug Use Disorders Identification Test (DUDIT) are both self-assessed questionnaires quantifying the amount of alcohol and drugs (non-prescribed) used by the patient, this aids in detecting any possible misuse or addiction that could lead to exclusion.

Morning-Eveningness Questionnaire (MEQ) assesses the circadian rhythm through 19 specific self-assessment questions. MEQ is a validated (6, 19) questionnaire determining a person's chronotype, pinpointing the appropriate sleeping-time, and also can give a valid indication as to what the optimal time would be for a patient to receive bright light therapy. A translated version was used which has shown high internal reliability among a Swedish cohort (20).

To follow anti-depressive response, the self-assessed version of Montgomery-Åsberg Depression Rating Scale (MADRS-S) which consists of 9 items with a scale of 7 on each item (0-6) rating severity of depressive symptoms. Self-rating on MADRS-S has shown good

correlation with expert assessment of depressive symptoms (21, 22) and is superior in measuring response to anti-depressive treatment compared with other rating scales (23).

To measure the severity of sleep disturbance experienced by the patients before entering the study we used the self-assessed Insomnia Severity Index (ISI) that is made up of 7 items with a scale of 5 (0-4) on each item. The ISI is a valid questionnaire that can detect clinical insomnia and give a relevant depiction of sleep disturbances (24, 25).

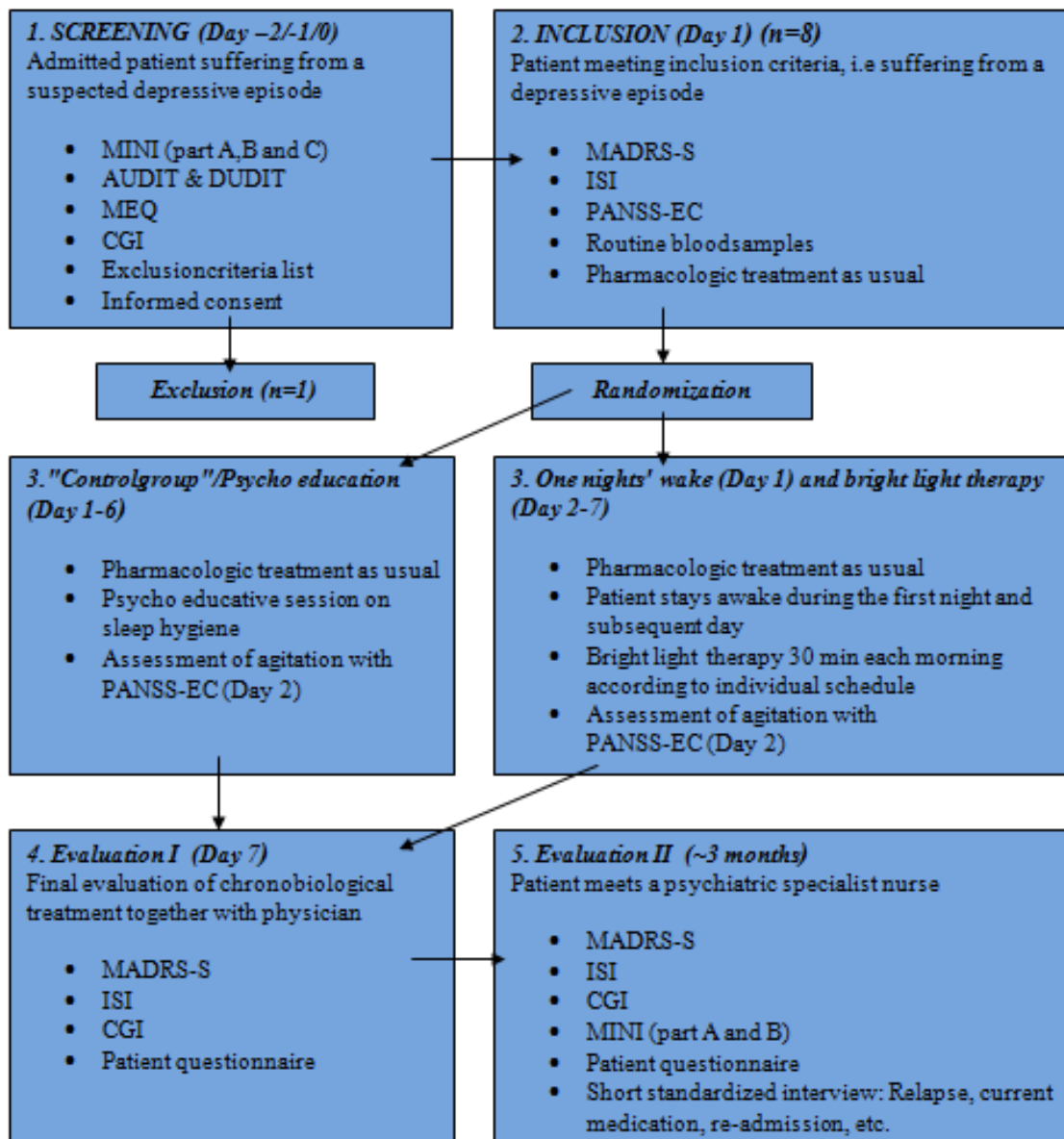
Clinical Global Impression of Severity (CGI-S) was used to take into consideration the physicians assessment in addition to the patients self-assessed MADRS-S. The estimation in the CGI-S is highly influenced by the amount of clinical experience and varies between physicians.

Positive And Negative Symptoms of Schizophrenia (PANSS) is a medical scale used on patients suffering from schizophrenia and contains several questions assessing agitation-level. The Positive And Negative Symptoms of Schizophrenia - Excited component (PANSS-EC) is a validated (26) modified version of the PANSS consisting of five items (Excitement, Hostility, Tension, Uncooperativeness and Poor impulse control) aimed at measuring the agitation level only in patients.

### **Study protocol**

Patients included in the trial were block randomized using a randomization programme online to either wake-therapy combined with light therapy in addition to conventional anti-depressive treatment or to psycho education on sleep hygiene in addition to conventional anti-depressive therapy. After randomization patients were informed on the protocol for the forthcoming week and the latter follow-up as depicted in figure 1.

**Figure 1.** Flow chart describing study protocol.



Patients in the wake- and bright light therapy were encouraged to stay awake for the whole night (day 1) and to go to sleep on the following night (day 2) on the appropriate sleep onset time as concluded in the MEQ. In the morning after wake-therapy (day 2) patients received 30 min of bright light therapy on the appropriate start time as concluded in the MEQ, bright light was thereafter administered on this time on the forthcoming days and in total, each patient received 6 sessions of bright light therapy during 6 days (day 2-7). Each session of bright light

therapy has a duration of 30 min, there is no need for longer sessions as the aim is merely to mimic a springtime sunrise (6).

The patients randomized to psycho education received a short psycho educative session in sleep hygiene, that was constructed by the author, based upon current cognitive behavioural therapy models concerning sleep disturbances (27), and carried out by a specialist nurse in psychiatry. The psycho educative template can be found in "Appendices". Considerations were made concerning the option not to offer anything to this group since it is the control group, however, such an approach could come across as a negative factor for patients in this group and could bias end results by introducing a potential nocebo effect.

Both groups received psychopharmacologic treatment as usual and physicians was blinded to which group a patient would be randomized to after screening and inclusion to the trial.

On day 1, before wake-therapy or psycho education, patients in both groups filled out the self-assessed MADRS-S and ISI. In addition, all patients were rated by the treating physician using CGI-S on day 1 (results not presented in this thesis). On day 7, after one night of wake-therapy and 6 times of bright light therapy or alternatively only psycho education on sleep hygiene, patients again filled out the MADRS-S, ISI and were assessed using CGI-S. Other randomized trials has used this time interval and it has been sufficient to establish significant differences between groups exposed to wake- and/or bright light therapy compared to control groups (16, 28, 29). Approximately three months after discharge, patients will meet a psychiatrist that has no knowledge of what treatment the patient was randomized to and again fill out the MADRS-S and ISI. Comparison can thereafter be made between the two groups concerning changes in the MADRS-S, ISI and CGI score.

All patients were also requested to fill out a customized feedback questionnaire concerning the wake- and bright light therapy alternatively the psycho educative session at day 1,7 and after 3 months. The questionnaire can be found in "Appendices".

On day 1 all patients in both groups was assessed by a doctor or nurse using the PANSS-EC. On day 2 all patients in both groups was subjected to a second assessment to evaluate any changes in agitation after initiation of either wake-therapy in addition to conventional anti-depressive treatment or conventional anti-depressive therapy only. The psycho educative group will be considered as a control group due to the fact that there is no expected significant change in agitation from one day to the other when unexposed to additional stressing factors.

Before patient enrolment the study protocol was registered at Clinical Trials (NCT02503124), which facilitates full disclosure of our findings regardless of the outcome and in turn helps other clinicians in customizing studies and avoid publication bias. The primary outcome registered in that protocol is the number of patients with a reduction  $>50\%$  on MADRS-S.

## Ethics

The ongoing clinical trial at Östra/Sahlgrenska University Hospital involving admitted patients suffering from depressive symptoms is performed to evaluate the effect of wake-and-light therapy and potentially include this treatment as a possible standard treatment available for this patient group. In general, negative effects of conducting the study are few if any.

Ethical aspects were taken into consideration when constructing the study design. The PANSS-EC interview is a non-invasive assessment and does not violate patient integrity. The assessment forms does not contain patient sensitive information and can't be connected to a specific patient by staff or any other person outside of the project. Ethical approval for the clinical trial has been granted by the regional ethics committee in Gothenburg, dnr Ö 11-2014, and the Helsinki Declaration provided the ethical guidelines for this master thesis. No individual is identifiable in the written document.

## **Data analysis and Statistical methods**

In order to guarantee anonymity all data has been depersonalized and collected into an excel sheet only accessible by the author. All statistical analyses were made using IBM SPSS statistics 21.0.0. (SPSS Inc, Chicago, IL, USA). To determine if the different sets of data from the two groups are significantly different from each other, a t-test has been used on the mean differences for each analysis. Based on power calculations a total of 50 patients will be included and at the writing of the thesis 8 patients have been randomized.



## Results

### Demographics

At present, a total of 8 patients have been randomized (mean age 34, 75 % women). The psycho educative group consists of five patients (mean age 29, 80 % women) and the wake-and bright light therapy group comprises three patients (mean age 42, 67 % women). All patients fulfilled the criteria for a depressive episode according to MINI and one had bipolar disorder.

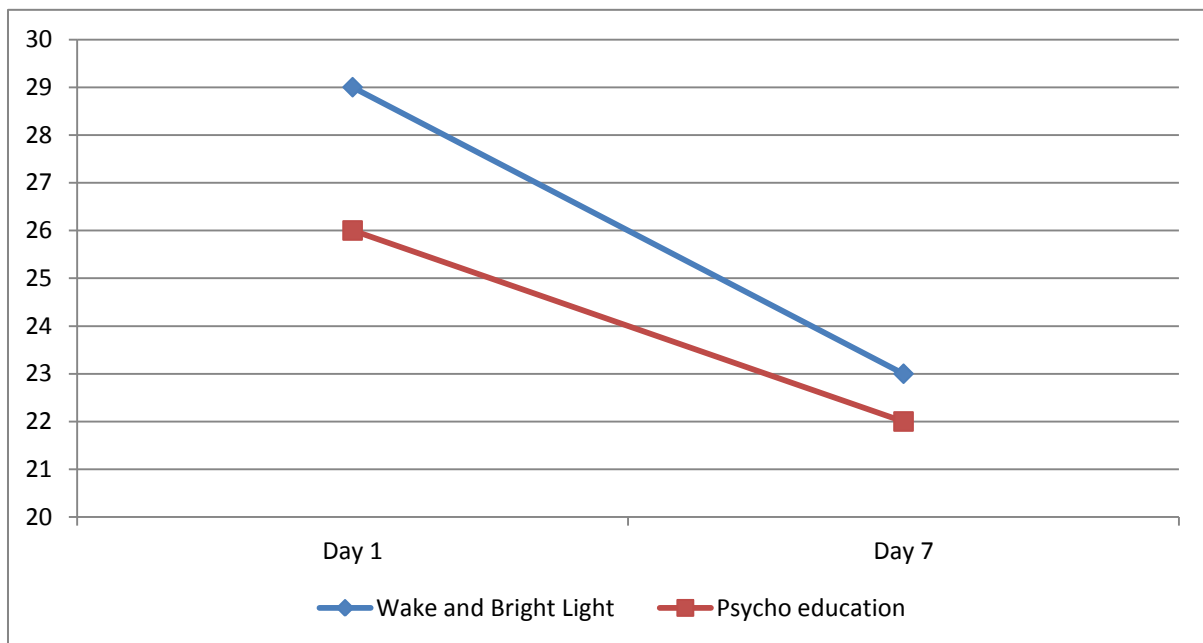
Differences in treatment was considerable and there was no intention of influencing the decision on which anti-depressant the patients should be treated with. Anti-depressants on day 7 is described for each patient as well as any mood stabilizing treatment, displayed in the demographic overview below (Table 1). Patient no. 2, in the psycho educative group, had a mood stabilizer for bipolar disorder. The same patient was re-admitted to a closed psychiatric ward shortly after discharge. None of the other patients had been re-admitted to a psychiatric ward when last checked on 24th of November 2015.

**Table 1. Overview of the first 8 patients randomized to Wake- and Bright Light Therapy or Psycho education**

Pat.	Treatment arm	Age/Sex	Antidepressant/Mood stabilizer	Re-admission
1	Psycho education	23/W	Sertralin / None	No
2	Psycho education	39/W	Venlafaxin + Mirtazapin / Valproate	Yes
3	Wake + bright light therapy	46/W	Escitalopram / None	No
4	Wake + bright light therapy	27/W	Escitalopram / None	No
5	Psycho education	38/M	Venlafaxin / None	No
6	Wake + bright light therapy	52/M	Anafranil / None	No
7	Psycho education	27/W	Citalopram / None	No
8	Psycho education	20/W	Sertralin / None	No

## Depression

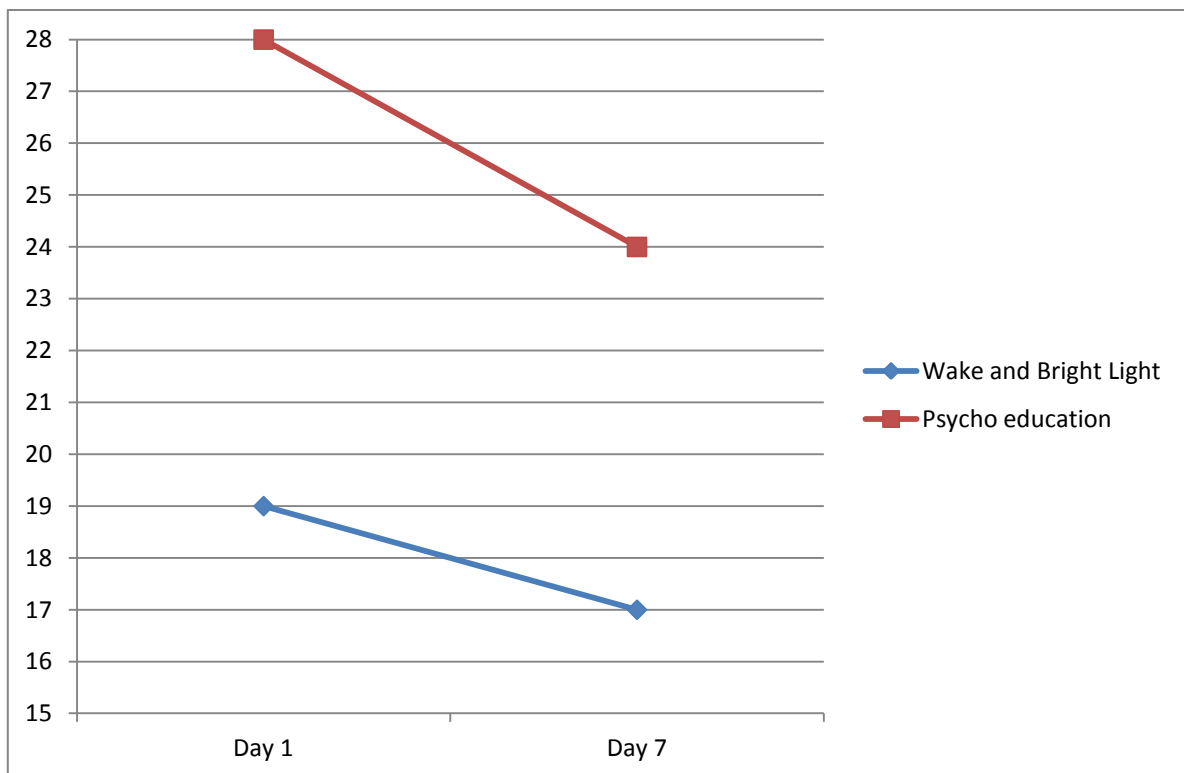
The mean reduction of MADRS-S score was 7.0 (Std.dev 12.4) in the whole group. This was non-significant ( $p=0.71$ ) between the groups. In the wake- and bright light therapy group the mean reduction was 4.7 (Std.dev 7.1) compared to the psycho educative group where the mean reduction was 8.4 (Std.dev 15.3). Analyzing the median for the groups there was a reduction of 5 points in the whole group. In the wake- and bright light therapy group the median reduction was 6 compared to the psycho educative group where the median reduction was 4 (Figure 2).



**Figure 2.** Median reduction in MADRS-S score on day 7 among randomized patients ( $n= 8$ ) to Psycho education ( $n= 5$ ) and wake-therapy combined with bright light ( $n= 3$ ) respectively.

## Insomnia

Concerning severity of insomnia, measured as reduction in ISI score, a mean reduction of 4.3 (Std.dev 5.3) was found in the whole group. This was non-significant ( $p=0.73$ ) between the groups. In the wake- and bright light therapy group the mean reduction was 3.3 (Std.dev 2.3) compared to the psycho educative group where the mean reduction was 4.8 (Std.dev 6.7). Analyzing the median for the groups there was a reduction of 3 in the whole group. In the wake- and bright light therapy group the median reduction was 2 compared to the psycho educative group where the median reduction was 4 (Figure 3).



**Figure 3.** Median reduction in ISI score on day 7 among randomized patients ( $n= 8$ ) to Psycho education ( $n= 5$ ) and wake-therapy combined with bright light ( $n= 3$ ) respectively.

## **Agitation**

No increased agitation measured with PANSS-EC was present for 7/8 patients on day 1 or day 2 respectively. Only one patient was scored 3 (mild) concerning excitement on the day after wake therapy. A mean increase of 0.3 (Std.dev 0.7) was found in the whole group. There was no significant difference in agitation level on day 2 between the groups ( $p=0.22$ ). In the wake- and bright light therapy group the mean increase was 0.7 (Std.dev 1.2) compared to the psycho educative group where there was no increase in agitation. The median alteration in both groups were 0.

## **Patient questionnaire**

Feedback from patients concerning how they perceived the chronotherapeutic intervention given revealed that overall experiences from participation was positive and generally all patients reported that they had somewhat been helped by the intervention, regardless of group. Patients in the wake- and bright light group overall thought that the intervention was a modern treatment, would have participated if they were asked again, would recommend it to a friend suffering from similar symptoms and that the intervention should be available for all patients that would like it. None thought that there were any side effects, however one patient complained that the brightness of the light source made it hard to constantly look at it for 30 minutes. When asked about if they had any difficulties with their chronobiologic treatment, two patients reported they had some difficulties which mainly concerned trying to keep awake during the first night.

All patients in the psycho educative group but one (no.8, see table 1) thought that the intervention was somewhat modern, would have participated if they were asked again, would recommend it to a friend suffering from similar symptoms and that the intervention should be available for all patients that would like it. Several thought that there were side effects, however they did not specify any side effect that logically could be related to the psycho educative measures, but rather side effects overall during the week. When asked about if they had any difficulties with their chronobiologic treatment, four patients reported they had difficulties, whilst one patient (no.5, see Table 1) had none. One of the patients (no.2, see table 1) was very positive towards psycho education, was very satisfied with it in all aspects , reported no side effects and commented that she would continue to work on sleep hygienic measures after discharge.

## Discussion

This randomized clinical trial has so far included 8 patients and the results presented are preliminary since a total of 50 patients will be included. So far the reduction in MADRS-S and ISI is not statistically significantly different. Due to the fact that the study sample is still small, with five patients in the control group and three patients in the wake- and bright light therapy group, statistic tests cannot yet be performed with certainty to reveal if there are significant positive anti-depressive effects to be drawn from the chronotherapeutic approach used in this study. Reported in this study are the mean and median reduction in MADRS-S and ISI score. We have emphasized the difference in median reduction rather than the mean, since the study population is small and at present consists of values with a large variability. A large proportion of the variance in the psycho educative group stems from one patient (no.2), the only bipolar patient so far, which reported 54 points (highest score) on MADRS-S upon inclusion and 19 points after one week. After discharge this patient was soon re-admitted and did then report the occurrence of a hypomanic/manic state shortly after being discharged. Hence, there are some concerns that this episode could have contributed to the sudden effect seen in MADRS-S for this patient.

When the study population reaches a larger size, it is more motivated to use a students t-test, comparing mean reduction in the groups, as well as Fishers exact test (e.g. how many patients obtains a 50% reduction in MADRS-S score after 7 days?) to more accurately describe the effects of chronotherapeutic treatment. Continuation of the study is still highly motivated as several earlier studies have proven to provide good effect on depressive episodes using chronotherapeutic treatment (8, 10-13).

Martiny et al (16) used a similar approach in a 9 week RCT which showed rapid and significant antidepressant response compared to placebo (exercise) after wake-therapy and bright light therapy in over 40 % of patients and total remission in almost 24 % after 1 week

of intervention. However, sleep time stabilization was also included in this study and could account for a part of the effect shown in that study. They also generalized the choice of antidepressant for patients, giving them duloxetine, which differs from the approach used in our protocol. As our study population so far indicates that a great variety of antidepressants are used, this in effect becomes a confounding factor for our results. Different psychopharmacologic treatment could account for the differences seen in anti-depressive response. But, on the other hand, as our patients are not subjected to generalized treatment they benefit from individualized treatment and instead, if differences ultimately can be seen in this trial, that are not directly related to a significant difference in antidepressants, then this chronotherapeutic approach could be used by a wider category of patients.

In this trial the patients randomized to psycho education are considered as controls. As in the study mentioned above, this group was not completely without intervention. One might argue that patients receiving a psycho educative session on sleep hygiene logically might experience a positive effect on both sleep disturbances and ultimately also on malaise. However, the session was short and given only once by a nurse without professional education on cognitive behavioral therapy. It was based on a short template (see Appendices) summarized by the author, whom likewise has restricted knowledge and experience on cognitive behavioral therapy. That said, patients experiencing effect, if any, from this intervention is likely to be positive which would tend to reduce the discrepancy in positive effect between the two groups. Therefore any significant difference between the two groups rather strengthens than weakens the thesis that wake-therapy combined with bright light quickens remission in depressed patients.

On the contrary, by actively informing about the study and potential effects during screening in order to include a patient it might affect the patient negatively if they were to be offered nothing and simply be told that they are "controls". By formally informing about two different

intervention protocols and that randomization will choose which kind, the patient still feels like something has been gained by accepting participation and the confounding factor of attention and extra care is somewhat reduced.

Although the Swedish population is generally well-educated in the English language, efforts were made to present all questionnaires and information in Swedish. This should have a tendency to minimize possible misunderstandings during self-assessment and increase compliance overall in the trial concerning instructions on wake- and bright light therapy as well as psycho educative measures.

MADRS-S is routinely used by the psychiatric care in Gothenburg and patients in this study had all been presented to this type of self-assessment prior to admission. Not all patients were familiar with the ISI, but instructions are clear and easy to understand, no patients reported any problems whilst filling out this questionnaire. As this type of self-assessment correlates well with objective expert opinion concerning depressive symptoms (21, 22) and insomnia (24, 25) we consider that changes in total score is a good reflection of improvement and practically without any rater bias.

Assessing agitation in this trial showed that there was little to nothing to measure as patients overall did not present with any symptoms of an agitated value. Only one patient presented with heightened excitation one the day after wake-therapy, excitation level was rated as mild. Due to logistic reasons, it was not possible at all times that patients could be rated according to PANSS-EC by the same rater. Therefore, on some patients, different raters have assessed agitation on day 1 and 2. However, clear and simple instructions were attached with the rating form on how to assess agitation. Although this approach entails that inter rating reliability has to be considered and could bias the result. One must also remember the fact that PANSS-EC is primarily aimed at measuring agitation or aggressiveness in psychotic patients and therefore the threshold for rating increased level of agitation is somewhat higher than one might have



wished. But the lack of tools in assessing agitation on depressed patients leaves no other choice but to use scales of this sort. A need for more thorough investigation concerning prevalence of agitation in depressed patients and how to best assess it seems to be still needed. Feedback from the patients that have underwent the study protocol so far revealed that overall patients are positive about participating and has not experienced any severe side effects, even if some side effects were reported on the sheet in the psycho educative group. Those described are more likely related to medications, however if there is a predominant occurrence of side effects in either group one must consider that they could relate to that specific intervention. Regardless of this, the feedback in general does support that the trial should proceed.

In the study mentioned earlier, performed by Martiny et al, they added a later follow-up of the same study population, where they noticed that response and remission rates continued to improve and was significantly higher for the wake- and bright light therapy group after 20 weeks (8), indicating that the effect of wake and bright light therapy may not only be considered as a procedure with merely short term effects. Potentially, our results from the three month follow-up in this study will contribute with more knowledge concerning the anti-depressive effect in terms of response, remission and prevalence of relapse in the somewhat longer perspective.

## Conclusion and Implications

In this randomized controlled trial involving the first 8 patients out of a total of 50 patients, a non-significant anti-depressive effect, measured as reduction in self-assessed MADRS-S score, from wake-therapy combined with bright light therapy in the morning for one consecutive week was found. A non-significant correlation concerning improved sleeping patterns, measured as reduction in self-assessed ISI score, was also established. Although non-significant, reduction in ISI score was greater in the control group. Concerns about possible increase of agitation when undergoing wake-therapy were appeasing as only one out of three patients were assessed with elevated excitation (one out of five items in the PANSS-EC) to a mild degree. Comparison between the groups revealed that agitation level was not significantly raised after wake therapy.

A need for further studies investigating the probable positive effects, and possible side effects, from chronotherapeutics is still much needed. The continuation of this randomized controlled trial will hopefully strengthen the scientific evidence of this interventional approach when treating patients suffering from depression so that remission may be greater and quicker.

## Acknowledgement

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## Populärvetenskaplig sammanfattning

### Randomiserad Klinisk Studie Gällande Effekten av En Hel Natts Vakenhet Efterföljt av Ljusterapi vid Depression

Depression är en vanligt förekommande sjukdom i den svenska befolkningen. Den behandling som i dagsläget är tillgänglig för personer som lider av depression består av i första hand kognitiv beteendeterapi och antidepressiva läkemedel, samt i svåra fall elektrokonvulsiv behandling. De flesta patienter som läggs in för psykiatrisk vård blir insatta på antidepressiva läkemedel, men den antidepressiva effekten av dessa dröjer normalt 4-6 veckor. Belastningen på den psykiatriska vården i Sverige är idag hög och oftast kan inte patienterna kvarstanna ända tills man sett den positiva effekten av antidepressiva. Ett behov av snabbare effekt och därmed kortare tid till återhämtning tycks finnas. Därför har en klinisk studie initierats för att undersöka om en hel natts vakenhet i kombination med en veckas ljusterapi varje morgon kan påskynda den antidepressiva effekten av läkemedel.

Det är sedan länge känt att vakenhet har en snabbt insättande antidepressiv effekt, problemet är att denna effekt ofta avtar efter det att patienten går och lägger sig på efterföljande natt. Vår teori var att man skulle kunna upprätthålla effekten genom att behandla patienterna med ljusterapi varje morgon i en vecka efter att man varit vaken en hel natt. Liknande studier som gjorts med denna kombination har noterat att detta verkar fungera. En del studier med vakenhetsterapi har sporadiskt rapporterat kring biverkningar av vakenhet såsom uppvarning, irritation och orolighet. Vi ville därför också noggrannare undersöka om patienterna uppvisade dessa symptom efter att ha varit vakna en hel natt.

För att mäta om denna metod verkligen är effektiv så skedde ett slumpmässigt urval där patienterna antingen mottog vakenhetsterapi i kombination med ljusterapi eller istället fick en kort utbildning i sömnvanor och sömnbeteende. Varken patienter eller läkare visste vilken

grupp som varje patient skulle väljas ut till. För att kunna mäta skillnaden mellan grupperna fick patienterna fylla i skattningsformulär gällande både depressiva symptom och sömnbesvär innan de gick med i studien. Sedan fyllde de i samma formulär när en vecka passerat.

Skillnaden i minskning av depressiva symptom och sömnbesvär kunde sedan jämföras.

Då det är en pågående studie som hittills består av 8 patienter så är nuvarande underlag för litet för att man ska kunna dra några slutsatser. Målet är att 50 patienter ska ha genomgått behandlingen och sedan kan noggrannare analys utföras. De preliminära resultaten visar på en median reduktion av antidepressiva symptom som är 50 % större i gruppen som genomgått vakenhets- och ljusterapi jämfört med gruppen som fick utbildning gällande sömnen. Den mediana minskningen av sömnbesvär var endast hälften så stor efter vakenhets- och ljusterapi jämfört med utbildning gällande sömn. Gällande ökad oro, irritabilitet och uppvarvning så kunde man inte se någon tydlig ökning av dessa symptom bland patienter som varit vakna en hel natt.

Sammantaget tycks vakenhets- och ljusterapi vid depression kunna ge en viss antidepressiv effekt, hur stor denna är kommer att visa sig när alla 50 patienter genomgått studien. Vår förhoppning är att denna behandlingsmetod kan bli en del av behandlingsarsenalen vid depression om den visar sig effektiv.

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## Appendices

### Psykoedukation i sömn

#### Introduktion

Patienter inkluderade i det pågående forskningsprojektet kring Kronobiologiska metoder som efter randomisering ingår i gruppen ”Psykoedukation i sömn” ska erhålla ett samtal à ca 20 min med läkare eller sjuksköterska kring sömnhygien. Mallen nedan är tänkt som ett stöd i detta samtal och baserar sig på rådande kognitiv beteendeterapi kring sömnstörningar (KBT inom psykiatri, Natur & Kultur 2013).

#### Beteendeanalys

Beteende rörande sömn är viktigt att kartlägga för att kunna ge patienten möjlighet till lämplig reflektion och insikt. Fråga in till:

- Typiskt sömnmönster, tag även hjälp av ISI-skattningsskalan
- Aktiviteter i förbindelse med sömn (fysisk träning, spännande bok/film,
- Intag av centralstimulerande medel (nikotin, koffein). När och hur mycket?
- Hur lång tid tar det från det att man lägger sig i sängen till insomning?
- Aktivitetsnivå under dagen

Målet med KBT gällande sömn är att patienten själv ska beskriva vad som är problematiskt med sin sömn och vad den tror är möjligt/lämpligt att förändra för att sömnen ska bli bättre. Målsättningen är alltså snarare självinsikt än ”goda råd”.

#### Skillnaden mellan Trötthet och sömnhet

En vanlig missuppfattning hos patienter med sömnbesvär är att de upplever ett behov av att sova när de känner sig ”trötta”. Trötthet kan betraktas som en känsla förknippad till hög grad av mental och/eller fysisk spänning/aktivering och kan inte förväntas avhjälpas av sömn enbart. Trötthet kan också ha sin grund i många kroppsliga sjukdomar och kan inte enbart skyllas på sömnen.

Sömnhet är relaterat till vissa kroppsliga upplevelser så som gäspningar, ”grus i ögonen”, svårighet att hålla ögonen öppna och muskulär avslappning. Dessa signaler ska av patienten tolkas som ett behov av att sova och det är då lämpligt att gå och lägga sig för att invänta den ofrivilliga insomningen.

#### Fem förtydliganden om sömn

Patientens inre och yttre händelser (stress, sociala konflikter etc) bidrar till en variation i sömnkvalitén.

Det finns inga tekniker som kan användas för att somna. Variation till en viss grad måste tillåtas eftersom sömnen inte står under viljemässig kontroll

En sömlös natt är ingen katastrof. Även om man sovit dåligt klarar man av morgondagen.

En natt av dålig sömn kompenseras automatiskt nästkommande nätter och resulterar i en djupare, mer utvilande sömn ( ökad deltasömn).

Genom nya kunskaper och vanor gällande sömn kan sömnen förbättras på sikt. Det är en process som tar tid.



## **Stimuluskontroll**

Det finns ett antal förhållningssätt och regler kring sömn som patienten behöver ha kännedom och insikt i för att på sikt uppnå och bibehålla en regelbunden dygnsrytm med god sömnkvalitet.

### **Lägg dig att sova enbart när du känner dig sömning**

Bestäm inte en regelbunden läggningstid på förhand

Lyssna till din inre sömning. Trötthet och sömning är olika upplevelser.

Vid tecken till sömning -> gå och lägg dig (ej dagtid)

### **Använd sängen enbart till att sova i**

Sängen ska förknippas med sömn

Undvik aktiverande sysselsättningar (Ex. tv-tittande, läsning, problemlösning etc.) i sängen

Sexuell aktivitet är tillåten

Viktigt att knyta tillbaka till beteendeanalysen här. Om patienten exempelvis läser och faller i sömn av detta är det fortsatt lämpligt beteende. Men om patienten utför aktiverande sysselsättningar som försvårar insomnandet så är det olämpligt beteende

### **Om du inte kan somna -> Stig upp och gör något annat**

För lång tid i vaket tillstånd i sängen medför negativ betingning mellan sömn och säng.

Ligg ej vaken längre än 20 min.

Stig istället upp och förflytta dig till annat rum

Ägna dig åt något som ej är krävande. Exempelvis läs något lättläst i en lugn och tyst miljö. Relatera tillbaka till beteendeanalys kring aktiviteter som patienten upplever som avslappnande och som bidrar till sömning.

När du märker tecken till sömning -> återvänd till sängen och invänta den ofrivilliga insomningen.

### **Om du fortfarande inte kan somna -> Stig upp på nytt**

En av de svårare reglerna att förhålla sig till.

Viktigt för att säkerställa en positiv betingning mellan sömn och säng.

Detta moment kan behöva genomföras flera gånger per natt i början.

### **Stig upp samma tid varje morgon**

Väckarklocka/alarm ska vara ställd på samma tid varje morgon. Alla dagar, även helg.

Stig upp när klockan/alarmet ringer varje morgon oavsett hur mycket du sovit eller hur trött du är.

Ligg inte kvar vaken i sängen efter väckningstiden.

### **Sov inte på dagtid**

För att förankra en hälsosam dygnsrytm.

För att tydligt koppla sömn till nattetid och sängen.

*Psykoedukativ mall utformad av Mats Widmark-Jensen  
för användning i Kronobiologisk studie vid Östra Sjukhuset*

## Utvärdering av kronobiologiska behandlingsmetoder på avdelning 363

Frågorna nedan skattas från 1 = instämmer inte alls till 5 = instämmer helt och gäller endast given kombinerad ljusterapi och vakenhetsterapi alternativt psykoedukation i sömnhygien under vårdtillfället.

1. Jag blev hjälpt av kronobiologisk behandling

1      2              3              4              5

2. Jag upplevde svårigheter med min kronobiologiska behandling

1      2              3              4              5

3. Detta känns som ett modernt sätt att behandla psykiska störningar

1      2              3              4              5

4. Jag upplevde detta som tvångsbehandling/tortyr

1      2              3              4              5

5. Om jag kunde välja igen skulle jag ha samtyckt till behandlingen

1      2              3              4              5

6. Jag skulle rekommendera behandlingen till en närstående med liknande besvär

1      2              3              4              5

7. Denna behandling borde vara tillgänglig för patienter som önskar denna

1      2              3              4              5

8. Jag upplevde inga biverkningar

1      2              3              4              5

I fall du upplevde biverkningar kan du vänligen beskriva dessa:

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Övriga kommentarer:

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Tack för din hjälp till att förbättra kronobiologisk behandlingsmetod!