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Title

Dynamic LED-light versus Static LED-light for depressed inpatients: study protocol for a randomized clinical study.

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ABSTRACT

Introduction: Retrospective studies conducted in psychiatric inpatient wards have shown a relation between the intensity of daylight in patient rooms and the length of stay, pointing to an antidepressant effect of ambient lighting conditions. Light therapy has shown a promising antidepressant effect when administered from a light box. The emergence of Light Emitting Diode technology has now made it possible to build luminaires into rooms and to dynamically mimic the spectral and temporal distribution of daylight. The objective of this study is to investigate the antidepressant efficacy of a newly developed dynamic LED-lighting system in an inpatient ward.

Methods and analysis: In all, 150 inpatients with a major depressive episode, as part of either Major Depressive Disorder or as part of a Bipolar Disorder, will be included. The design is a two-arm 1:1 randomised study with a dynamic LED-lighting arm and a static LED-lighting arm, both with usual treatment in an inpatient psychiatric ward. The primary outcome is the baseline adjusted *score* on the Hamilton Depression Rating Scale 6-item scale at week 3. The secondary outcomes are the mean score on the Suicidal Ideation Attributes Scale scale at week 3, the mean score on the Hamilton Depression Rating Scale 17-item at week 3, and the mean score on the WHOQOL-BREF at week 3. The spectral distribution of daylight and LED-light, with a specific focus on Non-Image-Forming light mediated through the intrinsically photosensitive Retinal Ganglion Cells, will be measured. Use of light luminaires will be logged. Assessors of Hamilton depression rating scale scores and data analysts will be blinded for treatment allocation. The study was initiated in May 2019 and will end in December 2021.

Ethics and dissemination: No ethical issues are expected. Results will be published in peer-reviewed journals, disseminated electronically and in print, and presented at symposia.

Trial registration number: ClinicalTrials.gov NCT03821506.

Keywords: Major Depressive Disorder, Bipolar Disorder, Lighting, Light, Inpatients, Chronotherapy, Randomized Controlled Trial.

Trial protocol number: RoomLight version 1.9.

Strengths and limitations of this study:

- This is the first randomized clinical trial investigating the antidepressant effect of a dynamic LED system in an inpatient psychiatric ward
- The study has a rigorous design and a large sample size enabling it to find a clinically relevant antidepressant effect
- Patient stay might not be of an adequate length to achieve full antidepressant effect of the lighting system

INTRODUCTION

Depression

Depressive episodes, either as part of a Major Depressive Disorder (MDD) or as part of a Bipolar Disorder (BD), is a prevalent and a leading cause of disability worldwide. Society suffers large direct and indirect losses due to lost work, sickness, and early retirements, and WHO ranks major depression as a significant contributor to the global burden of disease [1]. In Denmark alone, the costs of depression amount to an estimated 14 billion DKK per year. Depression can affect an individual to an extent that everyday activities and chores are insurmountable. These patients often have suicidal ideation and despair and need inpatient care including treatment with mood stabilizers, antipsychotics, antidepressants, psychoeducation, psychotherapy, and occupational therapy. Typically, these patients will still suffer from varying degrees of depression when discharged [2 3] and relapse, readmission, and even suicide, upon discharge, are major treatment challenges [4]. Despite intense efforts during the last decades there has been no breakthrough for neither drug development nor for any other treatment modality and 10-25% of patients are treatment resistant [5]. Thus, there is a need for the development of new treatment options [6]. Light therapy has shown an antidepressant effect in outpatients, when using light box administered treatment, but we need studies in more severely depressed inpatients [7]. The technological development has made it possible to mimic daylight using Light Emitting Diodes (LED) and to build these into building. This makes it possible to administer light therapy throughout the 24-hour day with dynamic spectral and temporal distribution of the light. The present efficacy study investigates the possible antidepressant effect of a new, dynamic type of

general lighting in the treatment of a major depressive episode either as part of an MDD or a BD in patients admitted to a specialized affective disorders ward.

Bright Light Therapy

Light has been used to treat medical conditions, such as melancholia or lethargy for at least a thousand years [8 9] and daylight has been considered important for centuries when building hospitals [10] . Animal research conducted through many decades has shown that dosage and timing of light have impact on reproduction, activity, and sleep [11] and in the 1980s it was discovered that light could suppress melatonin secretion, in humans [12], indicating that light gives cues to the brain about night time and season. The resultant clinical description of Seasonal Affective Disorder (SAD) and the theoretical analogy with hamster hibernation cycles led to the development of bright light treatment [13-16]. It was later discovered that light pulses applied in the morning phase advance the sleep-wake cycle (and other rhythms) whereas light applied in the evening delays the sleep-wake cycle (and other rhythms). This is named the Phase Response Curve (PRC) for light in humans [17 18] , and is the basis for the mechanism of "entrainment" – the synchronization of a self-sustaining oscillation (such as sleep) by an external forcing oscillation (such as daylight or artificially timed light). In 2000, a new non-visual retinal receptor, the intrinsically photosensitive retinal ganglion cells (ipRGC), was discovered in the human retina [19]. The ipRGC receptors have a peak spectral sensitivity for the blue portion of the light spectrum (460 nm – 480 nm) [20]. Since then it has been found, primarily through animal research, that the ipRGC regulates the circadian system through input to the suprachiasmatic nuclei (SCN) and the pineal gland, but also, through newly found pathways, to brain structures known to be involved in depressive illness [21-23]. This has given us a better understanding of how light can have a fast working antidepressant effect in humans and has stimulated research on the effect of using light with temporally shifting spectral compositions and intensity. The impact of the signals from the ipRGC is, among other effects, responsible for the ability of light to time and stabilize the sleep-wake cycle and to adjust the seasonal regulation of serotonin [24]. Light Emitting Diode (LED) -light can be tuned to be particularly rich or dim in the blue wavelength spectrum in contrast to conventional compact fluorescent light (CFL). Thus, LED-light can be adjusted to maximize the impact on the ipRGC system. The temporal regulation of the spectral composition and intensity of LED-light is clinically important. Too much blue light in the evening will delay the sleep-wake cycle, through the PRC mechanism, causing a

difficulty falling asleep (sleep onset insomnia) [25], whereas blue light in the morning will advance sleep and increase alertness.

There is an association between depression and late chronotypes [26] and late chronotypes is associated with nonresponse to treatment [27]. Furthermore, patients with depression are prone to drift to later sleep schedules [3]. We should thus expect that dynamic lighting with enriched blue morning light and low blue light content in the evening would prevent drifting or even phase advance the sleep-wake cycle and thus augment the antidepressant treatment response.

Since the publication of the first study on the effect of light therapy for depression by Rosenthal et al in 1984 [13], a large number of studies have been carried out to investigate the efficacy of bright light treatment on both seasonal and non-seasonal depression. Light is one of the most thoroughly investigated chronotherapeutic treatments in addition to wake-therapy [28] and sleep phase advance [29]. In 2004, Tuunainen and colleagues published the Cochrane systematic review "Light therapy for non-seasonal depression" [30]. The conclusion was that light therapy must be regarded as a promising treatment method, but because of the heterogeneity among the studies, methodological problems and a lack of systematic collection of adverse events (AE's), the recommendation of light therapy as a treatment of depression should be considered with some caution. In a systematic review from 2007, Even et al, found an additive effect of light therapy when used as augmentation to antidepressant therapy in non-seasonal depression [31]. In a systematic review from 2016, Perara et al, included 20 RCT's using light therapy for non-seasonal depression and found an overall small antidepressant effect (SMD -0.41; 95% CI -0.64 to -0.18), but with a high risk of bias and inconsistency between studies [32]. In subgroup analyses (stand-alone light therapy versus adjunctive light therapy, morning light therapy versus evening light therapy or other times of day, light therapy for in- versus outpatients, placebo light conditions versus non-light-based placebo conditions) some support was found for a better effect of light when used as monotherapy, in the morning, for outpatients, and when compared with non-light-based placebos. Only four of the 20 studies had a low risk of bias on all items on the Cochrane Risk of Bias Tool [33-36]. A Danish study found a significantly better effect of a combination of bright light therapy plus sertraline compared with dim red placebo light and sertraline, in 102 outpatients [33]. In a Canadian study 122 outpatients were compared in four groups: (a) active light plus active fluoxetine, (b) active light plus placebo fluoxetine, (c) inactive negative ion generator plus active

fluoxetine, (d) inactive negative ion generator plus placebo fluoxetine [34]. A significantly better effect was found in the group receiving the combination of active light plus active fluoxetine, as well as in the group receiving the combination of active light and placebo fluoxetine compared to the group receiving the combination of inactive negative ion generator plus placebo fluoxetine. A study performed in 84 elderly (> 60 years) outpatients with non-seasonal depression found a statistically significant beneficial effect of active versus placebo light treatment [35]. However, another study found no difference in depression outcome between groups, and a low reduction in depression severity across groups of 16 %, among 81 elderly outpatients (> 60 years) with non-seasonal depression, treated with bright or placebo light administered at three different time-points [36]. A more recent study showed significantly better effect of bright light treatment (BLT) compared to dim light treatment, when used as augmentation of mood stabilizing medication, in 46 patients with bipolar depression [37]. A recent review showed that the risk of a switch from depression to mania, in patients with BD disorder treated with light therapy, was no higher than with antidepressant drug therapy alone [38].

With conventional light therapy, patients are placed in front of a light box for 30-60 minutes in the morning [39]. In treatment with dynamic lighting, LED-light luminaires are built into the room and substitute the general room-lighting. In this way treatment is automatically administered to the patient if the patient is in the room. This enables the system to provide daytime lighting that can phase advance the circadian rhythms and provide an alerting effect. During evening and night, the light system provides low-intensity light with low blue wavelength content with minimal impact on the circadian system.

One of the main challenges with light therapy studies is the insufficient blinding of patients to light treatment conditions, and the lack of an appropriate control treatment (placebo). These challenges are not solved by using dynamic lighting as the change in color and intensity is readily seen by the patients.

In conclusion, there is some evidence for the effect of traditional light box administered treatment, primarily in seasonal and non-seasonal depression, less in bipolar depression, but very little evidence for the effect of dynamic lighting. Therefore, a rigorously designed large study using dynamic lighting in bipolar and unipolar depression is warranted.

Architecture, daylight and lighting in hospitals

In Denmark, daylight is scarce during the winter season [40] and in addition, cold rainy weather tends to keep people inside. This reduces overall light exposure because indoor light intensities seldom exceed 100-300 lux, whereas outdoor light intensities often are higher than 2000-3000 lx, even on an overcast day. Light exposure might therefore not be adequate to entrain the sleep-wake cycle, and other circadian rhythms, or to sustain normal levels of alertness and mood.

For counties with a northern location, the limited daylight during winter months make it pertinent to investigate how and if artificial LED-light can become an adjunct method to the treatment of depression in hospitals.

There are casuistic observations of an association between onset of depression and sudden drop in solar irradiation [41] and between measured light exposure and depression severity [42] and recent studies confirm ancient architectural principles about exposure to the morning sun, such as the late 19th century Nightingale pavilions facing southeast (SE) aiming to optimize exposure to the morning sun during winter darkness [43].

A few studies have been carried out to investigate the effect of daylight or dynamic lighting on patients with depression. The first documented daylight experiment was done by Wirz-Justice et al in 1996 with seasonal patients showing a better antidepressant effect of a one-hour walk outside compared to low-dose light therapy from a light box [44]. Some studies have investigated the possible influence of light exposure on length of inpatient stay in psychiatric hospitals, retrospectively. In a sample of 174 inpatients treated for bipolar or unipolar major depression in Alberta Canada (53.6ºN), Beauchemin et al found a length of stay of 16.9 days in bright rooms (east orientated) and 19.5 days in dimly lighted rooms (west facing or indoor courtyard) ($p< 0.05$), [45]. Benedetti et al investigated the length of inpatient stay for 187 patients with bipolar or unipolar depression in Milano, Italy (45.5ºN). For patients with bipolar depression then a mean length of stay was 19.8 days in east oriented rooms and 23.5 days in west oriented rooms ($p=0.02$), [46]. No difference was found for patients with unipolar depression. In Berlin, Germany (52.5 Nº), Staedt et al found a reduction in mean length of inpatient stay for patients with unipolar depression, from 25.91 (17.04) days to 22.04 (15.40) days ($p=0.023$) when the psychiatric clinic was moved to new facilities equipped with blue-enriched dynamic lighting system [47]. However, when controlled for age the statistical significance was lost ($p=0.083$). In Mallorca, Spain (39.7ºN), Canellas et al found

in a sample of 207 patient with depression as part of BD or MDD that the median inpatient stay was reduced from 14 days (Inter Quartile Range 8-19) to 11 days (Inter Quartile Range 6-15) (p=0.007) when the ward was moved from a basement location to a new facility where the accumulated light exposure per day was 300 % higher [48]. In a study from our own group, we documented extreme midday differences in daylight exposure between hospital rooms facing SE and hospital rooms facing NW. Measured on a clear day, these differences were 57.000 lx at the summer solstice, 38.000 lx at the autumn equinox and 19.000 lx at the winter solstice. In rooms facing SE the morning light was richer in the blue spectrum. We also found a significantly shorter inpatient stay for patients staying in SE facing room compared to NW facing rooms [2]. Latest, West et al examined the effect of dynamic light versus static light in a cluster randomization design in two cerebral stroke rehabilitation units in Copenhagen, Denmark (55.7 Nº). These patients were mostly bedridden, and the rooms were equipped with blinds that could regulate daylight. In the group randomized to dynamic light, patients had significantly lower mood scores, measured by the major depression inventory, compared with the group receiving static light (paper in press). Moreover, patients had significantly elevated melatonin plasma levels at endpoint compared to baseline and evolved a significant rhythmicity of melatonin (cosinor analysis) [49]. There is also some evidence that dynamic lighting stabilizes mood and improves sleep quality in individuals suffering from dementia [50-52].

In summary, the evidence base for dynamic lighting is still weak. There is only little knowledge on how LED-light should be implemented as well as the potentially beneficial or harmful effects of LED-light on patients with depression whether as part of a unipolar or bipolar disorder.

In hospitals, there will always be “a dark side of the building” where facades will receive very little – if any – morning sun during wintertime. Dynamic LED-lighting enables us to tune the lighting conditions individually for each room in a building to compensate for insufficient daylight.

In the present randomized trial, we investigate the efficacy of a dynamic LED lighting condition in inpatients treated for unipolar or bipolar depression. We have incorporated results from our recent four-room feasibility trial that focused on the performance of the new dynamic LED system and patient tolerability.

The study will be an addition to the knowledge in this transdisciplinary field, combining medical science, architecture, and engineering.

Objective

The objective of this study is to investigate the antidepressant effect of a newly developed dynamic LED-lighting system in an inpatient psychiatric ward. Patients with a current major depressive episode either as part of an MDD or a BD will be randomized to receive either Dynamic LED-lighting or Static LED-lighting in combination with treatment as usual. We hypothesize that the group receiving Dynamic LED-lighting will have a larger reduction in depression scores on the Hamilton Depression Rating Scale than the group receiving static LED-light and that the antidepressant effect of the intervention will be larger for individuals with BD.

METHODS AND ANALYSIS

Design

The study protocol is reported according to the SPIRIT statement of randomized studies of nonpharmacological treatment [53]. The study is a three-week, randomized, controlled, single-blind, parallel-group study with a balanced allocation ratio (1:1) of adult patients diagnosed with depression either as part of MDD or BD. Patients will be randomly assigned to either dynamic LED-lighting or Static LED-lighting with stratification for patients with a major depressive episode as part of a BD or as part of MDD. We expect a ratio of 2:1 for these two subgroups. Participants will be psychometrically assessed at baseline and once a week for a total of 3 weeks. All other treatment elements at the ward will continue as usual. Patients who are discharged or transferred to another ward during the three weeks study period, will be contacted for a follow-up assessment corresponding to the missing final assessment, to facilitate adherence to protocol.

Study setting

The study will be conducted at a specialized inpatient unit for affective disorders at the Mental Health Centre Copenhagen, located on the premises of Rigshospitalet. This ward delivers specialized treatment for patients with affective disorders (MDD, BD, and anxiety) consisting of psychoeducation, pharmacological treatment, electroconvulsive treatment, physiotherapy, and occupational therapy performed by a transdisciplinary team of psychiatrists, nurses, physiotherapists, and occupational therapists. The average period of admission is approximately 4-6 weeks. The ward has a capacity of 14 patients. The study intervention will include ten single

patient rooms each equipped with a lighting system that can provide either dynamic LED- or static LED-lighting.

Eligibility criteria

All patients admitted to the inpatient ward will be considered for participation. Patients are considered eligible for inclusion into the study if they comply with the inclusion and exclusion criteria listed below.

Inclusion criteria are: more than 18 years of age, a current major depressive episode as part of either MDD (DSM-IV) or BD (DSM-IV), in current and recent (a minimum of two months before admission) mood stabilizing treatment, informed consent, and speaks and understand Danish.

Exclusion criteria are: severe suicidality corresponding to a score > 2 on the Hamilton Depression Rating Scale item 3 or if the investigators are uncertain of the degree of suicidality, psychotic depressive features at time of inclusion or within the last two weeks, a Young Mania Ratings Scale (YMRS) score of 7 or above or a current hypomanic or manic episode, coercive measures of any kind.

Discontinuation criteria are: SARs, SUSARS, all listed exclusion criteria, and if the patient wants to leave the study. Intervention will be discontinued if one of the before mentioned criteria are fulfilled but we will ask patient for an endpoint assessment unless the patient wants to leave the study.

The eligibility criteria were chosen to represent a broad sample of the patient group to maximize the generalizability of the study results. Patients with severe suicidality is excluded because they are more often transferred to closed wards and thus lost to follow-up which reduces the quality of the study. The eligibility will be evaluated through case files and from interviews with the patients.

Interventions

The LED-technology provides new possibilities to adjust the spectral distribution and intensity of light during the 24-hour day. LED-lighting can thus be tuned to supply bright light rich in the blue, short wave region of the spectral range in the first part of the day, and warmer and less intense light with less blue light, later in the day and at night. This regulation should entrain and advance the sleep-wake cycle and thereby improve and stabilize mood. The Dynamic LED-light intervention

will also provide higher light intensities from the late morning and well into the afternoon with due consideration as to not cause glare or other visual discomfort (guided from the results from the feasibility study). The higher light intensity should provide added antidepressant and alerting effects. The intervention is used as an ad-on, non-pharmacological treatment [54]. The dynamic luminaires are tuned to mimic the temporal intensity and spectral distribution of daylight, in a SE-facing room, with two sets of timing – one for winter and one for summer.

Ten single rooms in the inpatient ward are equipped with the new LED-lighting system that can function either in static or dynamic mode in each room. The lighting system is operated from a control panel placed in a locked room at the ward. Patients who are admitted to single rooms and included in the study are randomly allocated to treatment with either dynamic LED-lighting or static LED-lighting.

Procedures for the Dynamic LED-light group

The dynamic LED-lighting consists of three lighting elements in each single patient room (A, B, C).

A: An LED-panel built into the window jamb (in the vertical part of the window frame) mimicking the natural sunlight (see figure 1). This panel is turned on at 06:00 till 18:00 in the summer period (from February 1 till October 31), and from 07:00 till 17:00 in the winter period (from November 1 till January 31). The dimension of the panel is 1950x310x60 mm. The light from this panel varies continuously in correlated colour temperature (CCT) from 1800 Kelvin dim, warm-light at dawn rising to 5500 Kelvin bright white light from 9:00 till 14:00. From 14:00 and onward the light from the panel is reduced in both intensity and CCT. The LED panel cannot be switched off by the patients, but a curtain can be drawn to reduce intensity. The panel contains Cool-White (CW), Warm-White (WW), and wide-spectrum Amber (A) LEDs.

B: Two luminaires containing CW/WW/A LEDs mounted in the ceiling with dynamic regulation of intensity and CCT during the whole 24-hour day. The light varies from 1800 Kelvin dim, warm light to 5500 Kelvin at an intensity brighter than normal in a patient room. The ceiling light can be turned off/on by the patient as preferred. During the summer, the dynamic LED-lighting is brightest between 09:00 and 14:00 and dimmest and warmest, from 23:00 to 06:00. In the winter period, the timings are changed to 09:30 to 13:30 and from 22:30 to 07:00 respectively.

C: A reading luminaire by the bed, with similar design and timing as the ceiling lighting and a

regulation of CCT from 2100 to 55000 Kelvin, with intensity kept relatively low, yet permitting reading while preventing too much suppression of melatonin in the evening. The reading luminaire can be turned off/on by the patient as preferred. The reading luminaire contains CW/WW/A LEDs. All transitions are made as slow, continuous fades to mimic the nature of daylight.

Procedures for the Static LED-light group

The Static LED-light intervention uses the same luminaires as the Dynamic LED-lighting intervention but with a different system configuration. This configuration is completely static with regards to intensity, CCT, and timing. The built-in window luminaire is turned off and the ceiling luminaires (B) and reading luminaire (C) are both set to 3000 Kelvin, at an intensity as expected in a typical patient room. Both ceiling and wall luminaires can be turned on/off as preferred by the patient.

The use of the ceiling and reading luminaires will be logged continuously in both groups. For comparative understanding of the difference in light exposure, Figure 2 shows the maximum cumulated exposure of LED-lighting for the two groups at the patients' bed for day and night separated for the rhodopic (night vision) and melanopic contributions (ipRGC contribution).

Concomitant care

All participant will be offered the usual psychopharmacological, psychotherapeutic and other treatments at the ward.

Outcomes

Diagnostic measures

The Mini International Neuropsychiatric Interview (M.I.N.I.) is used for diagnostic purposes by the investigators. This is a short, structured diagnostic interview based on the DSM-IV diagnostic system, and will be conducted to confirm depression diagnosis, assess comorbidity, and any exclusion criteria for participation in the study [55]. Investigators are certified in the use of the M.I.N.I. instrument.

Psychometrics and sociodemographics

Sociodemographic data are collected at baseline together with a treatment outcome expectancy rating [56]. Psychometric assessments are performed at baseline and at the weekly evaluations. The

rating window is set as the last three days for all instruments except for the Pittsburgh Sleep Quality Index (PSQI) [57] which in this study covers the last three weeks and the YMRS which by tradition covers the last seven days [58]. The severity of depression is assessed by the Hamilton Depression Rating scale, 17 item version (HAM-D_{17}) [59], which includes the HAM-D_6 subscale [60], and by the Bech-Rafaelsen Melancholia Rating Scale (MES) focusing more on the cognitive symptoms of depression [61]. The Hamilton rater is blinded to treatment allocation and is trained in the use of the HAM-D_{17} by repeated group ratings with co-researchers. The YMRS is an 11-item, interviewer-administered scale, used to assess manic or hypomanic symptoms. It has a score range from zero to 60 (highest severity of manic symptoms [58]. The Suicidal Ideation Attributes Scale (SIDAS) is a 5-item self-assessment scale with a score from zero to 50 (highest level of suicidal thinking) [62]. The UKU scale (side effect scale) is a generic side effect scale covering degree of expected side effects from medications and supplemented in this study with items covering light sensitivity, all with scores from 0 to 3 (3 is severe side-effect) [63]. Quality of life is assessed with the WHOQOL-BREF instrument measuring four life domains (physical health, psychological health, social relationships, environment) each with a score from zero to 100 (best) [64]. The Morningness-Eveningness Questionnaire (MEQ) is a 19 items self-assessed questionnaire constructed to assess chronotype. A score below 42 indicates “evening type” and a score above 58 indicates “morning type”; and a score between 42 and 58 indicates “intermediate type” [65]. Sleep quality is assessed by the PSQI containing 11 self-reported items. These items are transformed into 7 “component scores “, and a “global score”. The components scores are 1) “Subjective sleep quality”, 2) “Sleep latency”, 3) “Sleep duration”, 4) “Sleep efficiency”, 5) “Sleep disturbances”, 6) “Sleep medication” and, 7) “Daytime dysfunction”. A “Global Score” of five or above indicates poor sleep quality [57]. Patients are asked to estimate their mean weekly sleep onset and offset, number of awakenings, sleep quality, and duration and number of naps at each assessment. To evaluate the visual comfort in the room we use a newly designed Visual Comfort Scale covering satisfaction and experience of the lighting conditions, covering the last week [66] . To estimate the number of hours of exposure to the lighting condition participants evaluate how much time they have spent in their room during the last week (Room Occupancy Diary), [67]. To estimate the exposure to daylight and to the built-in LED-panel patients assess their use of curtains during the last week.

All events will be registered, and all Serious Adverse Events (SAE), Suspected Unexpected Serious

Adverse Events (SUSAR), and Serious Adverse Reactions (SAR) will be reported to the ethical committee immediately.

We collect data on the use of medication at baseline and at week 3 from patient medical charts. Including the use of ad lib. medication.

Light sensors will measure real-time intensity and spectral distribution of light in selected patient rooms during the whole 3-week period. Results of light measurements will be presented according to CIE S 026 [68].

Ranking of outcomes

The primary outcome is the baseline adjusted mean score on the HAM-D_6 scale at week 3.

The secondary outcomes are a) the mean score on the SIDAS scale at week 3, b) the mean score on the HAM-D_{17} scale at week 3, c) the mean score on the WHOQOL-BREF at week 3.

Exploratory outcomes are: a) the proportion of patients with one or more SEAs (according to ICH-GCP 1997), b) the mean score on the visual comfort scale covering all three weeks, c) the mean reduction in mg/day from baseline to week 3 of zopiclone, d) the mean reduction in mg/day from baseline to week 3 of zolpidem, e) the mean reduction in mg/day from baseline to week 3 of quetiapine, e) the mean reduction in mg/day from baseline to week 3 of oxazepam, f) the mean score on the PSQI scale at week 3, g) the mean score on the MEQ scale at week 3, h), the mean score on the HAM-D_6 scale at 6 month.

A separate report will be made focussing on the total use of electrical energy for lighting in the static lighting group compared to the interventional LED-light group for a one year period.

Participants timeline

Enrolment and start of intervention are performed within 5 days of admission to the ward. Assessments are performed at enrolment and once weekly for 3 weeks (see Spirit flow diagram in Ex 1).

Sample size and power estimations

Sample size calculation was done using the SAS 9.4 software.

In a previous study [2], in patients from the same ward, we found a mean HAM-D_{17} score at admission of 23. This corresponds to a HAM-D_6 score of 13. The number of participants has been estimated from an expected baseline-to-endpoint score reduction, on the HAM-D_6 from 13 to 8 in

the dynamic light group, and from 13 to 10 in the static light group. Hence, the minimal important difference is two points on the HAM-D_6 scale. With an expected standard deviation of 3, an alfa value of 0.05, and a power of 90%, we will need a total of 98 patients for the primary outcome. However, to be able to perform explorative analyses we will aim at 150 patients.

Power estimations of secondary outcomes

a) SIDAS scale: we expect a SIDAS score of 20 at baseline with a standard deviation of 8 and a reduction to a score of 5 in the dynamic light group and to 10 in the static light group. With an alfa value of 0.05 and a sample size of 98 participants, a power of 0.82 is estimated. With a sample size of 150, power would be 0.95.

b) HAM-D_{17} scale: we expect a HAM-D_{17} score of 23 at baseline with a standard deviation of 6 and a reduction to 14 in the active dynamic group and to 17.5 and the static light group. With an alfa value of 0.05 and a sample size of 98 participants, a power of 0.82 is estimated. With a sample size of 150, power would be 0.95.

c) WHOQOL-BREF questionnaire: We expect a WHOQOL-BREF score of 20 at baseline with a standard deviation of 17 and an increase to 45 in the dynamic light group and to 35 in the static light group. With an alfa value of 0.05 and a sample size of 98 participants, a power of 0.82 is estimated. With a sample size of 150, power would be 0.95.

Recruitment

The investigators will be in bi-weekly contact with the staff at the ward and will follow the flow of admissions. When a new patient is admitted to the ward and is occupying one of the ten rooms with light equipment, the staff will give the patient the opportunity to meet the investigator if no exclusion criteria are apparent. The patient will have the opportunity to read the participant information paper and the investigator will give a detailed oral information regarding the study. The oral information and written material will include information regarding the importance of obtaining outcome data in the case of drop-out due to early discharge and after 6 month. The patient will be asked to decide on participation within two days. If the patient accepts, the informed consent will be signed, and the inclusion and baseline assessments will begin. The patient record and the M.I.N.I. interview will be used to confirm the patient's eligibility. Included patients will be allocated to the next study number through the electronic case report form in

OpenClinica [69], administered by the Copenhagen Study Unit. When submitted, the system randomizes the participant to one of the two treatment groups: *Dynamic LED-group* or *Static LED-group.* This information is given to the patient. The estimated mean stay of patients is 1 month and with 10 light equipped room a total number of patients per year is 140. With an expected inclusion rate of 50% we expect to finish last patient last visit June 2021.

Allocation

The randomization will be web-based with a 1 (experimental intervention) to 1 (control intervention) allocation with a stratification for BD. A total of 150 patients will be randomized in the study. The primary investigator will enroll participants into the study. The randomization is performed through the OpenClinica system, after participant's data are entered into the eCRF, and all inclusion criteria are fulfilled, and no exclusion criteria are fulfilled.

Blinding

It is not possible to disguise the lighting condition to participants primarily due to the extra light panel in the window that will be active in the dynamic lighting group. The depression outcome assessors will perform the assessment in a separate office in another department and will be blinded to treatment allocation. Participants are asked not to reveal their treatment allocation to the Hamilton assessor. Other investigators and data managers will not be blinded. The blinding will be broken in the event of a SAR or SUSAR.

Statistical analyses will be performed with the two intervention groups coded as 'A' and 'B' by two blinded statisticians employed at the CTU. The statisticians will independently and blindly analyze all data and present the results in two independent reports. A third investigator will compare these reports and discrepancies will be discussed. Both statistical reports will be published on CTU's website. Based on the statistical reports, two blinded conclusions will be drawn by the steering group: one assuming 'A' is the experimental group and 'B' is the control group – and one assuming the opposite. Based on these two blinded conclusions, two abstracts will be written and published on CTU's website. When the blinding is broken, the 'correct' abstract will be chosen and the conclusions in this abstract will not be revised.

Data collection

All assessments are carried out by psychometrically trained investigators (research nurse and

senior consultant). The Hamilton ratings are conducted by a certified Hamilton rater blinded for group allocation. Hamilton certification is based on supervised group ratings with a difference of less than +/- two points on the HAM-D_{17} scale from the gold standard (most experienced rater). Study duration is 3 weeks, including baseline assessment (pre-intervention) and final assessment (post-intervention). Patients who are transferred to another light-equipped room in the ward, during the three-week period, can continue with their scheduled assessments and the lighting condition in the new room will be set according to the allocation. It will be mentioned at

Data management

Data will be collected through an electronic case report form (eCRF) developed by Copenhagen Study Unit (CTU) in OpenClinica. Data in the eCRF is considered source data. The eCRF will use range checks for validation of entered data, and there will be an audit trail to monitor data entry. Data will be stored on servers locally at CTU with daily back-up. Data will also be collected from light sensors stored on independent hard drives. These data are also considered source data. Only pen-and-paper data are the informed consent and participants list. All data will be available to all authors.

Statistical methods

Continuous scale scores, including sleep scores, will be analyzed in a linear regression model using available data from all included participants (intention to treat). Results are given as mean, with confidence limits, standard deviation, and p-values. A detailed statistical analysis plan will be published separately before the randomization of the last participant. The significance level is set at 5 % two-sided. Subgroup analyses will be performed for BD/MDD diagnosis. Missing data will be handled by multiple imputation techniques. No interim analyses are planned.

Data monitoring and auditing

According to Danish law, only drug studies are required to comply with Good Clinical Practice guidelines (GCP) [70]. We will, however, adhere to the GCP rules to secure study quality. Data analyses, performed by the primary investigator, will be supervised by a statistician. The study is subject to auditing from the regional ethical committee.

Harm

We do not expect that the study will expose participants to any serious hazard as their usual

clinical management is maintained and the side effect profile of bright light is low [33] . All AEs will be recorded until the end of the follow-up period, and regulatory rules for reporting of SAEs and SARs will be adhered to. Any harm due to the study procedures is covered by the Danish Patient Compensation Association. The study will be stopped if there is a clinical suspicion of harm of the intervention, or if new evidence emerges that participants can come to harm due to the intervention.

ETHICS AND DISSEMINATION

Ethics

The study is approved by the Regional Committee on Health Research Ethics with approval number H-19004525. The study is approved by the Danish Data Protection Agency with approval number VD-2018-515. All participants will provide written informed consent before enrolment into the study. Informed consent will be obtained by the primary research investigator or a delegated study investigator. The study will be stopped if participants develop serious side effects. Patients can leave the study at any time at their own discretion and without any further effect on their continuous treatment at the ward. Any forthcoming protocol amendments will be submitted to the Ethical committee and the Danish Data Protection Agency for approval. Written and oral information will be given at the ward, between the first and the fifth day of admission. The information will be given only by trained study investigators. The information will be given in an undisturbed office at the ward. Prior to the information visit, the patient will be informed of the opportunity to bring a friend or relative (third party). The patient will be given up to two days to consider participation before giving the informed consent.

Personnel at the ward will present information from patient records to permit investigators to determine any exclusion criteria. Patients eligible for enrolment will be asked by staff at the ward to participate in an information meeting. At inclusion, the patient will produce their civil registration number, name, and sociodemographic data, to the investigators. These data will be entered into the eCRF system and a participant-ID will be generated as part of the randomization process. Participants name, civil registration number and study number (from the eCRF) will be stored in a participant' identification list in a secured data repository. Personal data in the eCRF

will only be used for randomization purposes, after which only the participant-ID will be used. At the end of the study all paper material containing data will be transferred to a secure data repository. All study data will be handled according to the General Data Protection Regulation. The final data set will be accessible to all persons in the study group.

We do not expect any ethical issues. All regulatory rules will be followed, and the expected side effects of the dynamic lighting systems are rare and mild. We have taken precautions to find and deal with any emergent manic and suicidal symptoms.

Dissemination

Results will be published in peer-reviewed international journals, as posters, and as oral presentations at international symposia. All data whether negative, positive or inconclusive will be reported in full. All members of the study group are co-authors with a pre-arranged order. No professional writers will be used. Depending on the journal of publication, part of the protocol, statistical code, and dataset will be publicly available. All participants will be informed of the trail results.

Declarations

Ethics approval and consent to participate

The study has been approved by the Committee on Health Research Ethics for the Capital region of Denmark (approval number H-19004525). All participants will provide written informed consent before enrollment into the study.

The study is approved by the Danish Data Protection agency (approval number VD-2018-515).

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Author contributions

CV: Design, planning, data acquisition, drafting, and agreement of accountability for all aspects of the work.

ASA: Design, planning, data acquisition, drafting, and agreement of accountability for all aspects of the work.

TSH: Planning, drafting, and agreement of accountability for all aspects of the work.

PMP: Data acquisition, drafting, and agreement of accountability for all aspects of the work.

CDH: Design, planning, drafting, and agreement of accountability for all aspects of the work.

UK: Design, planning, drafting, and agreement of accountability for all aspects of the work.

SD: Planning, drafting, and agreement of accountability for all aspects of the work.

EEP: Planning, drafting, and agreement of accountability for all aspects of the work.

JE: Planning, drafting, and agreement of accountability for all aspects of the work.

JJ: Planning, drafting, and agreement of accountability for all aspects of the work.

HØM: Planning, drafting, and agreement of accountability for all aspects of the work.

IH: Planning, drafting, and agreement of accountability for all aspects of the work.

KM: Design, planning, data acquisition, drafting, and agreement of accountability for all aspects of the work.

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Competing interests

TSH is an employee of Chromaviso that has supplied the lighting system. There are no financial or other interests for any other authors.

Patient and public involvement

Patients were involved in the testing of tolerability of the lighting system. This influenced the setting of the dynamic lighting system. Patient also assisted in developing the Visual Comfort Scale that is used in the study to estimate tolerability. Both involvements were done before the start of the study.

Data Availability Statement

We will make data from this study available on reasonable request once the results are published.

Figure legends

Figure 1. The left-hand picture shows how the LED panel is mimicking sunlight reflections on the wall. The right-hand side of the picture shows natural sunlight reflexions on the wall.

Figure 2. Equivalent daylight illuminance hours (EDI) from the Dynamic and Static LED-lighting system separated for Rhodopic and Melanopic contributions.

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The left-hand picture shows how the LED panel is mimicking sunlight reflections on the wall. The right-hand side of the picture shows natural sunlight reflexions on the wall.

304x171mm (96 x 96 DPI)

EDI dose[1]	Dynamic Day[2] 06-22	Dynamic Night[3] 22-06	Static Day 06-22	Static Night[3] 22-06	Units
Rhodopic	4,407	51	483	242	EDI lux * hours
Melanopic	4,205	41	432	216	EDI lux * hours

(1) Cumulated dose of equivalent daylight (D65) illuminance hours.

(2) Dose values for summer period. Dosis for winter period is 20% lower during daytime.

(3) EDI levels at night with light turned on. The patient is able to turn off the light at all times.

Equivalent daylight illuminance hours (EDI) from the Dynamic and Static LED-lighting system separated for Rhodopic and Melanopic contributions.

361x147mm (96 x 96 DPI)

Figure 2. SPIRIT flowdiagram

	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT	***-3 days***	**0**	**0**	***1 w***	***2 w***	***3 w***
ENROLMENT:						
Eligibility screen	x					
Informed consent	x					
Allocation		x				
INTERVENTIONS:						
[Dynamic LED-light group]			◆—	—	—	—◆
[Static LED-light group]			◆—	—	—	—◆
ASSESSMENTS:						
[M.I.N.I., age, other diagnoses from patient charts, sociodemographics]	x	x				
[HAM-D_{17}, MES, MDI, WHOQOL-BREF]			x	x	x	x
[PSQI, MEQ, YMRS, SIDAS, UKU, SAE]			x			x
[Diaries for sleep, visual comfort, room occupancy, use of curtains]			x	x	x	x
[Measurement of light intensity and spectral distribution]			x	x	x	X

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*: "Dynamic LED-light versus Static LED-light for depressed inpatients: study protocol for a randomized clinical study"

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__3_____
	2b	All items from the World Health Organization Trial Registration Data Set	All included in clinicaltrials.gov
Protocol version	3	Date and version identifier	__3_____
Funding	4	Sources and types of financial, material, and other support	__21_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__20-21_____
	5b	Name and contact information for the trial sponsor	__1_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__21____

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__NA_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__4-9_____
	6b	Explanation for choice of comparators	___10_____
Objectives	7	Specific objectives or hypotheses	___10_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___10_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	___10_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__11_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__ 11-13_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	___11_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	___11_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___13____

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	___13-16_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____16_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____15-16____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____16_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____17_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____17_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____17_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____17_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____17_____
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols: all data	16
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval: approved	20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	18-19
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary material

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Dynamic LED-light versus Static LED-light for depressed inpatients: study protocol for a randomized clinical study

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Title

Dynamic LED-light versus Static LED-light for depressed inpatients: study protocol for a randomized clinical study.

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ABSTRACT

Introduction: Retrospective studies conducted in psychiatric inpatient wards have shown a relation between the intensity of daylight in patient rooms and the length of stay, pointing to an antidepressant effect of ambient lighting conditions. Light therapy has shown a promising antidepressant effect when administered from a light box. The emergence of Light Emitting Diode technology has made it possible to build luminaires into rooms and to dynamically mimic the spectral and temporal distribution of daylight. The objective of this study is to investigate the antidepressant efficacy of a newly developed dynamic LED-lighting system in an inpatient ward.

Methods and analysis: In all, 150 inpatients with a major depressive episode, as part of either Major Depressive Disorder or as part of a Bipolar Disorder, will be included. The design is a two-arm 1:1 randomised study with a dynamic LED-lighting arm and a static LED-lighting arm, both as add-on to usual treatment in an inpatient psychiatric ward. The primary outcome is the baseline adjusted *score* on the Hamilton Depression Rating Scale 6-item scale at week 3. The secondary outcomes are the mean score on the Suicidal Ideation Attributes Scale scale at week 3, the mean score on the Hamilton Depression Rating Scale 17-item at week 3, and the mean score on the WHOQOL-BREF at week 3. The spectral distribution of daylight and LED-light, with a specific focus on Non-Image-Forming light mediated through the intrinsically photosensitive Retinal Ganglion Cells, will be measured. Use of light luminaires will be logged. Assessors of Hamilton depression rating scale scores and data analysts will be blinded for treatment allocation. The study was initiated in May 2019 and will end in December 2021.

Ethics and dissemination: No ethical issues are expected. Results will be published in peer-reviewed journals, disseminated electronically and in print, and presented at symposia.

Trial registration number: ClinicalTrials.gov NCT03821506.

Keywords: Major Depressive Disorder, Bipolar Disorder, Lighting, Light, Inpatients, Chronotherapy, Randomized Controlled Trial.

Trial protocol number: RoomLight final version .

Strengths and limitations of this study:

- This is the first randomized clinical trial investigating the antidepressant effect of a dynamic LED system in an inpatient psychiatric ward
- The study has a rigorous design and a large sample size enabling it to find a clinically relevant antidepressant effect
- Patient stay might not be of an adequate length to achieve full antidepressant effect of the lighting system
- Light measurements will not accurately reflect corneal light exposure as we do not use wearable light sensors

INTRODUCTION

Depression

Depressive episodes, either as part of a Major Depressive Disorder (MDD) or as part of a Bipolar Disorder (BD), are a prevalent and leading cause of disability worldwide. Society suffers large direct and indirect losses due to lost work, sickness, and early retirements, and WHO ranks major depression as a significant contributor to the global burden of disease [1]. In Denmark alone (population of 5.8 million), the costs of depression amount to an estimated 1.87 billion Euro per year. Depression can affect an individual to an extent that everyday activities and chores are insurmountable. These patients often have suicidal ideation and despair and need inpatient care including treatment with mood stabilizers, antipsychotics, antidepressants, psychoeducation, psychotherapy, and occupational therapy. Typically, these patients will still suffer from varying degrees of depression when discharged [2 3] and relapse, readmission, and even suicide, upon discharge, are major treatment challenges [4]. Despite intense efforts during the last decades there has been no breakthrough for neither drug development nor for any other treatment modality and 10-25% of patients are treatment resistant [5]. Thus, there is a need for the development of new treatment options [6]. Light therapy has shown an antidepressant effect in outpatients, when using light box administered treatment, but studies in more severely depressed inpatients are warranted [7]. The technological development has made it possible to some extent to mimic the temporal changes in intensity and spectral distribution of daylight with Light Emitting Diodes (LED) built tinto buildings. However, in this study we do not aim at creating actual daylight

characteristics in the rooms but to provide a tailored spectral illuminance to enhance alertness, mood improvement and circadian regulation. This includes a focus on ipRGC influenced responses.

The present efficacy study thus investigates the possible antidepressant effect of a new, dynamic type of general lighting in the treatment of a major depressive episode either as part of an MDD or a BD in patients admitted to a specialized affective disorders ward.

Bright Light Therapy

Light has been used to treat medical conditions, such as melancholia or lethargy for at least a thousand years [8 9] and daylight has been considered important for centuries when building hospitals [10]. Animal research conducted through many decades has shown that dosage and timing of light have impact on reproduction, activity, and sleep [11] , and in the 1980s it was discovered that light could suppress melatonin secretion, in humans [12], indicating that light gives cues to the brain about night time and season. The resultant clinical description of Seasonal Affective Disorder (SAD) and the theoretical analogy with hamster hibernation cycles led to the development of bright light treatment [13-16]. It was later discovered that light pulses applied in the morning phase advance the sleep-wake cycle (and other rhythms) whereas light applied in the evening delays the sleep-wake cycle (and other rhythms). This is named the Phase Response Curve (PRC) for light in humans [17 18] , and is the basis for the mechanism of "entrainment" – the synchronization of a self-sustaining oscillation (such as sleep) by an external forcing oscillation (such as daylight or artificially timed light). In 2000, a new non-visual retinal receptor, the intrinsically photosensitive retinal ganglion cells (ipRGC), was discovered in the human retina [19]. The ipRGC receptors have a peak spectral sensitivity for the short-wavelength portion of the light spectrum (460 nm – 480 nm) [20]. Since then it has been found, primarily through animal research, that the ipRGC regulates the circadian system through input to the suprachiasmatic nuclei (SCN) and the pineal gland, but also, through newly found pathways, to brain structures known to be involved in depressive illness [21-24]. This has given us a better understanding of how light can have a fast working antidepressant effect in humans and has stimulated research on the effect of using light with temporally shifting spectral compositions and intensity. The impact of the signals from the ipRGC is, among other effects, responsible for the ability of light to time and stabilize the sleep-wake cycle and to adjust the seasonal regulation of serotonin [25]. Light Emitting Diode (LED) -light can be tuned to be

particularly rich in the short-wavelength wavelength spectrum in contrast to conventional compact fluorescent light (CFL). Thus, LED-light can be adjusted to maximize the impact on the ipRGC system. The temporal regulation of the spectral composition and intensity of LED-light is clinically important. Too much short-wavelength light in the evening will delay the sleep-wake cycle, through the PRC mechanism, causing a difficulty falling asleep (sleep onset insomnia) [26], whereas short-wavelength light in the morning will advance sleep and increase alertness. It should be noted that prereceptoral filters such as the lens tends to shift the spectral sensitivity of the melanopsin receptor to longer wavelengths.

There is an association between depression and late chronotypes [27] and late chronotypes is associated with nonresponse to treatment [28]. Furthermore, patients with depression are prone to drift to later sleep schedules [3]. We should thus expect that dynamic lighting with enriched short-wavelength morning light and low short-wavelength light content in the evening would prevent drifting or even phase advance the sleep-wake cycle and thus augment the antidepressant treatment response [29].

Since the publication of the first study on the effect of light therapy for depression by Rosenthal et al in 1984 [13], a large number of studies have been carried out to investigate the efficacy of bright light treatment on both seasonal and non-seasonal depression. Light is one of the most thoroughly investigated chronotherapeutic treatments in addition to wake-therapy [30] and sleep phase advance [31]. In 2004, Tuunainen and colleagues published the Cochrane systematic review "Light therapy for non-seasonal depression" [32]. The conclusion was that light therapy must be regarded as a promising treatment method, but because of the heterogeneity among the studies, methodological problems and a lack of systematic collection of adverse events (AE's), the recommendation of light therapy as a treatment of depression should be considered with some caution. In a systematic review from 2007, Even et al, found an additive effect of light therapy when used as augmentation to antidepressant therapy in non-seasonal depression [33]. In a systematic review from 2016, Perera et al included 20 RCT's using light therapy for non-seasonal depression and found an overall small antidepressant effect (SMD -0.41; 95% CI -0.64 to -0.18), but with a high risk of bias and inconsistency between studies [34]. In subgroup analyses (stand-alone light therapy versus adjunctive light therapy, morning light therapy versus evening light therapy or other times of day, light therapy for in- versus outpatients, placebo light conditions

versus non-light-based placebo conditions) some support was found for a better effect of light when used as monotherapy, in the morning, for outpatients, and when compared with non-light-based placebos. Only four of the 20 studies had a low risk of bias on all items on the Cochrane Risk of Bias Tool [35-38]. A Danish study found a significantly better effect of a combination of bright light therapy plus sertraline compared with dim red placebo light and sertraline, in 102 outpatients [35]. In a Canadian study 122 outpatients were compared in four groups: (a) active light plus active fluoxetine, (b) active light plus placebo fluoxetine, (c) inactive negative ion generator plus active fluoxetine, (d) inactive negative ion generator plus placebo fluoxetine [36]. A significantly better effect was found in the group receiving the combination of active light plus active fluoxetine, as well as in the group receiving the combination of active light and placebo fluoxetine compared to the group receiving the combination of inactive negative ion generator plus placebo fluoxetine. A study performed in 84 elderly (> 60 years) outpatients with non-seasonal depression found a statistically significant beneficial effect of active versus placebo light treatment [37]. However, another study found no difference in depression outcome between groups, and a low reduction in depression severity across groups of 16 %, among 81 elderly outpatients (> 60 years) with non-seasonal depression, treated with bright or placebo light administered at three different time-points [38]. A more recent study showed significantly better effect of bright light treatment (BLT) compared to dim light treatment, when used as augmentation of mood stabilizing medication, in 46 patients with bipolar depression [39]. A recent review showed that the risk of a switch from depression to mania, in patients with BD disorder treated with light therapy, was no higher than with antidepressant drug therapy alone [40].

With conventional light therapy, patients are placed in front of a light box for 30-60 minutes in the morning [41]. Even though it is technical possible to produce a tuneable light box, commercial light boxes often only deliver fixed spectral distributions. In treatment with dynamic LED-lighting, built-in luminaires can provide temporal changing intensity and spectral distribution and they substitute the general room-lighting. One of the main study design challenges with light therapy studies is the insufficient blinding of patients to light treatment conditions, and the lack of an appropriate control treatment (placebo). These challenges are not solved by using dynamic lighting as the change in color and intensity is readily seen by the patients.

In conclusion, there is some evidence for the effect of traditional light box administered

treatment, primarily in seasonal and non-seasonal depression, less in bipolar depression, but very little evidence for the effect of dynamic lighting. Therefore, a rigorously designed large study using dynamic lighting in patients with bipolar and unipolar depression is warranted.

Architecture, daylight and lighting in hospitals

In Denmark (latitude 56º), daylight is scarce during the winter season [42] and in addition, cold rainy weather tends to keep people inside. This reduces overall light exposure because indoor light intensities seldom exceed 100-300 lux, whereas outdoor light intensities often are higher than 2000-3000 lx, even on an overcast day. Light exposure might therefore not be adequate to entrain the sleep-wake cycle, and other circadian rhythms, or to sustain normal levels of alertness and mood.

For counties with a northern location, the limited daylight during winter months make it pertinent to investigate how and if artificial LED-light can become an adjunct method to the treatment of depression in hospitals.

There are casuistic observations of an association between onset of depression and sudden drop in solar irradiation [43] and between measured light exposure and depression severity [44].

Recent studies confirm ancient architectural principles about exposure to the morning sun, such as the late 19th century Nightingale pavilions facing southeast (SE) aiming to optimize exposure to the morning sun during winter darkness [45]. Thus, these few studies have been carried out to investigate the effect of daylight or dynamic lighting on patients with depression. The first documented daylight experiment was done by Wirz-Justice et al in 1996 with seasonal patients showing a better antidepressant effect of a one-hour walk outside compared to low-dose light therapy from a light box [46]. Some studies have investigated the possible influence of light exposure on length of inpatient stay in psychiatric hospitals, retrospectively. In a sample of 174 inpatients treated for bipolar or unipolar major depression in Alberta Canada (53.6ºN), Beauchemin et al found a length of stay of 16.9 days in bright rooms (east orientated) and 19.5 days in dimly lighted rooms (west facing or indoor courtyard) ($p< 0.05$), [47]. Benedetti et al investigated the length of inpatient stay for 187 patients with bipolar or unipolar depression in Milano, Italy (45.5ºN). For patients with bipolar depression then mean length of stay was 19.8 days in east oriented rooms and 23.5 days in west oriented rooms ($p=0.02$), [48]. No difference was found for patients with unipolar depression. In Berlin, Germany (52.5 Nº), Staedt et al found a reduction in mean length of

inpatient stay for patients with unipolar depression, from 25.91 (17.04) days to 22.04 (15.40) days (p=0.023) when the psychiatric clinic was moved to new facilities equipped with short-wavelength enriched dynamic lighting system [49]. However, when controlled for age the statistical significance was lost (p=0.083). In Mallorca, Spain (39.7ºN), Canellas et al found in a sample of 207 patient with depression as part of BD or MDD that the median inpatient stay was reduced from 14 days (Inter Quartile Range 8-19) to 11 days (Inter Quartile Range 6-15) (p=0.007) when the ward was moved from a basement location to a new facility where the accumulated light exposure per day was 300 % higher [50]. In a study from our own group, we documented extreme midday differences in daylight exposure between hospital rooms facing SE and hospital rooms facing NW. Measured on a clear day, these differences were 57,000 lx at the summer solstice, 38,000 lx at the autumn equinox and 19,000 lx at the winter solstice. We found a significantly shorter inpatient stay for patients staying in SE facing room compared to NW facing rooms [2]. Latest, West et al examined the effect of dynamic light versus static light in a cluster randomization design in two cerebral stroke rehabilitation units in Copenhagen, Denmark (55.7 Nº). These patients were mostly bedridden, and the rooms were equipped with blinds that could regulate daylight. In the group randomized to dynamic light, patients had significantly lower mood scores, measured by the major depression inventory, compared with the group receiving static light [51]. Moreover, patients had significantly elevated melatonin plasma levels at endpoint compared to baseline and evolved a significant rhythmicity of melatonin (cosinor analysis) [52]. There is also some evidence that dynamic lighting stabilizes mood and improves sleep quality in individuals suffering from dementia [53-55].

In summary, the evidence base for dynamic lighting is still weak. There is only little knowledge on how LED-light should be implemented as well as the potentially beneficial or harmful effects of LED-light on patients with depression whether as part of a unipolar or bipolar disorder.

In hospitals, there will always be “a dark side of the building” where facades will receive very little – if any – morning sun during wintertime. Dynamic LED-lighting enables us to tune the lighting conditions individually for each room in a building to compensate for insufficient daylight.

In the present randomized trial, we investigate the efficacy of a dynamic LED lighting condition in inpatients treated for unipolar or bipolar depression. We have incorporated results from our recent four single-room feasibility trial (paper submitted for publication) that focused on the performance of the new dynamic LED system and patient tolerability.

The present study will be an addition to the knowledge in this transdisciplinary field, combining medical science, architecture, and engineering.

Objective

The objective of this study is to investigate the antidepressant effect of a newly developed dynamic LED-lighting system in an inpatient psychiatric ward. Patients with a current major depressive episode either as part of MDD or a BD will be randomized to receive either Dynamic LED-lighting or Static LED-lighting in combination with treatment as usual. We hypothesize that the group receiving Dynamic LED-lighting will have a larger reduction in depression scores on the Hamilton Depression Rating Scale than the group receiving static LED-light and that the antidepressant effect of the intervention will be largest for individuals with BD.

METHODS AND ANALYSIS

Design

The study protocol is reported according to the SPIRIT statement of randomized studies of nonpharmacological treatment [56]. The study is a three-week, randomized, controlled, single-blind, parallel-group study with a balanced allocation ratio (1:1) of adult patients diagnosed with depression either as part of MDD or BD. Patients will be randomly assigned to either dynamic LED-lighting or Static LED-lighting with stratification for patients with a major depressive episode as part of a BD or as part of MDD. We expect a ratio of 2:1 for these two subgroups. Participants will be psychometrically assessed at baseline and once a week for a total of 3 weeks. All other treatment elements at the ward will continue as usual. Patients who are discharged or transferred to another ward during the three weeks study period, will be contacted for a follow-up assessment corresponding to the missing final assessment, to facilitate adherence to protocol.

Study setting

The study will be conducted at a specialized inpatient unit for affective disorders at the Mental Health Centre Copenhagen, located on the premises of Rigshospitalet. This ward delivers specialized treatment for patients with affective disorders (MDD, BD) consisting of psychoeducation, pharmacological treatment, electroconvulsive treatment, physiotherapy, and occupational therapy performed by a transdisciplinary team of psychiatrists, nurses, physiotherapists, and occupational therapists. The average period of admission is approximately 4-

6 weeks. The ward has a capacity of 14 patients. The study intervention will include ten single patient rooms each equipped with a lighting system that can provide either dynamic LED- or static LED-lighting.

Eligibility criteria

All patients admitted to the inpatient ward will be considered for participation. Patients are considered eligible for inclusion into the study if they comply with the inclusion and exclusion criteria listed below.

Inclusion criteria are: more than 18 years of age, a current major depressive episode as part of either MDD (DSM-IV) or BD (DSM-IV), BD patients should be in current and recent (a minimum of two months before admission) mood stabilizing treatment, informed consent, and speaks and understand Danish.

Exclusion criteria are: severe suicidality corresponding to a score > 2 on the Hamilton Depression Rating Scale item 3 or if the investigators are uncertain of the degree of suicidality, psychotic depressive features at time of inclusion or within the last two weeks, abuse of alcohol and/or drugs, a Young Mania Ratings Scale (YMRS) score of 7 or above or a current hypomanic or manic episode, coercive measures of any kind.

Discontinuation criteria are: Serious Adverse Reactions (SARs), Suspected Unexpected Serious Adverse Reactions (SUSARS), all listed exclusion criteria, and if the patient wishes to leave the study. Intervention will be discontinued if one of the before mentioned criteria are fulfilled but we will ask the patient for an endpoint assessment unless the patient wants to leave the study.

The eligibility criteria were chosen to represent a broad sample of the patient group to maximize the generalizability of the study results. Patients with severe suicidality is excluded because they are more often transferred to closed wards and thus lost to follow-up which reduces the quality of the study. The eligibility will be evaluated through case files and from interviews with the patients. The eligibility criteria are assessed from case records, the Hamilton depression rating scale, the Young mania rating Scale, and the M.I.N.I. instrument which also contains a section on alcohol and drug abuse.

Interventions

In this study the treatment with dynamic LED-lighting provides temporal change in intensity and

spectral distribution throughout the 24-hour day. LED luminaires are built into the room and substitute the general room lighting. In this way treatment is administered to the patient, throughout the day, when the patient is in the room, with a planned specified temporal and spectral distribution. This enables the system to provide brighter daytime lighting aiming at a phase advance of the circadian rhythms and to provide an alerting and mood enhancing effect. This is attempted by supplying more bright light rich in the short-waved region of the spectral range in the first part of the day, and warmer and less intense light with less short-wavelength light, later in the day and at night. This regulation should entrain and advance the sleep-wake cycle and thereby improve and stabilize mood. Due consideration has been taken as to not cause glare or other visual discomfort (guided from the results from our feasibility study). During evening and night, the light system provides low-intensity light with low short-wavelength wavelength content and thus with minimal impact on the circadian system to avoid sleep disturbances.
The intervention is used as an add-on, non-pharmacological treatment [57]. The dynamic luminaires are tuned to mimic the temporal intensity and spectral distribution of daylight, in a SE-facing room, with two sets of timing – one for winter and one for summer. It is important to note, that the temporal composition does not possess the daily variation as seen in nature, but it is defined as one reoccurring temporal composition for summer and one for winter.

Ten single rooms in the inpatient ward are equipped with the new LED-lighting system that can function either in static or dynamic mode in each room. The lighting system is operated from a control panel placed in a locked room at the ward. Patients who are admitted to single rooms and included in the study are randomly allocated to treatment with either dynamic LED-lighting or static LED-lighting.

Dynamic LED-light group

The dynamic LED-lighting consists of three lighting elements in each single patient room (A, B, C).
A: An LED-panel built into the window jamb (in the vertical part of the window frame) mimicking the natural sunlight (see figure 1) as it is reflected in the window jamb from a white surface (RAL 9010)

This panel is turned on at 06:00 till 18:00 during the summer period (from February 15 till October 31), and from 07:00 till 17:00 during the winter period (from November 1 till February 14). The

dimension of the panel is 1950x310x60 mm. The light from this panel varies continuously in correlated colour temperature (CCT) from 1800 K dim, warm-white light at 06:00 in the summer and 07:00 in the winter, rising to 5500 K bright white light from 9:00 till 14:00. From 14:00 and onward the light from the panel is reduced in both intensity and CCT, until fading out at 4000 K at 18:00 during the summer period and 17:00 during the winter period. This built-in LED panel cannot be switched off by the patients, but a curtain can be drawn to reduce intensity. The panel contains Cool-White (CW), Warm-White (WW), and wide-spectrum Amber (A) LEDs.
Daylight at dawn is rich in shortwave light [58] , but we opted for a rather lower CCT at dawn (06:00/7:00) partly to mimic sunlight reflections in the window jamb on a white surface but also because we believe, from clinical experience, that patients find it more calming to be woken up in light with a lower CCT. Patients in this study is expected to have high levels of anxiety and depression at awakening and a too high CCT might induce agitation. B: Two additional luminaires containing CW/WW/A LEDs are mounted in the ceiling with dynamic regulation of intensity and CCT during the whole 24-hour day. This light also varies from 1800 K dim, warm-white light to 5500 K at an intensity brighter than in a conventional patient room. The ceiling light can be turned off/on by the patient as preferred. During the summer, the dynamic LED-lighting is brightest between 09:00 and 14:00 and dimmest and warmest, from 23:00 to 06:00. In the winter period, the timings are changed to 09:30 to 13:30 and from 22:30 to 07:00 respectively.
C: A reading luminaire by the bed, with similar design and timing as the ceiling lighting and a regulation of CCT from 2100 to 5500 K, with intensity kept relatively low, yet permitting reading while preventing too much suppression of melatonin in the evening. The reading luminaire can be turned off/on by the patient as preferred. The reading luminaire contains CW/WW/A LEDs.
All transitions are made as slow, imperceptible fades to mimic the nature of daylight through the daytime.

Static LED-light group

The Static LED-light intervention uses the same luminaires as the Dynamic LED-lighting intervention. In the Static LED-light intervention light output is completely static with regards to intensity, CCT, and timing. The built-in window luminaire is permanently turned off and the ceiling luminaires (B) and reading luminaire (C) are both set to 3000 K, at an intensity as expected in a

typical patient room. Both ceiling and wall luminaires can be turned on/off as preferred by the patient.

The use of the ceiling and reading luminaires will be logged continuously in both groups. In both groups there is a daylight contribution to the indoor illumination from windows.

Light measurements

The spectral irradiance from the LED lighting systems was measured both horizontally and vertically in one of the patient rooms with blackout blinds in the window to exclude all daylight. The temporal distribution over a day, of the α-opic irradiances (S-cone, M-cone, L-cone, Rhodopic, and Melanopic) from the luminaires in the dynamic setting (A,B, and C) and in the static setting (B, and C) were calculated *horizontally* from measurements 0.8 m above the floor (1 m from one corner of the room, 1m out from the wall) just above the pillow of the patient bed using a Gigahertz Optik BTS-256-EF spectrometer ranging from 360-750 nm in 1 nm resolution. *Vertical* irradiances were measured simultaneously at 1.70 m above the floor on the wall adjacent to the pillow of the patient bed using a Konika Minolta CL-500A spectrometer ranging from 360-780 in 1 nm resolution.

The α-opic irradiances were calculated from the measured spectral irradiances (unit of W/m^2nm). The α-opic irradiances (unit of W/m^2) are the effective photobiological irradiances with the spectral irradiance spectrally weighed with the α-opic action spectrum [59].

The results from the measurements are shown in figure 2. Figure 2 (a) show results from the horizontal measurements with the dynamic setting shown in full lines and the static setting in dashed lines at specific times if the day and correspondingly figure 2 (b) shows results from the vertical measurements.

During the study period light sensors will measure real-time illuminance in all patient rooms. This illuminance sensor (Wireless Sensor Tag Pro ALS) will be placed on the wall beside the bed 170 cm above the floor and close to the head end of the bed. Spectral light measurements will only be recorded in one patient room for each geographical orientation (S, E, W, and N) throughout the whole study period with a custom-built spectral sensor (AS7265X Multi Spectral Chipset, AMS)

situated also on the wall beside the bed 170 cm above the floor and close to the head end of the bed. In the same four rooms daylight will be measured with the same custom-built spectral sensor mounted in the windows facing outwards.

Figure 3 shows the measurement point from where the horizontal and vertical spectral measurement of the LED lighting was done. In the same figure the placement of the luminaires and the placement of the illuminance and spectral sensors are shown. Results of light measurements will be presented according to CIE S026 [59].

A suggestion on how to report light exposure in human clinical trials has been suggested in a recent paper by Spitschan et al [60]. In this clinical trial we will be able to report the α-opic irradiances of the planned LED lighting at referenced locations. Ideally, we should measure the light intensity and spectral distribution of the light that hits the cornea, but in this patient group we have decided not to use wearable light sensors due to reliability issues pertaining to the correct placement and use of such sensors.

Concomitant care

All participant will be offered the usual treatments at the ward. This includes nursing support to secure a daily structure, psychopharmacologic drug therapy, electroconvulsive treatment, psychotherapeutic and psychoeducative methods, physiotherapeutic groups, and occupational therapy.

Outcomes

Diagnostic measures

The Mini International Neuropsychiatric Interview (M.I.N.I.) is used for diagnostic purposes by the investigators. This is a short, structured diagnostic interview based on the DSM-IV diagnostic system, and will be conducted to confirm depression diagnosis, assess comorbidity, and any exclusion criteria for participation in the study [61]. Investigators are certified in the use of the M.I.N.I. instrument.

Psychometrics and sociodemographics

Sociodemographic data are collected at baseline together with a treatment outcome expectancy rating [62]. Psychometric assessments are performed at baseline and at the weekly evaluations. The rating window is set as the last three days for all instruments except for the Pittsburgh Sleep Quality Index (PSQI) [63] which in this study covers the last three weeks and the YMRS which by tradition covers the last seven days [64]. The severity of depression is assessed by the Hamilton Depression Rating scale, 17 item version (HAM-D_{17}) [65], which includes the HAM-D_6 subscale [66], and by the Bech-Rafaelsen Melancholia Rating Scale (MES) focusing more on the cognitive symptoms of depression [67]. The Hamilton rater is blinded to treatment allocation and is trained in the use of the HAM-D_{17} by repeated group ratings with co-researchers. The YMRS is an 11-item, interviewer-administered scale, used to assess manic or hypomanic symptoms. It has a score range from zero to 60 (highest severity of manic symptoms [64]. The Suicidal Ideation Attributes Scale (SIDAS) is a 5-item self-assessment scale with a score from zero to 50 (highest level of suicidal thinking) [68]. The UKU scale (side effect scale) is a generic side effect scale covering degree of expected side effects from medications and supplemented in this study with items covering light sensitivity, all with scores from 0 to 3 (3 is severe side-effect) [69]. Quality of life is assessed with the WHOQOL-BREF instrument measuring four life domains (physical health, psychological health, social relationships, environment) each with a score from zero to 100 (best) [70]. The Morningness-Eveningness Questionnaire (MEQ) is a 19 items self-assessed questionnaire constructed to assess chronotype. A score below 42 indicates “evening type” and a score above 58 indicates “morning type”; and a score between 42 and 58 indicates “intermediate type” [71]. Sleep quality is assessed by the PSQI containing 11 self-reported items. These items are transformed into 7 “component scores “, and a “global score”. The components scores are 1) “Subjective sleep quality”, 2) “Sleep latency”, 3) “Sleep duration”, 4) “Sleep efficiency”, 5) “Sleep disturbances”, 6) “Sleep medication” and, 7) “Daytime dysfunction”. A “Global Score” of five or above indicates poor sleep quality [63]. Patients are asked to estimate their mean weekly sleep onset and offset, number of awakenings, sleep quality, and duration and number of naps at each assessment. To evaluate the visual comfort in the room we use a newly designed Visual Comfort Scale covering satisfaction and experience of the lighting conditions, covering the last week [72] . To estimate the number of hours of exposure to the lighting condition participants evaluate how much time they have spent in their room during

the last week (Room Occupancy Diary) in the time-periods 6-12 am , noon to 6 pm, and 6 pm to 12 pm.[73]. To estimate the exposure to daylight and to the built-in LED-panel patients assess their use of curtains during the last week.

All events will be registered, and all SAEs, SUSARs, and SARs will be reported to the ethical committee immediately.

We collect data on the use of medication at baseline and at week 3 from patient medical charts. Including the use of ad lib. medication.

Ranking of outcomes

The primary outcome is the baseline adjusted mean score on the HAM-D_6 scale at week 3.

The secondary outcomes are a) the mean score on the SIDAS scale at week 3, b) the mean score on the HAM-D_{17} scale at week 3, c) the mean score on the WHOQOL-BREF at week 3.

Exploratory outcomes are: a) the proportion of patients with one or more SEAs (according to ICH-GCP 1997), b) the mean score on the visual comfort scale covering all three weeks, c) the mean reduction in mg/day from baseline to week 3 of zopiclone, d) the mean reduction in mg/day from baseline to week 3 of zolpidem, e) the mean reduction in mg/day from baseline to week 3 of quetiapine, e) the mean reduction in mg/day from baseline to week 3 of oxazepam, f) the mean score on the PSQI scale at week 3, g) the mean score on the MEQ scale at week 3, h), the mean score on the HAM-D_6 scale at 6 month.

A separate report will be made focussing on the total use of electrical energy for lighting in the static lighting group compared to the interventional LED-light group for a one year period.

Participants timeline

Enrolment and start of intervention are attempted to be within 5 days of admission to the ward. Assessments are performed at enrolment and once weekly for 3 weeks (see Spirit flow diagram in Ex 1).

Sample size and power estimations

Sample size calculation was done using the SAS 9.4 software using proc power for a two-sample independent sample t-test.

In a previous study [2], on patients from the same ward, we found a mean HAM-D_{17} score at admission of 23. This corresponds to a HAM-D_6 score of 13. The number of participants has been

estimated from an expected baseline-to-endpoint score reduction, on the HAM-D_6 from 13 to 8 in the dynamic light group, and from 13 to 10 in the static light group. Hence, the minimal important difference is two points on the HAM-D_6 scale. With an expected standard deviation of 3, an alpfa value of 0.05, and a power of 90%, we will need a total of 98 patients for the primary outcome. However, to be able to perform explorative analyses we will aim at 150 patients.

Power estimations of secondary outcomes

a) SIDAS scale: we expect a SIDAS score of 20 at baseline with a standard deviation of 8 and a reduction to a score of 5 in the dynamic light group and to 10 in the static light group. With an alpha value of 0.05 and a sample size of 98 participants, a power of 0.82 is estimated. With a sample size of 150, power would be 0.95.

b) HAM-D_{17} scale: we expect a HAM-D_{17} score of 23 at baseline with a standard deviation of 6 and a reduction to 14 in the active dynamic group and to 17.5 and the static light group. With an alpha value of 0.05 and a sample size of 98 participants, a power of 0.82 is estimated. With a sample size of 150, power would be 0.95.

c) WHOQOL-BREF questionnaire: We expect a WHOQOL-BREF score of 20 at baseline with a standard deviation of 17 and an increase to 45 in the dynamic light group and to 35 in the static light group. With an alpha value of 0.05 and a sample size of 98 participants, a power of 0.82 is estimated. With a sample size of 150, power would be 0.95.

Recruitment

The investigators will be in bi-weekly contact with the staff at the ward and will follow the flow of admissions. When a new patient is admitted and is occupying one of the ten rooms with light equipment, the staff will give the patient the invitation to meet the investigator if no exclusion criteria are apparent. The patient will have the opportunity to read the participant information paper and the investigator will give a detailed oral information regarding the study. The oral information and written material will include information regarding the importance of obtaining outcome data in the case of drop-out due to early discharge and after 6 months. The patient will be asked to decide on participation within two days. If the patient accepts, the informed consent will be signed, and the inclusion and baseline assessments will begin. The patient record and the M.I.N.I. interview will be used to confirm the patient's eligibility. Included patients will be

allocated to the next study number through the electronic case report form in OpenClinica [74], administered by the Copenhagen Study Unit. When submitted, the system randomizes the participant to one of the two treatment groups: *Dynamic LED-group* or *Static LED-group.* This information is given to the patient. The estimated mean stay of patients is 1 month and with 10 light equipped room a total number of patients per year is 140. With an expected inclusion rate of 50% we expect to finish last patient last visit June 2021.

Allocation

The randomization will be web-based with a 1 (experimental intervention) to 1 (control intervention) allocation with a stratification for BD. A total of 150 patients will be randomized in the study. The primary investigator will enroll participants into the study. The randomization is performed through the OpenClinica system, when participant's data have been entered in the eCRF, and all inclusion criteria are fulfilled, and no exclusion criteria are fulfilled.

Blinding

It is not possible to disguise the lighting condition to participants primarily due to the extra light panel in the window that will be active in the dynamic lighting group. The depression outcome assessors will perform the assessment in a separate office in another department and will be blinded to treatment allocation. Participants are asked not to reveal their treatment allocation to the Hamilton assessor. Other investigators and data managers will not be blinded. The blinding will be broken in the event of a SAR or SUSAR.

Statistical analyses will be performed with the two intervention groups coded as 'A' and 'B' by two blinded statisticians employed at the CTU. The statisticians will independently and blindly analyze all data and present the results in two independent reports. A third investigator will compare these reports and discrepancies will be discussed. Both statistical reports will be published on CTU's website. Based on the statistical reports, two blinded conclusions will be drawn by the steering group: one assuming 'A' is the experimental group and 'B' is the control group – and one assuming the opposite. Based on these two blinded conclusions, two abstracts will be written and published on CTU's website. When the blinding is broken, the 'correct' abstract will be chosen and the conclusions in this abstract will not be revised.

Data collection

All assessments are carried out by psychometrically trained investigators (research nurse and senior consultant). The Hamilton ratings are conducted by a certified Hamilton rater blinded for group allocation. Hamilton certification is based on supervised group ratings with a difference of less than +/- two points on the HAM-D_{17} scale from the gold standard (most experienced rater). Study duration is 3 weeks, including baseline assessment (pre-intervention) and final assessment (post-intervention). Patients who are transferred to another light-equipped room in the ward, during the three-week period, can continue with their scheduled assessments and the lighting condition in the new room will be set according to the allocation. It will be mentioned at

Data management

Data will be collected through an electronic case report form (eCRF) developed by Copenhagen Study Unit (CTU) in OpenClinica. Data in the eCRF is considered source data. The eCRF will use range checks for validation of entered data, and there will be an audit trail to monitor data entry. Data will be stored on servers locally at CTU with daily back-up. Data will also be collected from light sensors stored on independent hard drives. These data are also considered source data. Only pen-and-paper data are the informed consent and participants list. All data will be available to all authors.

Statistical methods

Continuous scale scores, including sleep scores, will be analyzed in a linear regression model using available data from all included participants (intention to treat). Results are given as mean, with confidence limits, standard deviation, and p-values. A detailed statistical analysis plan will be published separately before the randomization of the last participant. The significance level is set at 5 % two-tailed. Subgroup analyses will be performed for BD/MDD diagnosis. Missing data will be handled by multiple imputation techniques. No interim analyses are planned.

Data monitoring and auditing

According to Danish law, only drug studies are required to comply with Good Clinical Practice guidelines (GCP) [75]. We will, however, adhere to the GCP rules to secure study quality. Data analyses, performed by the primary investigator, will be supervised by a statistician. The study is subject to auditing from the regional ethical committee.

Harm

We do not expect that the study will expose participants to any serious hazard as their usual clinical management is maintained and the side effect profile of bright light is low [35 76] . All AEs will be recorded until the end of the follow-up period, and regulatory rules for reporting of SAEs and SARs will be adhered to. Any harm due to the study procedures is covered by the Danish Patient Compensation Association. The study will be stopped if there is a clinical suspicion of harm of the intervention, or if new evidence emerges that participants can come to harm due to the intervention.

ETHICS AND DISSEMINATION

Ethics

The study is approved by the Regional Committee on Health Research Ethics with approval number H-19004525. The study is approved by the Danish Data Protection Agency with approval number VD-2018-515. All participants will provide written informed consent before enrolment into the study. Informed consent will be obtained by the primary research investigator or a delegated study investigator. The study will be stopped if participants develop serious side effects. Patients can leave the study at any time at their own discretion and without any further effect on their continuous treatment at the ward. Any forthcoming protocol amendments will be submitted to the Ethical committee and the Danish Data Protection Agency for approval. Written and oral information will be given at the ward, between the first and the fifth day of admission. The information will be given only by trained study investigators. The information will be given in an undisturbed office at the ward. Prior to the information visit, the patient will be informed of the opportunity to bring a friend or relative (third party). The patient will be given up to two days to consider participation before giving the informed consent.

Personnel at the ward will present information from patient records to permit investigators to determine any exclusion criteria. Patients eligible for enrolment will be asked by staff at the ward to participate in an information meeting. At inclusion, the patient will produce their civil registration number, name, and sociodemographic data, to the investigators. These data will be entered into the eCRF system and a participant-ID will be generated as part of the randomization

process. Participants name, civil registration number and study number (from the eCRF) will be stored in a participant' identification list in a secured data repository. Personal data in the eCRF will only be used for randomization purposes, after which only the participant-ID will be used. At the end of the study all paper material containing data will be transferred to a secure data repository. All study data will be handled according to the General Data Protection Regulation. The final data set will be accessible to all persons in the study group.

We do not expect any ethical issues. All regulatory rules will be followed, and the expected side effects of the dynamic lighting systems are rare and mild. We have taken precautions to find and deal with any emergent manic and suicidal symptoms.

Dissemination

Results will be published in peer-reviewed international journals, as posters, and as oral presentations at international symposia. All data whether negative, positive or inconclusive will be reported in full. All members of the study group are co-authors with a pre-arranged order. No professional writers will be used. Depending on the journal of publication, part of the protocol, statistical code, and dataset will be publicly available. All participants will be informed of the trail results.

Declarations

Ethics approval and consent to participate

The study has been approved by the Committee on Health Research Ethics for the Capital region of Denmark (approval number H-19004525). All participants will provide written informed consent before enrollment into the study.

The study is approved by the Danish Data Protection agency (approval number VD-2018-515).

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Author contributions

CV: Design, planning, data acquisition, drafting, and agreement of accountability for all aspects of the work.

ASA: Design, planning, data acquisition, drafting, and agreement of accountability for all aspects of the work.

TSH: Planning, drafting, and agreement of accountability for all aspects of the work.

PMP: Data acquisition, drafting, and agreement of accountability for all aspects of the work.

CDH: Design, planning, drafting, and agreement of accountability for all aspects of the work.

UK: Design, planning, drafting, and agreement of accountability for all aspects of the work.

EEP: Planning, drafting, and agreement of accountability for all aspects of the work.

JE: Planning, drafting, and agreement of accountability for all aspects of the work.

JJ: Planning, drafting, and agreement of accountability for all aspects of the work.

HØM: Planning, drafting, and agreement of accountability for all aspects of the work.

IH: Planning, drafting, and agreement of accountability for all aspects of the work.

KM: Design, planning, data acquisition, drafting, and agreement of accountability for all aspects of the work.

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Competing interests

TSH is an employee of Chromaviso that has supplied the lighting system. There are no financial or other interests for any other authors.

Patient and public involvement

Patients were involved in the testing of tolerability of the lighting system. This influenced the setting of the dynamic lighting system. Patient also assisted in developing the Visual Comfort Scale that is used in the study to estimate tolerability. Both involvements were done before the start of the study.

Data Availability Statement

We will make data from this study available on reasonable request once the results are published.

Figure legends

Figure 1. The left-hand picture shows how the LED panel is mimicking sunlight reflections on the wall. The right-hand side of the picture shows natural sunlight reflexions on the wall.

Figure 2 (a) and (b). The figures show temporal distribution of horizontal (a) and vertical (b) α - opic irradiance of the LED-lighting with daylight blacked out. Dynamic LED-light intervention is shown as solid lines and static LED-light intervention is shown as dashed lines. Measurement points and equipment are described in the *Light measurement* section. The depicted timelines are for the summer intervention profile. Winter intervention profile differs in the way that the period between 06:00 – 18:00 during summer is contracted 1 hour in each end to 07:00 – 17:00 to enhance patient tolerability.

Figure 3. The figure shows the placement of the luminaries where A is the LED panel built into the window jamb, B is the two ceiling luminaires and C is the reading luminaire. Mv and Mh indicates the measurement point for the vertical (Mv) and horizontal (Mh) spectral LED measurements performed in a patient room with blackout blind in the window to exclude daylight. SL indicates the permanent placement of the illuminance and the spectral room sensors and SDL the permanent placement of the spectral daylight sensor.

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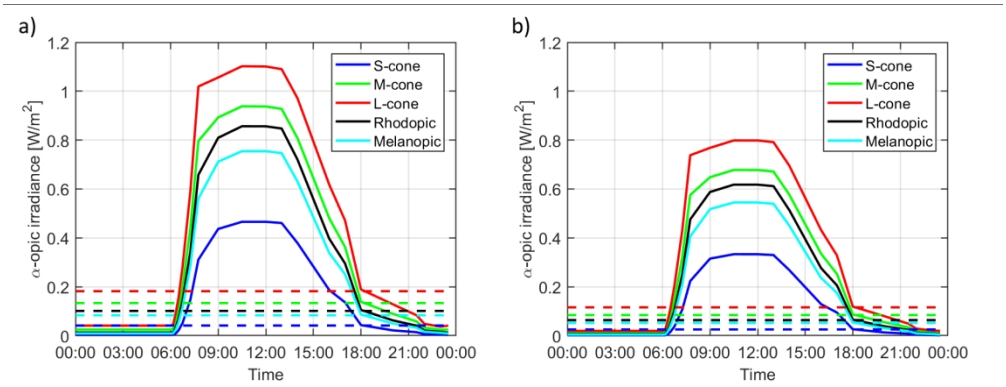
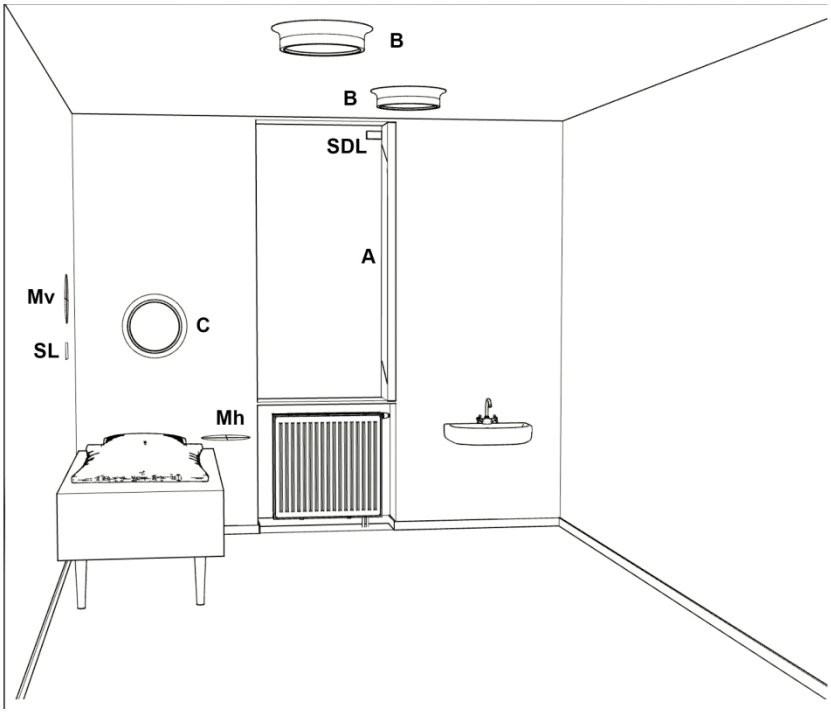
The left-hand picture shows how the LED panel is mimicking sunlight reflections on the wall. The right-hand side of the picture shows natural sunlight reflexions on the wall.

304x171mm (96 x 96 DPI)



The figures show temporal distribution of horizontal (a) and vertical (b) α -opic irradiance of the LED-lighting with daylight blacked out. Dynamic LED-light intervention is shown as solid lines and static LED-light intervention is shown as dashed lines. Measurement points and equipment are described in the Light measurement section. The depicted timelines are for the summer intervention profile. Winter intervention profile differs in the way that the period between 06:00 – 18:00 during summer is contracted 1 hour in each end to 07:00 – 17:00 to enhance patient tolerability.



The figure shows the placement of the luminaries where A is the LED panel built into the window jamb, B is the two ceiling luminaires and C is the reading luminaire. Mv and Mh indicates the measurement point for the vertical (Mv) and horizontal (Mh) spectral LED measurements performed in a patient room with blackout blind in the window to exclude daylight. SL indicates the permanent placement of the illuminance and the spectral room sensors and SDL the permanent placement of the spectral daylight sensor.

209x147mm (300 x 300 DPI)

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Dynamic LED-light versus Static LED-light for depressed inpatients: study protocol for a randomized clinical study

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Title

Dynamic LED-light versus Static LED-light for depressed inpatients: study protocol for a randomized clinical study.

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ABSTRACT

Introduction: Retrospective studies conducted in psychiatric inpatient wards have shown a relation between the intensity of daylight in patient rooms and the length of stay, pointing to an antidepressant effect of ambient lighting conditions. Light therapy has shown a promising antidepressant effect when administered from a light box. The emergence of Light Emitting Diode technology has made it possible to build luminaires into rooms and to dynamically mimic the spectral and temporal distribution of daylight. The objective of this study is to investigate the antidepressant efficacy of a newly developed dynamic LED-lighting system installed in an inpatient ward.

Methods and analysis: In all, 150 inpatients with a major depressive episode, as part of either a Major Depressive Disorder or as part of a Bipolar Disorder, will be included. The design is a two-arm 1:1 randomised study with a dynamic LED-lighting arm and a static LED-lighting arm, both as add-on to usual treatment in an inpatient psychiatric ward. The primary outcome is the baseline adjusted *score* on the 6-item Hamilton Depression Rating Scale at week 3. The secondary outcomes are the mean score on the Suicidal Ideation Attributes Scale at week 3, the mean score on the 17-item Hamilton Depression Rating Scale at week 3, and the mean score on the WHOQOL-BREF at week 3. The spectral distribution of daylight and LED-light, with a specific focus on light mediated through the intrinsically photosensitive Retinal Ganglion Cells, will be measured. Use of light luminaires will be logged. Assessors of Hamilton depression rating scale scores and data analysts will be blinded for treatment allocation. The study was initiated in May 2019 and will end in December 2021.

Ethics and dissemination: The study was approved by the Committee on Health Research Ethics of the Capital Region of Denmark. No ethical issues are expected. Results will be published in peer-reviewed journals, disseminated electronically and in print, and presented at symposia.

Trial registration number: ClinicalTrials.gov NCT03821506.

Keywords: Major Depressive Disorder, Bipolar Disorder, Lighting, Light, Inpatients, Chronotherapy, Randomized Controlled Trial.

Trial protocol number: Room-Light final version.

Strengths and limitations of this study:

- This is the first randomized clinical trial investigating the antidepressant effect of a dynamic LED system in an inpatient psychiatric ward
- The study has a rigorous design and a large sample size enabling it to find a clinically relevant antidepressant effect
- Patient stay might not be of an adequate length to achieve full antidepressant effect of the lighting system
- Light measurements will not accurately reflect corneal light exposure as wearable light sensors are not used

INTRODUCTION

Depression

Depressive episodes, either as part of a Major Depressive Disorder (MDD) or as part of a Bipolar Disorder (BD), are a prevalent and leading cause of disability worldwide. Society suffers large direct and indirect losses due to lost work, sickness, and early retirements, and WHO ranks major depression as a significant contributor to the global burden of disease [1]. In Denmark alone (population of 5.8 million), the costs of depression amount to an estimated 1.87 billion Euro per year. Depression can affect an individual to an extent that everyday activities and chores are insurmountable. These patients often have suicidal ideation and despair and need inpatient care including treatment with mood stabilizers, antipsychotics, antidepressants, psychoeducation, psychotherapy, and occupational therapy. Typically, these patients will still suffer from varying degrees of depression when discharged [2 3] and relapse, readmission, and even suicide, upon discharge, are major treatment challenges [4]. Despite intense efforts during the last decades there has been no breakthrough for neither drug development nor for any other treatment modality and 10-25% of patients are treatment resistant [5]. Thus, there is a need for the development of new treatment options [6]. Light therapy has shown an antidepressant effect in outpatients, when using light box administered treatment, but studies in more severely depressed inpatients are warranted [7]. The technological development has made it possible to some extent to mimic the

temporal changes in intensity and spectral distribution of daylight with Light Emitting Diodes (LED) built into buildings. However, in this study we do not aim at creating actual daylight characteristics in the rooms but to provide a tailored spectral illuminance to enhance alertness, mood improvement and circadian regulation. This includes a focus on intrinsically photosensitive Retinal Ganglion Cells (ipRGC) influenced responses.

The present efficacy study thus investigates the possible antidepressant effect of a new, dynamic type of general room lighting in the treatment of a major depressive episode either as part of an MDD or a BD in patients admitted to anaffective disorders ward.

Bright Light Therapy

Light has been used to treat medical conditions, such as melancholia or lethargy for at least a thousand years [8] and daylight has been considered important for centuries when building hospitals [9]. Animal research conducted through many decades has shown that dosage and timing of light have impact on reproduction, activity, and sleep [10] , and in the 1980s it was discovered that light could suppress melatonin secretion, in humans [11], indicating that light gives cues to the brain about night time and season. The resultant clinical description of Seasonal Affective Disorder (SAD) and the theoretical analogy with hamster hibernation cycles led to the development of bright light treatment [12-15]. It was later discovered that light pulses applied in the morning phase advance the sleep-wake cycle (and other rhythms) whereas light applied in the evening delays the sleep-wake cycle (and other rhythms). This is named the Phase Response Curve (PRC) for light in humans [16 17] , and is the basis for the mechanism of "entrainment" – the synchronization of a self-sustaining oscillation (such as sleep) by an external forcing oscillation (such as daylight or artificially timed light). In 2000, a new non-visual retinal receptor, the intrinsically photosensitive retinal ganglion cells (ipRGC), was discovered in the human retina [18]. The ipRGC receptors have a peak spectral sensitivity for the short-wavelength portion of the light spectrum (460 nm – 480 nm) [19]. Since then it has been found, primarily through animal research, that the ipRGC regulates the circadian system through input to the suprachiasmatic nuclei (SCN) and the pineal gland, but also, through newly found pathways, to brain structures known to be involved in depressive illness [20-23]. This has given us a better understanding of how light can have a fast working antidepressant effect in humans and has stimulated research on the effect of using light with temporally shifting

spectral compositions and intensity. The impact of the signals from the ipRGC is, among other effects, responsible for the ability of light to time and stabilize the sleep-wake cycle and to adjust the seasonal regulation of serotonin [24]. LED-light can be tuned to be particularly rich in the short-wavelength spectrum in contrast to conventional compact fluorescent light (CFL). Thus, LED-light can be adjusted to maximize the impact on the ipRGC system. The temporal regulation of the spectral composition and intensity of LED-light is clinically important. Too much short-wavelength light in the evening will delay the sleep-wake cycle, through the PRC mechanism, causing a difficulty falling asleep (sleep onset insomnia) [25], whereas short-wavelength light in the morning will advance sleep and increase alertness. It should be noted that prereceptoral filters such as the lens tends to shift the spectral sensitivity of the melanopsin receptor to longer wavelengths. There is an association between depression and late chronotypes [26] and late chronotypes is associated with nonresponse to treatment [27]. Furthermore, patients with depression are prone to drift to later sleep schedules [3]. We should thus expect that dynamic lighting with enriched short-wavelength morning light and low content short-wavelength light in the evening would prevent drifting or even phase advance the sleep-wake cycle and thus augment the antidepressant treatment response [28].

Since the publication of the first study on the effect of light therapy for depression by Rosenthal et al in 1984 [12], a large number of studies have been carried out to investigate the efficacy of bright light treatment on both seasonal and non-seasonal depression. Light is one of the most thoroughly investigated chronotherapeutic treatments in addition to wake-therapy [29] and sleep phase advance [30]. In 2004, Tuunainen and colleagues published the Cochrane systematic review “Light therapy for non-seasonal depression” [31]. The conclusion was that light therapy must be regarded as a promising treatment method, but because of the heterogeneity among the studies, methodological problems and a lack of systematic collection of adverse events (AE’s), the recommendation of light therapy as a treatment of depression should be considered with some caution. In a systematic review from 2007, Even et al, found an additive effect of light therapy when used as augmentation to antidepressant therapy in non-seasonal depression [32]. In a systematic review from 2016, Perera et al included 20 RCT’s using light therapy for non-seasonal depression and found an overall small antidepressant effect (SMD -0.41; 95% CI -0.64 to -0.18), but with a high risk of bias and inconsistency between studies [33]. In subgroup analyses (stand-

alone light therapy versus adjunctive light therapy, morning light therapy versus evening light therapy or other times of day, light therapy for in- versus outpatients, placebo light conditions versus non-light-based placebo conditions) some support was found for a better effect of light when used as monotherapy, in the morning, for outpatients, and when compared with non-light-based placebos. Only four of the 20 studies had a low risk of bias on all items on the Cochrane Risk of Bias Tool [34-37]. A Danish study found a significantly better effect of a combination of bright light therapy plus sertraline compared with dim red placebo light and sertraline, in 102 outpatients [34]. In a Canadian study 122 outpatients were compared in four groups: (a) active light plus active fluoxetine, (b) active light plus placebo fluoxetine, (c) inactive negative ion generator plus active fluoxetine, (d) inactive negative ion generator plus placebo fluoxetine [35]. A significantly better effect was found in the group receiving the combination of active light plus active fluoxetine, as well as in the group receiving the combination of active light and placebo fluoxetine compared to the group receiving the combination of inactive negative ion generator plus placebo fluoxetine. A study performed in 84 elderly (> 60 years) outpatients with non-seasonal depression found a statistically significant beneficial effect of active versus placebo light treatment [36]. However, another study found no difference in depression outcome between groups, and a low reduction in depression severity across groups of 16 %, among 81 elderly outpatients (> 60 years) with non-seasonal depression, treated with bright or placebo light administered at three different time-points [37]. A more recent study showed significantly better effect of bright light treatment (BLT) compared to dim light treatment, when used as augmentation of mood stabilizing medication, in 46 patients with bipolar depression [38]. A recent review showed that the risk of a switch from depression to mania, in patients with BD disorder treated with light therapy, was no higher than with antidepressant drug therapy alone [39].

With conventional light therapy, patients are seatedin front of a light box for 30-60 minutes in the morning [40]. Even though it is technical possible to produce a tuneable light box, commercial light boxes often only deliver fixed spectral distributions. In treatment with dynamic LED-lighting, built-in luminaires can provide temporal changing intensity and spectral distribution and they substitute the general room-lighting. One of the main study design challenges with light therapy studies is the insufficient blinding of patients to light treatment conditions, and the lack of an appropriate control treatment (placebo). These challenges are not solved by using dynamic lighting as the

change in color and intensity is readily seen by the patients.

In conclusion, there is some evidence for the effect of traditional light box administered treatment, primarily in seasonal and non-seasonal depression, less in bipolar depression, but very little evidence for the effect of dynamic lighting. Therefore, a rigorously designed large study using dynamic lighting in patients with bipolar and unipolar major depression is warranted.

Architecture, daylight and lighting in hospitals

In Denmark (latitude 56°), daylight is scarce during the winter season [41] and in addition, cold rainy weather tends to keep people inside. This reduces overall light exposure because indoor light intensities seldom exceed 100-300 lux, whereas outdoor light intensities often are higher than 2000-3000 lx, even on an overcast day. Light exposure might therefore not be adequate to entrain the sleep-wake cycle, and other circadian rhythms, or to sustain normal levels of alertness and mood.

For counties with a northern location, the limited daylight during winter months make it pertinent to investigate how and if artificial LED-light can become an adjunct method to the treatment of depression in hospitals.

There are casuistic observations of an association between onset of depression and sudden drop in solar irradiation [42] and between measured light exposure and depression severity [43].

Recent studies confirm ancient architectural principles about exposure to the morning sun, such as the late 19th century Nightingale pavilions facing southeast (SE) aiming to optimize exposure to the morning sun during winter darkness [44]. Thus, these few studies have been carried out to investigate the effect of daylight or dynamic lighting on patients with depression. The first documented daylight experiment was done by Wirz-Justice et al in 1996 with seasonal patients showing a better antidepressant effect of a one-hour walk outside compared to low-dose light therapy from a light box [45]. Some studies have investigated the possible influence of light exposure on length of inpatient stay in psychiatric hospitals, retrospectively. In a sample of 174 inpatients treated for bipolar or unipolar major depression in Alberta Canada (53.6ºN), Beauchemin et al found a length of stay of 16.9 days in bright rooms (east orientated) and 19.5 days in dimly lighted rooms (west facing or indoor courtyard) ($p < 0.05$), [46]. Benedetti et al investigated the length of inpatient stay for 187 patients with bipolar or unipolar depression in Milano, Italy (45.5ºN). For patients with bipolar depression then mean length of stay was 19.8 days in east oriented rooms

and 23.5 days in west oriented rooms (p=0.02), [47]. No difference was found for patients with unipolar depression. In Berlin, Germany (52.5 Nº), Staedt et al found a reduction in mean length of inpatient stay for patients with unipolar depression, from 25.91 (17.04) days to 22.04 (15.40) days (p=0.023) when the psychiatric clinic was moved to new facilities equipped with short-wavelength enriched dynamic lighting system [48]. However, when controlled for age the statistical significance was lost (p=0.083). In Mallorca, Spain (39.7ºN), Canellas et al found in a sample of 207 patient with depression as part of BD or MDD that the median inpatient stay was reduced from 14 days (Inter Quartile Range 8-19) to 11 days (Inter Quartile Range 6-15) (p=0.007) when the ward was moved from a basement location to a new facility where the accumulated light exposure per day was 300 % higher [49]. In a study from our own group, we documented extreme midday differences in daylight exposure between hospital rooms facing SE and hospital rooms facing NW. Measured on a clear day, these differences were 57,000 lx at the summer solstice, 38,000 lx at the autumn equinox and 19,000 lx at the winter solstice. We found a significantly shorter inpatient stay for patients staying in SE facing room compared to NW facing rooms [2]. Latest, West et al examined the effect of dynamic light versus static light in a cluster randomization design in two cerebral stroke rehabilitation units in Copenhagen, Denmark (55.7 Nº). These patients were mostly bedridden, and the rooms were equipped with blinds that could regulate daylight. In the group randomized to dynamic light, patients had significantly lower mood scores (better), measured by the major depression inventory, compared with the group receiving static light [50]. Moreover, patients had significantly elevated melatonin plasma levels at endpoint compared to baseline and evolved a significant rhythmicity of melatonin (cosinor analysis) [51]. There is also some evidence that dynamic lighting stabilizes mood and improves sleep quality in individuals suffering from dementia [52-54].

In summary, the evidence base for dynamic lighting is still weak. There is only little knowledge on how LED-light should be implemented as well as the potentially beneficial or harmful effects of LED-light on patients with depression whether as part of a unipolar or bipolar disorder.

In hospitals, there will always be “a dark side of the building” where facades will receive very little – if any – morning sun during wintertime. Dynamic LED-lighting enables us to tune the lighting conditions individually for each room in a building to compensate for insufficient daylight.

In the present randomized trial, we investigate the efficacy of a dynamic LED lighting condition in

inpatients with unipolar or bipolar depression. We have incorporated the results from our recent four single-room feasibility trial (paper submitted for publication) that focused on the performance and patient tolerability of the same dynamic LED system as used in this study. The present study will be an addition to the knowledge in this transdisciplinary field, combining medical science, architecture, and engineering.

Objective

The objective of this study is to investigate the antidepressant effect of a newly developed dynamic LED-lighting system in an inpatient psychiatric ward. Patients with a current major depressive episode either as part of MDD or a BD will be randomized to receive either Dynamic LED-lighting or Static LED-lighting in combination with treatment as usual. We hypothesize that the group receiving Dynamic LED-lighting will have a larger reduction in depression scores on the Hamilton Depression Rating Scale than the group receiving static LED-light and that the antidepressant effect of the intervention will be largest for individuals with BD.

METHODS AND ANALYSIS

Design

The study protocol is reported according to the SPIRIT statement of randomized studies of nonpharmacological treatment [55]. The study is a three-week, randomized, controlled, single-blind, parallel-group study with a balanced allocation ratio (1:1) of adult patients diagnosed with depression either as part of MDD or BD. Patients will be randomly assigned to either dynamic LED-lighting or Static LED-lighting with stratification for patients with a major depressive episode as part of a BD or as part of MDD. We expect a ratio of 2:1 for these two subgroups. Participants will be psychometrically assessed at baseline and once a week for a total of 3 weeks. All other treatment elements at the ward will continue as usual. Patients who are discharged or transferred to another ward during the three weeks study period, will be contacted for a follow-up assessment corresponding to the missing final assessment, to facilitate adherence to protocol.

Study setting

The study will be conducted at a specialized inpatient unit for affective disorders at the Mental Health Centre Copenhagen, located on the premises of Rigshospitalet. This ward delivers specialized treatment for patients with affective disorders (MDD, BD) consisting of

psychoeducation, pharmacological treatment, electroconvulsive treatment, physiotherapy, and occupational therapy performed by a transdisciplinary team of psychiatrists, nurses, physiotherapists, and occupational therapists. The average period of admission is approximately 4-6 weeks. The ward has a capacity of 14 patients. The study intervention will include ten single patient rooms each equipped with a lighting system that can provide either dynamic LED- or static LED-lighting.

Eligibility criteria

All patients admitted to the inpatient ward will be considered for participation. Patients are considered eligible for inclusion into the study if they comply with the inclusion and exclusion criteria listed below.

Inclusion criteria are: more than 18 years of age, a current major depressive episode as part of either MDD (DSM-IV) or BD (DSM-IV), BD patients should be in current and recent (a minimum of two months before admission) mood stabilizing treatment, informed consent, and speaks and understand Danish.

Exclusion criteria are: severe suicidality corresponding to a score > 2 on the Hamilton Depression Rating Scale item 3 or if the investigators are uncertain of the degree of suicidality, psychotic depressive features at time of inclusion or within the last two weeks, abuse of alcohol and/or drugs, a Young Mania Ratings Scale (YMRS) score of 7 or above or a current hypomanic or manic episode, coercive measures of any kind.

Discontinuation criteria are: Serious Adverse Reactions (SARs), Suspected Unexpected Serious Adverse Reactions (SUSARS), all listed exclusion criteria, and if the patient wishes to leave the study. Intervention will be discontinued if one of the before mentioned criteria are fulfilled but we will ask the patient for an endpoint assessment unless the patient wants to leave the study.

The eligibility criteria were chosen to represent a broad sample of the patient group to maximize the generalizability of the study results. Patients with severe suicidality is excluded because they are more often transferred to closed wards and thus lost to follow-up which reduces the quality of the study. The eligibility will be evaluated through case files and from interviews with the patients. The eligibility criteria are assessed from case records, from the Hamilton depression rating scale, the Young mania rating Scale, and the M.I.N.I. instrument which also contains a section on alcohol and drug abuse.

Interventions

In this study the treatment with dynamic LED-lighting provides temporal change in intensity and spectral distribution throughout the 24-hour day. LED luminaires are built into the room and substitute the general room lighting. In this way treatment is administered to the patient, throughout the day, when the patient is in the room, with a planned specified temporal and spectral distribution. This enables the system to provide brighter daytime lighting aiming at a phase advance of the circadian rhythms and to provide an alerting and mood enhancing effect. This is attempted by supplying more bright light rich in the short-waved region of the spectral range in the first part of the day, and warmer and less intense light with less short-wavelength light, later in the day and at night. This regulation should entrain and advance the sleep-wake cycle and thereby improve and stabilize mood. Due consideration has been taken as to not cause glare or other visual discomfort (guided from the results from our feasibility study). During evening and night, the light system provides low-intensity light with low short-wavelength wavelength content and thus with minimal impact on the circadian system to avoid sleep disturbances.

The intervention is used as an add-on, non-pharmacological treatment [56]. The dynamic luminaires are tuned to mimic the temporal intensity and spectral distribution of daylight, in a SE-facing room, with two sets of timing – one for winter and one for summer. It is important to note, that the temporal composition does not possess the daily variation as seen in nature, but it is defined as one reoccurring temporal composition for summer and one for winter.

Ten single rooms in the inpatient ward are equipped with the new LED-lighting system that can function either in static or dynamic mode in each room. The lighting system is operated from a control panel placed in a locked room at the ward. Patients who are admitted to single rooms and included in the study are randomly allocated to treatment with either dynamic LED-lighting or static LED-lighting.

<u>Dynamic LED-light group</u>

The dynamic LED-lighting consists of three lighting elements in each single patient room (A, B, C).

A: An LED-panel built into the window jamb (in the vertical part of the window frame) mimicking the natural sunlight (see figure 1) as it is reflected in the window jamb from a white surface (RAL 9010)

This panel is turned on at 06:00 till 18:00 during the summer period (from February 15 till October 31), and from 07:00 till 17:00 during the winter period (from November 1 till February 14). The dimension of the panel is 1950x310x60 mm. The light from this panel varies continuously in correlated colour temperature (CCT) from 1800 K dim, warm-white light at 06:00 in the summer and 07:00 in the winter, rising to 5500 K bright white light from 9:00 till 14:00. From 14:00 and onward the light from the panel is reduced in both intensity and CCT, until fading out at 4000 K at 18:00 during the summer period and 17:00 during the winter period. This built-in LED panel cannot be switched off by the patients, but a curtain can be drawn to reduce intensity. The panel contains Cool-White (CW), Warm-White (WW), and wide-spectrum Amber (A) LEDs.

Daylight at dawn is rich in shortwave light [57] , but we opted for a rather lower CCT at dawn (06:00/7:00) partly to mimic sunlight reflections in the window jamb on a white surface but also because we believe, from clinical experience, that patients find it more calming to be woken up in light with a lower CCT. Patients in this study is expected to have high levels of anxiety and depression at awakening and a too high CCT might induce agitation. B: Two additional luminaires containing CW/WW/A LEDs are mounted in the ceiling with dynamic regulation of intensity and CCT during the whole 24-hour day. This light also varies from 1800 K dim, warm-white light to 5500 K at an intensity brighter than in a conventional patient room. The ceiling light can be turned off/on by the patient as preferred. During the summer, the dynamic LED-lighting is brightest between 09:00 and 14:00 and dimmest and warmest, from 23:00 to 06:00. In the winter period, the timings are changed to 09:30 to 13:30 and from 22:30 to 07:00 respectively.

C: A reading luminaire by the bed, with similar design and timing as the ceiling lighting and a regulation of CCT from 2100 to 5500 K, with intensity kept relatively low, yet permitting reading while preventing too much suppression of melatonin in the evening. The reading luminaire can be turned off/on by the patient as preferred. The reading luminaire contains CW/WW/A LEDs.

All transitions are made as slow, imperceptible fades to mimic the nature of daylight through the daytime.

Static LED-light group

The Static LED-light intervention uses the same luminaires as the Dynamic LED-lighting intervention. In the Static LED-light intervention light output is completely static with regards to

intensity, CCT, and timing. The built-in window luminaire is permanently turned off and the ceiling luminaires (B) and reading luminaire (C) are both set to 3000 K, at an intensity as expected in a typical patient room. Both ceiling and wall luminaires can be turned on/off as preferred by the patient. The use of the ceiling and reading luminaires will be logged continuously in both groups. In both groups there is a daylight contribution to the indoor illumination from windows.

Light measurements

The spectral irradiance from the LED lighting systems was measured both horizontally and vertically in one of the patient rooms with blackout blinds in the window to exclude all daylight. The temporal distribution over a day, of the α-opic irradiances (S-cone, M-cone, L-cone, Rhodopic, and Melanopic) from the luminaires in the dynamic setting (A,B, and C) and in the static setting (B, and C) were calculated *horizontally* from measurements 0.8 m above the floor (1 m from one corner of the room, 1m out from the wall) just above the pillow of the patient bed using a Gigahertz Optik BTS-256-EF spectrometer ranging from 360-750 nm in 1 nm resolution. *Vertical* irradiances were measured simultaneously at 1.70 m above the floor on the wall adjacent to the pillow of the patient bed using a Konika Minolta CL-500A spectrometer ranging from 360-780 in 1 nm resolution.

The α-opic irradiances were calculated from the measured spectral irradiances (unit of W/m^2nm). The α-opic irradiances (unit of W/m^2) are the effective photobiological irradiances with the spectral irradiance spectrally weighed with the α-opic action spectrum [58].

The results from the measurements are shown in figure 2. Figure 2 (a) show results from the horizontal measurements with the dynamic setting shown in full lines and the static setting in dashed lines at specific times if the day and correspondingly figure 2 (b) shows results from the vertical measurements.

During the study period light sensors will measure real-time illuminance in all patient rooms. This illuminance sensor (Wireless Sensor Tag Pro ALS) will be placed on the wall beside the bed 170 cm above the floor and close to the head end of the bed. Spectral light measurements will only be recorded in one patient room for each geographical orientation (S, E, W, and N) throughout the whole study period with a custom-built spectral sensor (AS7265X Multi Spectral Chipset, AMS) situated also on the wall beside the bed 170 cm above the floor and close to the head end of the bed. In the same four rooms daylight will be measured with the same custom-built spectral sensor

mounted in the windows facing outwards.

Figure 3 shows the measurement point from where the horizontal and vertical spectral measurement of the LED lighting was done. In the same figure the placement of the luminaires and the placement of the illuminance and spectral sensors are shown. Results of light measurements will be presented according to CIE S026 [58].

A suggestion on how to report light exposure in human clinical trials has been suggested in a recent paper by Spitschan et al [59]. In this clinical trial we will be able to report the α-opic irradiances of the planned LED lighting at referenced locations. Ideally, we should measure the light intensity and spectral distribution of the light that hits the cornea, but in this patient group we have decided not to use wearable light sensors due to reliability issues pertaining to the correct placement and use of such sensors.

Concomitant care

All participant will be offered the usual treatments at the ward. This includes nursing support to secure a daily structure, psychopharmacologic drug therapy, electroconvulsive treatment, psychotherapeutic and psychoeducative methods, physiotherapeutic groups, and occupational therapy. These concomitant treatments will have a foreseeable antidepressant effect that cannot be controlled for. However, this effect will be equally divided between the two groups due to the randomised design.

Outcomes

Diagnostic measures

The Mini International Neuropsychiatric Interview (M.I.N.I.) is used for diagnostic purposes by the investigators. This is a short, structured diagnostic interview based on the DSM-IV diagnostic system, and will be conducted to confirm depression diagnosis, assess comorbidity, and any exclusion criteria for participation in the study [60]. Investigators are certified in the use of the M.I.N.I. instrument.

Psychometrics and sociodemographics

Sociodemographic data are collected at baseline together with a treatment outcome expectancy rating [61]. Psychometric assessments are performed at baseline and at the weekly evaluations. The

rating window is set as the last three days for all instruments except for the Pittsburgh Sleep Quality Index (PSQI) [62] which in this study covers the last three weeks and the YMRS which by tradition covers the last seven days [63]. The severity of depression is assessed by the Hamilton Depression Rating scale, 17 item version (HAM-D_{17}) [64], which includes the HAM-D_6 subscale [65], and by the Bech-Rafaelsen Melancholia Rating Scale (MES) focusing more on the cognitive symptoms of depression [66]. The Hamilton rater is blinded to treatment allocation and is trained in the use of the HAM-D_{17} by repeated group ratings with co-researchers. The YMRS is an 11-item, interviewer-administered scale, used to assess manic or hypomanic symptoms. It has a score range from zero to 60 (highest severity of manic symptoms) [63]. The Suicidal Ideation Attributes Scale (SIDAS) is a 5-item self-assessment scale with a score from zero to 50 (highest level of suicidal thinking) [67]. The UKU scale (side effect scale) is a generic side effect scale covering degree of expected side effects from medications and supplemented in this study with items covering light sensitivity, all with scores from 0 to 3 (3 is severe side-effect) [68]. Quality of life is assessed with the WHOQOL-BREF instrument measuring four life domains (physical health, psychological health, social relationships, environment) each with a score from zero to 100 (best) [69]. The Morningness-Eveningness Questionnaire (MEQ) is a 19 items self-assessed questionnaire constructed to assess chronotype. A score below 42 indicates “evening type” and a score above 58 indicates “morning type”; and a score between 42 and 58 indicates “intermediate type” [70]. Sleep quality is assessed by the PSQI containing 11 self-reported items. These items are transformed into 7 “component scores “, and a “global score”. The components scores are 1) “Subjective sleep quality”, 2) “Sleep latency”, 3) “Sleep duration”, 4) “Sleep efficiency”, 5) “Sleep disturbances”, 6) “Sleep medication” and, 7) “Daytime dysfunction”. A “Global Score” of five or above indicates poor sleep quality [62]. Patients are asked to estimate their mean weekly sleep onset and offset, number of awakenings, sleep quality, and duration and number of naps at each assessment. To evaluate the visual comfort in the room we use a newly designed Visual Comfort Scale covering satisfaction and experience of the lighting conditions, covering the last week [71] . To estimate the number of hours of exposure to the lighting condition participants evaluate how much time they have spent in their room during the last week (Room Occupancy Diary) in the time-periods 6-12 am , noon to 6 pm, and 6 pm to 12 pm.[72]. To estimate the exposure to daylight and to the built-in LED-panel participants assess their use of curtains during the last week.

We believe that the participants will be able to fill in all the planned rating scales as many of these scales are quite short. However, we do offer to divide the inclusion visit on two days for patients with more pronounced cognitive impairment whether due to their illness or any sedating effect of psychotropic drugs.

It would have been valuable both to measure melatonin to assess circadian phase and of interest to use actimetry to get a more detailed information on sleep, but we have judged that these measures would be too complicated for participants to use together with the other procedures.

All events will be registered, and all SAEs, SUSARs, and SARs will be reported to the ethical committee immediately.

We collect data on the use of medication at baseline and at week 3 from patient medical charts. Including the use of ad lib. medication.

Ranking of outcomes

The primary outcome is the baseline adjusted mean score on the HAM-D_6 scale at week 3.

The secondary outcomes are a) the mean score on the SIDAS scale at week 3, b) the mean score on the HAM-D_{17} scale at week 3, c) the mean score on the WHOQOL-BREF at week 3.

Exploratory outcomes are: a) the proportion of patients with one or more SAEs (according to ICH-GCP 1997), b) the mean score on the visual comfort scale covering all three weeks, c) the mean reduction in mg/day from baseline to week 3 of zopiclone, d) the mean reduction in mg/day from baseline to week 3 of zolpidem, e) the mean reduction in mg/day from baseline to week 3 of quetiapine, e) the mean reduction in mg/day from baseline to week 3 of oxazepam, f) the mean score on the PSQI scale at week 3, g) the mean score on the MEQ scale at week 3, h), the mean score on the HAM-D_6 scale at 6 month.

A separate report will be made focussing on the total use of electrical energy for lighting in the static lighting group compared to the interventional LED-light group for a one year period.

Participants timeline

Enrolment and start of intervention are attempted to be within 5 days of admission to the ward. Assessments are performed at enrolment and once weekly for 3 weeks (see Spirit flow diagram in Ex 1).

Sample size and power estimations

Sample size calculation was done using the SAS 9.4 software using proc power for a two-sample independent sample t-test.

In a previous study [2], on patients from the same ward, we found a mean HAM-D_{17} score at admission of 23. This corresponds to a HAM-D_6 score of 13. The number of participants has been estimated from an expected baseline-to-endpoint score reduction, on the HAM-D_6 from 13 to 8 in the dynamic light group, and from 13 to 10 in the static light group. Hence, the minimal important difference is two points on the HAM-D_6 scale. With an expected standard deviation of 3, an alpfa value of 0.05, and a power of 90%, we will need a total of 98 patients for the primary outcome. However, to be able to perform explorative analyses we will aim at 150 patients.

Power estimations of secondary outcomes

a) SIDAS scale: we expect a SIDAS score of 20 at baseline with a standard deviation of 8 and a reduction to a score of 5 in the dynamic light group and to 10 in the static light group. With an alpha value of 0.05 and a sample size of 98 participants, a power of 0.82 is estimated. With a sample size of 150, power would be 0.95.

b) HAM-D_{17} scale: we expect a HAM-D_{17} score of 23 at baseline with a standard deviation of 6 and a reduction to 14 in the active dynamic group and to 17.5 and the static light group. With an alpha value of 0.05 and a sample size of 98 participants, a power of 0.82 is estimated. With a sample size of 150, power would be 0.95.

c) WHOQOL-BREF questionnaire: We expect a WHOQOL-BREF score of 20 at baseline with a standard deviation of 17 and an increase to 45 in the dynamic light group and to 35 in the static light group. With an alpha value of 0.05 and a sample size of 98 participants, a power of 0.82 is estimated. With a sample size of 150, power would be 0.95.

Recruitment

The investigators will be in daily contact with the staff at the ward and will follow the flow of admissions. When a new patient is admitted and is occupying one of the ten rooms with light equipment, the staff will give the patient an invitation to meet the investigator if no exclusion criteria are apparent. The patient will have the opportunity to read the participant information paper and the investigator will give a detailed oral information regarding the study. The oral

information and written material will include information regarding the importance of obtaining outcome data in the case of drop-out due to early discharge and after 6 months. The patient will be asked to decide on participation within two days. If the patient accepts, the informed consent will be signed, and the inclusion and baseline assessments will begin. The patient record and the M.I.N.I. interview will be used to confirm the patient's eligibility. Included patients will be allocated to the next study number through the electronic case report form in the OpenClinica system [73], administered by the Copenhagen Study Unit. When submitted, the system randomizes the participant to one of the two treatment groups: *Dynamic LED-group* or *Static LED-group.* This information is given to the patient. The estimated mean stay of patients is 1 month and with 10 light equipped room a total number of patients per year is 140. With an expected inclusion rate of 50% we expect to finish last patient last visit June 2021.

Allocation

The randomization will be web-based with a 1 (experimental intervention) to 1 (control intervention) allocation with a stratification for BD. A total of 150 patients will be randomized in the study. The primary investigator will enroll participants into the study. The randomization is performed through the OpenClinica system, when participant's data have been entered in the eCRF, and all inclusion criteria and no exclusion criteria are fulfilled.

Blinding

It is not possible to disguise the lighting condition to participants, primarily due to the extra light panel in the window that will be active in the dynamic lighting group. The depression outcome assessors will perform the assessment in a separate office in another department and will be blinded to treatment allocation. Participants are asked not to reveal their treatment allocation to the Hamilton assessor. Other investigators and data managers will not be blinded. The blinding will be broken in the event of a SAR or SUSAR.

Statistical analyses will be performed with the two intervention groups coded as 'A' and 'B' by two blinded statisticians employed at the CTU. The statisticians will independently and blindly analyze all data and present the results in two independent reports. A third investigator will compare these reports and discrepancies will be discussed. Both statistical reports will be published on CTU's website. Based on the statistical reports, two blinded conclusions will be drawn by the

steering group: one assuming 'A' is the experimental group and 'B' is the control group – and one assuming the opposite. Based on these two blinded conclusions, two abstracts will be written and published on CTU's website. When the blinding is broken, the 'correct' abstract will be chosen and the conclusions in this abstract will not be revised.

Data collection

All assessments are carried out by psychometrically trained investigators (research nurse and senior consultant). The Hamilton ratings are conducted by a certified Hamilton rater blinded for group allocation. Hamilton certification is based on supervised group ratings with a difference of less than +/- two points on the HAM-D_{17} scale from the gold standard (most experienced rater). Study duration is 3 weeks, including baseline assessment (pre-intervention) and final assessment (post-intervention). Patients who are transferred to another light-equipped room in the ward, during the three-week period, can continue with their scheduled assessments and the lighting condition in the new room will be set according to the allocation.

Data management

Data will be collected through an electronic case report form (eCRF) developed by Copenhagen Study Unit (CTU) in OpenClinica. Data in the eCRF is considered source data. The eCRF will use range checks for validation of entered data, and there will be an audit trail to monitor data entry. Data will be stored on servers locally at CTU with daily back-up. Data will also be collected from light sensors stored on independent hard drives. These data are also considered source data. The only pen-and-paper data are the informed consent and participants list. All data will be available to all authors.

Statistical methods

Continuous scale scores, including sleep scores, will be analyzed in a linear regression model using available data from all included participants (intention to treat). The primary (HAM-D_6) and secondary outcomes (SIDAS and HAM-D_{17}, and WHOQOL-BREF) will be entered in separate analyses as dependent variables in the linear regression model. Treatment group (static or dynamic), gender, length of actual depressive episode, bipolar/unipolar illness, and baseline values of the dependent variable will be entered as explanatory variables. Results are given as mean, with confidence limits, standard deviation, and p-values. A detailed statistical analysis plan will be

published separately before the randomization of the last participant. The significance level is set at 5 % two-tailed. Subgroup analyses will be performed for BD/MDD diagnosis. Missing data will be handled by multiple imputation techniques [74]. No interim analyses are planned.

Data monitoring and auditing

According to Danish law, only drug studies are required to comply with Good Clinical Practice guidelines (GCP) [75]. We will, however, adhere to the GCP rules to secure study quality. Data analyses, performed by the primary investigator, will be supervised by a statistician. The study is subject to auditing from the regional ethical committee.

Harm

We do not expect that the study will expose participants to any serious hazard as their usual clinical management is maintained and the side effect profile of bright light is low [34 76] . All AEs will be recorded until the end of the follow-up period, and regulatory rules for reporting of SAEs and SARs will be adhered to. Any harm due to the study procedures is covered by the Danish Patient Compensation Association. The study will be stopped if there is a clinical suspicion of harm of the intervention, or if new evidence emerges that participants can come to harm due to the intervention.

ETHICS AND DISSEMINATION

Ethics

The study is approved by the Committee on Health Research Ethics of the Capital Region of Denmark with approval number H-19004525. The study is approved by the Danish Data Protection Agency with approval number VD-2018-515. All participants will provide written informed consent before enrolment into the study. Informed consent will be obtained by the primary research investigator or a delegated study investigator. The study will be stopped if participants develop serious side effects. Patients can leave the study at any time at their own discretion and without any further effect on their continuous treatment at the ward. Any forthcoming protocol amendments will be submitted to the Ethical committee and the Danish Data Protection Agency for approval. Written and oral information will be given at the ward, between the first and the fifth day of admission. The information will be given only by trained study investigators. The

information will be given in an undisturbed office at the ward. Prior to the information visit, the patient will be informed of the opportunity to bring a friend or relative (third party). The patient will be given up to two days to consider participation before giving the informed consent.

Personnel at the ward will present information from patient records to permit investigators to determine any exclusion criteria. Patients eligible for enrolment will be asked by staff at the ward to participate in an information meeting. At inclusion, the patient will produce their civil registration number, name, and sociodemographic data, to the investigators. These data will be entered into the eCRF system and a participant-ID will be generated as part of the randomization process. Participants name, civil registration number and study number (from the eCRF) will be stored in a participant' identification list in a secured data repository. Personal data in the eCRF will only be used for randomization purposes, after which only the participant-ID will be used. At the end of the study all paper material containing data will be transferred to a secure data repository. All study data will be handled according to the General Data Protection Regulation. The final data set will be accessible to all persons in the study group.

We do not expect any ethical issues. All regulatory rules will be followed, and the expected side effects of the dynamic lighting systems are rare and mild. We have taken precautions to find and deal with any emergent manic and suicidal symptoms.

Dissemination

Results will be published in peer-reviewed international journals, as posters, and as oral presentations at international symposia. All data whether negative, positive or inconclusive will be reported in full. All members of the study group are co-authors with a pre-arranged order. No professional writers will be used. Depending on the journal of publication, part of the protocol, statistical code, and dataset will be publicly available. All participants will be informed of the trail results.

Declarations

Ethics approval and consent to participate

The study has been approved by the Committee on Health Research Ethics for the Capital region of Denmark (approval number H-19004525). All participants will provide written informed consent

before enrollment into the study.

The study is approved by the Danish Data Protection agency (approval number VD-2018-515).

Acknowledgement

Jais Elvekjær, New Psychiatry Bispebjerg.

Author contributions

CV: Design, planning, data acquisition, drafting, and agreement of accountability for all aspects of the work.

ASA: Design, planning, data acquisition, drafting, and agreement of accountability for all aspects of the work.

TSH: Planning, drafting, and agreement of accountability for all aspects of the work.

PMP: Data acquisition, drafting, and agreement of accountability for all aspects of the work.

CDH: Design, planning, drafting, and agreement of accountability for all aspects of the work.

UK: Design, planning, drafting, and agreement of accountability for all aspects of the work.

EEP: Planning, drafting, and agreement of accountability for all aspects of the work.

JE: Planning, drafting, and agreement of accountability for all aspects of the work.

JJ: Planning, drafting, and agreement of accountability for all aspects of the work.

HØM: Planning, drafting, and agreement of accountability for all aspects of the work.

IH: Planning, drafting, and agreement of accountability for all aspects of the work.

KM: Design, planning, data acquisition, drafting, and agreement of accountability for all aspects of the work.

All authors read and approved the final manuscript.

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Competing interests

TSH is an employee of Chromaviso that has supplied the lighting system. There are no financial or other interests for any other authors.

Patient and public involvement

Patients were involved in the testing of tolerability of the lighting system. This influenced the setting of the dynamic lighting system. Patient also assisted in developing the Visual Comfort Scale that is used in the study to estimate tolerability. Both involvements were done before the start of the study.

Data Availability Statement

We will make data from this study available on reasonable request once the results are published.

Figure legends

Figure 1. The left-hand picture shows how the LED panel is mimicking sunlight reflections on the wall. The right-hand side of the picture shows natural sunlight reflexions on the wall.

Figure 2 (a) and (b). The figures show temporal distribution of horizontal (a) and vertical (b) α - opic irradiance of the LED-lighting with daylight blacked out. Dynamic LED-light intervention is shown as solid lines and static LED-light intervention is shown as dashed lines. Measurement points and equipment are described in the *Light measurement* section. The depicted timelines are for the summer intervention profile. Winter intervention profile differs in the way that the period between 06:00 – 18:00 during summer is contracted 1 hour in each end to 07:00 – 17:00 to enhance patient tolerability.

Figure 3. The figure shows the placement of the luminaries where A is the LED panel built into the window jamb, B is the two ceiling luminaires and C is the reading luminaire. Mv and Mh indicates the measurement point for the vertical (Mv) and horizontal (Mh) spectral LED measurements performed in a patient room with blackout blind in the window to exclude daylight. SL indicates the permanent placement of the illuminance and the spectral room sensors and SDL the permanent placement of the spectral daylight sensor.

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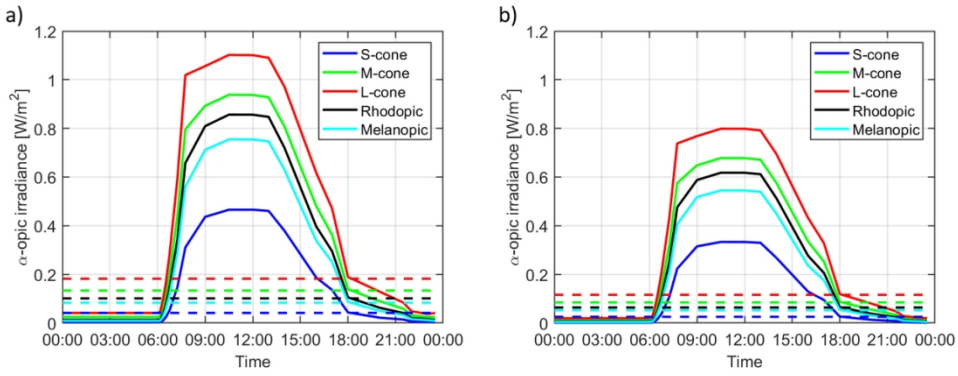
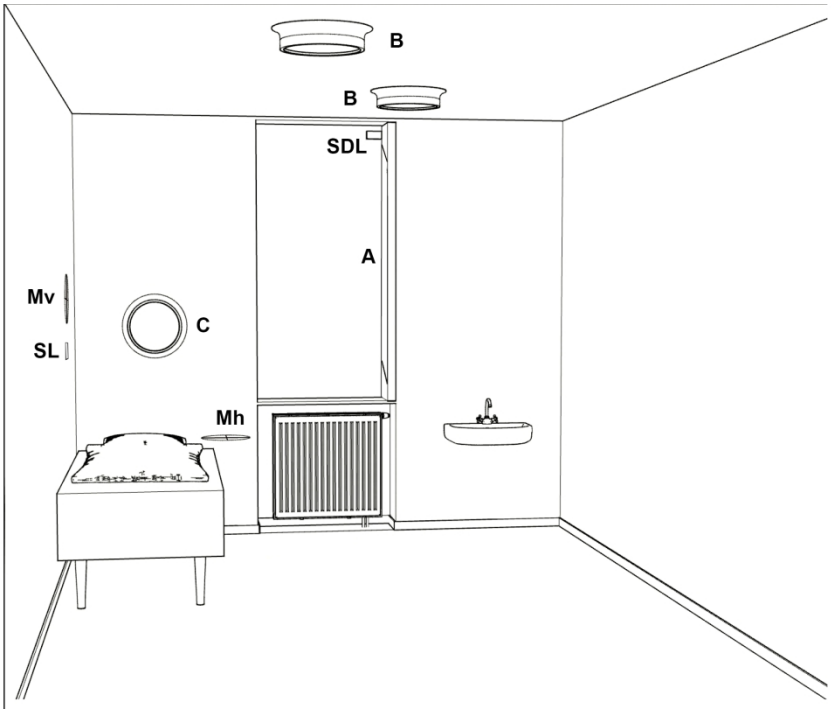
The left-hand picture shows how the LED panel is mimicking sunlight reflections on the wall. The right-hand side of the picture shows natural sunlight reflexions on the wall.

58x79mm (300 x 300 DPI)



The figures show temporal distribution of horizontal (a) and vertical (b) α -opic irradiance of the LED-lighting with daylight blacked out. Dynamic LED-light intervention is shown as solid lines and static LED-light intervention is shown as dashed lines. Measurement points and equipment are described in the Light measurement section. The depicted timelines are for the summer intervention profile. Winter intervention profile differs in the way that the period between 06:00 – 18:00 during summer is contracted 1 hour in each end to 07:00 – 17:00 to enhance patient tolerability.

112x44mm (300 x 300 DPI)



The figure shows the placement of the luminaries where A is the LED panel built into the window jamb, B is the two ceiling luminaires and C is the reading luminaire. Mv and Mh indicates the measurement point for the vertical (Mv) and horizontal (Mh) spectral LED measurements performed in a patient room with blackout blind in the window to exclude daylight. SL indicates the permanent placement of the illuminance and the spectral room sensors and SDL the permanent placement of the spectral daylight sensor.

209x147mm (300 x 300 DPI)