Novel Augmentation Strategies in Major Depression

Martiny, Klaus

Published in:
Danish Medical Journal

Publication date:
2017

Document version
Publisher's PDF, also known as Version of record

Novel Augmentation Strategies in Major Depression

Klaus Martiny

This review has been accepted as a thesis together with 7 previously published papers by University of Copenhagen on the 10th August 2016 and was defended on the 4th of November 2016

Official opponents:
Hans Ågren and Raben Rosenberg

Correspondence:
Klaus Martiny
Psychiatric Center Copenhagen, Rigshospitalet
University of Copenhagen, Denmark
Tel 0045-38647100
E-mail: klaus.martiny@regionh.dk

Dan Med J 2017;64(3):B5338

General introduction

Papers

This dissertation is based on the following 7 publications:

- Martiny K, Lunde M, Undén M, Dam H, Bech P (2006). The lack of sustained effect of bright light, after discontinuation, in non-seasonal major depression. *Psychol Med* 36: 1247-1252.
- Martiny K, Lunde M, Undén M, Dam H, Bech P (2009). High cortisol awakening response is associated with an impairment of the effect of bright light therapy. *Acta Psychiatr Scand* 120: 196-202.
- Martiny K, Lunde M, Bech P, Plenge P (2012). A short-term double-blind randomized controlled pilot trial with active or placebo pindolol in patients treated with venlafaxine for major depression. *Nord J Psychiatry* 66: 147-154.
- Martiny K, Lunde M, Bech P (2010). Transcranial low voltage pulsed electromagnetic fields in patients with treatment-resistant depression *Biol Psychiatry* 68: 163-169.
- Martiny K, Refsgaard E, Lund V, Lunde M, Sørensen L, Thougaard B, Lindberg L, Bech P (2012). Nine weeks randomised trial comparing a chronotherapeutic intervention (wake and light therapy) to exercise in major depression. *J Clin Psychiatry* 73: 1234-1243.
- Martiny K, Refsgaard E, Lund V, Lunde M, Sørensen L, Thougaard B, Lindberg L, Bech P (2013). The day-to-day acute effect of wake therapy in patients with major depression using the HAM-D_6 as primary outcome measure: results from a randomised controlled trial. *PLoS One* 28;8: e67264.
- Martiny K, Refsgaard E, Lund V, Lunde M, Thougaard B, Lindberg L, Bech P (2015). Maintained superiority of chronotherapeutics vs. exercise in a 20-week randomized follow-up trial in major depression. *Acta Psychiatr Scand* 131: 446-457.

Major depression

The diagnostic concepts of depression, as described in the DSM-IV (now DSM-5) and the ICD-10 classifications (1, 2), are based on algorithms setting rules for counting clinical symptoms assessed through an interview with the patient. These symptoms do point to an array of underlying neurobiological defects (3). However, treatment of individual symptoms of depression does not lead to a resolution of the depressive state. Depression is not cured by improving sleep by sleep agents, by using stimulants against lack of energy, by making the patient exercise for psychomotor retardation, or by comforting a patient suffering from feelings of hopelessness. The lack of etiological foundation makes progress, in terms of development of treatment methods, difficult.
Development of new treatment methods have thus relied on a combination of clinical observation, neuropsychopharmacology, psychology, and psychometric. Rating scales makes it possible to assess treatment outcome with high validity and reliability.
The course of a depressive episode can be depicted as running through a number of stages: progression to a major depressive episode, varying levels of response to treatment, in some patients leading to remission. Remitted patients who develop a new depressive episode in less than four/six months of remission are defined as having a relapse, and patients developing a new depressive episode after more than four/six months of remission are defined as having a recurrence. Recovery signifies a continued remission (of more than four/six months). These timeframes depending on definition (4, 5). The risk of a new episode increases with every new episode and depression is, by nature, a recurrent disorder (6).
The use of antidepressants is now a standard for moderate or severe depression. Onset of action is often slow for those who respond and often several months pass before remission is achieved. In a substantial proportion of patients remission is only achieved after several changes in medication, therapies and settings (7), and approximately 30 % of patients will not obtain remission (8), thus being treatment resistant. The risk of suicide increases with time spent in depression (9, 10). Strategies to improve outcome include: optimizing antidepressant drug treatment, combination strategies, or augmentation strategies. Optimizing antidepressant drug treatment includes enhancing treatment adherence, ensuring adequate dosage, ensuring adequate duration of antidepressant treatment, or switching to an antidepressant with another pharmacologically profile. In patients

started on an antidepressant and showing no improvement after a few weeks of treatment (11) a change of therapy should be considered (12). Combination strategies involve the use of two antidepressant medications, typically of different classes. Augmentation strategies involves the addition of a second drug or non-drug therapy to existing antidepressant therapy such as lithium, thyroid hormone or exercise (13, 14).

Available antidepressant treatment options

Since the introduction of electro convulsive treatment (ECT) in the 1930's and the development of tricyclic antidepressant drugs in the 1950's, depression has been an illness that we do consider treatable both by medications. Antidepressants were initially only considered useful for a very small minority of patients (15). Since the 1950´s several classes of antidepressants have been introduced. The overall efficacy has probably not increased since the tricyclic antidepressants were marketed (16), but side effect profiles have changed and toxicity is reduced.

As remission is often difficult to achieve, the use of combination and augmentation strategies with antidepressants and other drugs is widely used, even though the evidence for many combinations is sparse (17, 18). Combination treatment and drug augmentation carry a risk of more side effects, are expensive for the patient and society, often require more specialized settings, and thus makes treatment more costly. Most importantly, they are often not adequate to secure remission.

The last decade or more has seen a great surge of research into psychological therapies, mainly concerning cognitive behavioural therapy (CBT), that has been shown to be efficacious alone and when used as an augmenting therapy in combination with antidepressants (19). Research into non-drug augmentation strategies has been sparse.

Experimental treatments

Due to the low efficacy of existing antidepressant therapies a number of experimental therapies have been tested. These can be divided into pharmacological, psychological, chonotherapeutic, medical devices, and physical therapies. Experimental psychological therapies are not touched further upon. The list below highlights the experimental methods where some research has been done, each supplied with a key reference.

Pharmacological: Pindolol (20), Thyroid hormones (21), Methylfolate (22), Omega3 fatty acids (23), Precursors of neurotransmitters (24, 25), Modafinil (26), Psychostimulants (27), Hypericum (28, 29).

Chonotherapeutic: Sleep deprivation (30, 31), Light therapy (32), Dawn-Dusk-Stimulation (DDS), (33), Sleep Phase Advance (34), Sleep time stabilisation (35, 36), Melatonin (37).

Medical devices: Repetitive Transcranial Magnetic Stimulation (rTMS) (38), Transcranial Direct Current Stimulation (tDCS) (39), Vagus Nerve Stimulation (VNS) (40), Pulsed ElectroMagnetic Fields (PEMF) (41), Magnetic Seizure Therapy (MST) (42), low intensity negative ion generators (43).

Physical: Exercise (44), Body Awareness Therapy (BAT) (45), Acupuncture (46).

Contents of this thesis

This thesis is based on four studies using new augmentation modalities. The four studies investigate, in randomized controlled trials, the efficacy of these augmentation modalities when used in combination with antidepressant drugs treatment. The aim was thus to induce a larger or faster antidepressant effect. In the included studies we have investigated the effects of bright light therapy (bright versus dim light therapy), the beta-blocker pindolol (active pindolol versus placebo), weak pulsating electromagnetic fields (active pemf versus sham), and a chronotherapeutic intervention including wake therapy, sleep time stabilisation, and sleep hygiene (versus exercise).

Background information is described in separate chapters for each study. Directions for the use of these augmentation methods and ideas for further development are addressed. The published papers are included as part of the thesis.

1. Bright Light Study

Study specifics

Protocol title: Long term bright light therapy in patients in pharmacological treatment for major depression: Augmented effect and improved quality of life? (original Danish title: "*Langtidslysterapi hos patienter i farmakologisk behandling for major depression: Hurtigere effekt og bedre livskvalitet?*").

ClinicalTrials.gov Identifier: not required at the time of publication.

Abbreviation in text: "bright light study"

Principal Investigator Site: Mental Health Centre North Zealand, Research Unit, University Hospital of Copenhagen.

This chapter is based on papers published after the PhD thesis "adjunctive bright light in nonseasonal major depression":

- Martiny K, Lunde M, Undén M, Dam H, Bech P (2006). The lack of sustained effect of bright light, after discontinuation, in non-seasonal major depression. *Psychol Med* 36: 1247-1252.
- Martiny K, Lunde M, Undén M, Dam H, Bech P (2009). High cortisol awakening response is associated with an impairment of the effect of bright light therapy. *Acta Psychiatr Scand* 120: 196-202.

Introduction

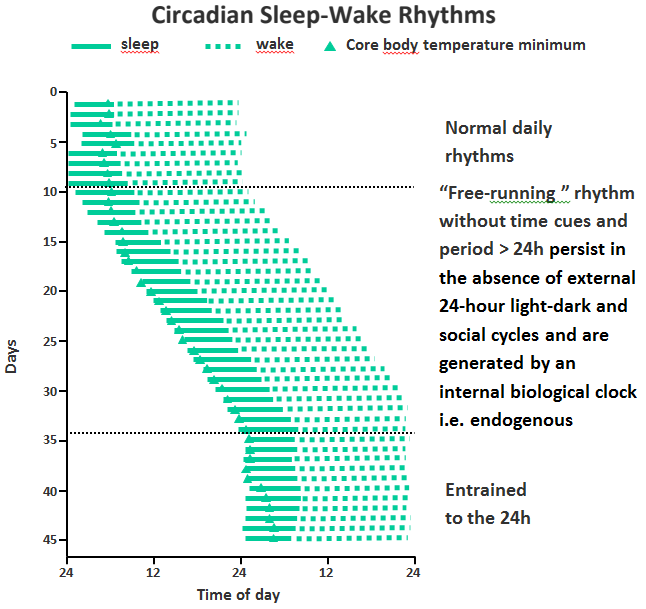
The bright light study investigated the use of bright white light to augment antidepressant drug therapy in patients with a major depressive episode.

Light is ubiquitous and linked to our most important sense, vision. We know that light has been used in medicine for at least a thousand years to treat different medical conditions such as melancholia or lethargy (31, 47) and hospitals were built to secure maximum daylight for patients staying there: " The aspect of a site, which will determine that of the buildings, should, wherever there is a choice in the matter, be such as to command the greatest amount of sunlight at all seasons." (48). Niels Ryberg Finsen was awarded the Nobel Prize in 1903 for the use of light to treat lupus vulgaris (49) and light is still used as a treatment option in dermatology (and sunlight feared due to a risk of skin cancers).

From animal research it has been known for decades that dosage and timing of light has a profound impact on the regulation of a number of biological rhythms including reproduction and sleep (50), and in the 1980s it was discovered that in humans, like in animals, the synthesis of melatonin could be suppressed by light (51), and that light in this way induced adjustments of the timing of the melatonin cycle that informs the brain about night time and season (52). Light thus entrains (entrainment = the synchronization of a self-sustaining oscillation such as sleep by a forcing

oscillation such as light) the timing of sleep (see figure 1.1). Humans isolated in dim light conditions have a circadian "free running" period of approx. 24.18 hours and sufficient natural or appropriate indoor light is necessary to properly entrain the human sleep-wake cycle to the 24 hour day (53) and prevent drifting of the sleep-wake cycle. The solar day is built into our physiology as "clock genes", present in most of the cells of the body (54), and manifesting their own endogenous circadian rhythm under influence of the suprachiasmatic nuclei (SCN), the biological clock. As far as we know the impact of light on human physiology is only mediated through the retina. The classical view of the central projections that transmit the light signal from the retina, and there is probably a clock in the retina itself gating light input (55, 56), is via the retino-hypothalamic tract (RHT) that directly impact on the SCN (57, 58). From the SCN the light signal is mediated through the paraventricular nucleus of the hypothalamus (PVN), via the intermediolateral nucleus of the spinal cord (IML), to the superior cervical ganglion (SCG) and finally to the pineal gland where light signals inhibit melatonin synthesis. The SCN generates the melatonin rhythm and melatonin itself feeds back to the SCN acting through M1 and M2 receptors (59, 60).

Figure 1.1. Schematic drawing to show entrainment of sleep and core body temperature



Redrawn with permission from Anna Wirz-Justice, Centre for Chronobiology University of Basel

The discovery of an unique, primarily non-visual, photoreceptor, the intrinsically photosensitive retinal ganglion cells (ipRGC) in the human retina in 2000 (61), with a peak spectral sensitivity around 480 nm (blue wavelength) (62), and elucidation of the newly found pathways by which light influences the circadian and other systems, mainly by this non-visual input (63, 64, 65), has, however, given us a fuller understanding of the pathways by which the antidepressant effect of light might work. In the mouse, melanopsin containing photoreceptors project to a widespread area of the brain (66) other than the SCN, namely the intergeniculate leaflet (IGL), the raphe nuclei (RN), the olivary pretectal nucleus (OPN), the ventral division of the lateral geniculate nucleus (LGv), the preoptic area, and a number of other brain areas known to be related to the circadian system (67, 68). Recently a rhythm generating clock has been detected in the neocortex of the rat pointing to primary (SCN) and secondary time keepers within the brain (69), and a hypothesis has been proposed, based on animal and human translational research, that circadian rhythms in different parts of the brain might be out of synchrony in patients with depression (70, 71). Until recently, light was believed to work solely through the circadian system but new animal research suggests that irregular light schedules can affect mood and learning without any major disruptions in circadian rhythms or sleep (72). This has been termed the "direct pathway" in contrast to the "indirect pathway". In support of the "direct pathway" it has been found that light is able to affect human mood and alertness acutely within hours (73, 74).

Light has been found to impact regulation of neural circuits and neurotransmitter function. Fisher et al (75) found that three weeks of bright light significantly negatively affected the threat-related reactivity in corticolimbic circuits that is modulated by serotonin. Lam et al (76) found that tryptofan depletion in SAD patients successfully treated with bright light therapy induced relapse also pointing to a serotonergic mechanism behind the antidepressant effect of light. Finally Carlson et al (77) found seasonal variation of monoamines post mortem and Lambert et al (78) found that turnover of serotonin by the brain was lowest in winter and with a relation between serotonin production and the duration of bright sunlight.

The clinical description of Seasonal Affective Disorder (SAD) and the theoretical analogy with hamster hibernation cycles led to the development of bright light treatment in the early 1980s (79, 80, 81). SAD is characterized by repeated seasonal depressions, almost exclusively in the winter period (winter depressions), and in a majority of patients associated with atypical features such as increased need for sleep, weight gain, and carbohydrate craving (82). Three main hypotheses for the antidepressant effect of light in SAD have been put forward:

1. The *phase–shift hypothesis* proposes that the shorter days of winter cause a circadian phase delay of melatonin secretion relative to the sleep-wake cycle. Sleep is also delayed to some degree but there is a Phase Angle Difference (PAD= time interval between two circadian markers) between melatonin and sleep rhythm. Bright light treatment corrects this abnormality (83, 84) by phase advancing the circadian rhythm of melatonin, leading to a normalization of the PAD, and resulting in an antidepressant effect. The description of the ability of light to phase advance the sleep-wake cycle and other rhythms when applied in the morning, and to phase delay when administered in the evening results in a human "phase response curve" (PRC = describing a phase advance or a phase delay effect of light on the circadian system as a function of the time of administration) to light (85,86). Researchers of the phase-shift hypothesis believe that the most important issue is to correct the Phase Angle Difference (PAD) between Dim Light Melatonin Onset (DLMO= the time point in the evening when melatonin production rises in dim light conditions, used as a marker for assessing the circadian rhythm) and midsleep (87). The normal PAD is supposed to be 6 hours, e.g. a 6-hour interval between the DLMO and midsleep.

Results from later studies have not uniformly supported this hypothesis, but maybe these studies did not produce sufficiently large phase advances (88) to test the hypothesis. However, in the study by Terman et al (89) the magnitude of antidepressant response to morning (but not evening) bright light therapy was correlated to the degree of phase advance of melatonin onset (DLMO) relative to sleep, and thus resulting in a change in PAD.

As a clinical applicable rule these authors recommend timing of bright light therapy at 8.5 hours after DLMO or alternatively 2.5 hours after sleep midpoint used as a proxy for DLMO for greatest antidepressant effect. A refinement of the therapeutic timing of light for a given patient was introduced by the use of the Morningness-Eveningness (MEQ = questionnaire assessing morning- and eveningness) score to establish individual optimal timing for light treatment (90). The *phase-shift hypothesis* is furthermore in agreement with clinical observation and research showing a powerful positive or deleterious effect on mood of a phase-advance or a phase-delay of the sleep-wake cycle in patients with depression (91).

2. The *photoperiod hypothesis* propose that a lengthening of the daily photoperiod by administering bright light in the morning *and* in the evening (92) would alleviate depression by simulating longer photoperiods as in the summer.

3. The *photon-counting hypothesis* claiming that SAD develops due to too low levels of light in wintertime and that supplementing bright light corrects this unbalance (93).

The history of light treatment has been covered in several textbooks (94, 95, 96, 31). In Denmark psychiatrist Henrik Dam was probably the first psychiatrist to seriously acknowledge light as a treatment modality in psychiatry and to incorporate it into psychiatric research and practice (97, 98). At the time when this study was planned, bright light therapy was well investigated as a treatment for seasonal depression, but only few studies had examined the effect in non-seasonal depression, even though non-seasonal mood disorders had for some time been known to harbour a number of circadian and seasonal dysfunctions (99).

In Denmark, situated at latitude 56 degrees and with an abundance of cloudy misty weather, sunlight is scarce in winter (100). As a consequence of rainy and misty weather with low light levels, people tend to stay indoors, thus further reducing individual light exposure. Whereas indoor light intensities seldom reach above 100-300 lux, outdoor light intensities are often above 2000-3000 lux, even on cloudy days, and reach more than 50.000 lux on many days. The entraining effect of light is responsible for humans staying in tune with the astronomical day, sleeping at night and being awake during the day, and indoor lighting levels is often inadequate to entrain the sleep-wake cycle.

Since the seminal paper by Rosenthal et al in 1984 (79), a large number of trials have been carried out investigating the efficacy of bright light treatment in a number of conditions. The research on light in humans first focused on seasonal depression, including the stability of the SAD construct (101) and the timing and dosage of light, and later non-seasonal depression. The interest into the biological effects of light has since broadened into basic neurophysiology, visual retinal function (102), retinal photosensitive ganglion cells (62), the pathways from the retina to the SCN and beyond (103), interaction with and function of the pineal gland (104), central and peripheral clock genes (105), cortisol (106), and sleep (107). Light applications have also been tested in a number of psychiatric and somatic conditions such as eating disorders (108), obesity (109), circadian sleep disturbances (110), depression during pregnancy and postpartum (111, 112), shift work distress (113), and visual impairment (114). Newer areas are the impact of light on working in space (115), phase delay induced by blue-backlight LED computer screens (116), and reproduction (117). Research has also expanded to architecture focusing on how to develop the best artificial lighting to complement natural daylight (118). For the purpose of this thesis only data concerned with the impact of bright light on depression is touched upon.

Recent reviews of clinical trials investigating the antidepressant effect of bright light have established an antidepressant effect in both seasonal and nonseasonal depression (119,120, 32, 121). The impact of bright light on depression symptoms has now been shown to be fast, within hours (73), and clinically relevant improvement sets in quickly within days (122), and the treatment is well tolerated (123).

At the time when this study was started, the evidence base for non-seasonal depression was weaker than for seasonal depression even though the first light study ever performed, by Kripke and co-workers in 1983, was in non-seasonal depression (124). That bright light administrated during winter would alleviate seasonal depression seemed to have a theoretical basis but what would be the rationale for an effect of bright light in non-seasonal depression:

1. We hypothesised that light would have a general antidepressant effect across diagnostic subgroups, corresponding to what we would now call a *direct effect* of light on mood and alertness independent off changes in the circadian system and that patients with depression might have too low ambient indoor light levels in the winter (and maybe in summer depending on a variety of factors such as window glazing and size, and geographical orientation of rooms etc.).

2. Following the *photon-count* hypothesis, we predicted that patients with manifest depression probably received lower light levels due to a tendency to stay indoors, this caused by core depression symptoms such as lack of motivation and lack of energy and also by accompanying anxiety, and with resultant phase delayed sleep (eveningness) (125, 126). These patients would have less opportunity to get natural light in the morning where the antidepressant effect would be largest.

For some individuals, therefore, the light thresholds for maintaining well-being might not be reached in wintertime (or even summer time) thus worsening a pre-existing depression.

3. Seasonality is prevalent both in the general population, also in Denmark (127, 98), and in depressed patients, confirmed in our previous work (123) and later by others (128). Therefore we believed that even in non-seasonal depressed patients there would be some degree of seasonality and that these patients would exhibit a phase delayed melatonin rhythm and according to the *phase–shift hypothesis* would benefit from morning bright light therapy. Investigations have shown that during wintertime, patients with SAD have a reduced retinal rod sensitivity, as measured by photopic electroretinogram (ERG) luminance response (129), later confirmed and reviewed (102, 130), we believed this to apply also to seasonality in non-seasonal depression. It must be emphasised that the concept of a distinct seasonal depression type (=SAD) was not supported by the DSM-IV and is not supported by the DSM-5 either, where seasonality is a specifier to recurrent major depressive disorder.

4. In patients without any seasonality we considered that habitual low light exposure might lead to an inadequate entrainment of the sleep-wake cycle (free running) causing gradual phase delay of the sleep-wake cycle which is known to worsen depression (91).

Thus, in summary, we expected that low light levels and temporal misalignment of light caused by season, low ambient indoor light levels, behavioural retreat, phase delayed rhythms, and decreased retinal sensitivity to light, would have contributed to the development of a depressive episode and that light working through direct and indirect pathways would act as an antidepressant.

Methods and materials

A detailed description of the study is given in the supplementum covering the PhD thesis (123). Patients were allocated from general practitioners and specialist psychiatric practices and assessed at the Research Unit at Mental Health Centre North Zealand and at a psychiatric research unit. Patients were randomised, after a computer generated random list, into either bright light treatment or dim red light treatment with a block size of four, and all patients were started on sertraline in a 50 mg daily dosage. Patients were treated daily with bright or dim light for five weeks and then followed for further four weeks, to assess effects of stopping light treatment. The light treatment was taken in the morning, the bright white light for one hour daily, and the dim red light treatment for 30 minutes. The bright light box, used in other light studies (SMIFA) (122), was delivered to the patients for daily treatment at home. The illuminating surface measured 61 cm in width and 41 cm in height and the light box emitted 10'000 lux at a distance of 40 cm with a colour temperature of 5500 K (blue-white). For the dim light condition the same light boxes were used with a red transparent folio inserted between the fluorescent light fixtures and the diffusing screen, and the intensity was reduced electronically to an output of 50 lux at 40 cm distance. Patients were given oral and written instructions on how to take light and were informed that it was not known which colour of light was most effective. To attain blinding for the assessors, an external secretary delivered light boxes to the patients. Code letters were transferred to opaque sealed envelopes and delivered to the patients with instructions not to reveal group assignment to assessors. The study was monitored (Norma A/S) and approved by the Regional Scientific Ethical Committees and the Danish Medicines Agency and the Danish Data Committee. All patients were assessed at baseline and weekly with depression scales, sleep logs, a side effect scale, light timing diary, and medication logs, for six weeks, with a final assessment after an additional three weeks. Both light conditions were stopped after five weeks and in the following four weeks the sertraline dosage could be increased to a maximum of 150 mg daily according to patients' condition.

The primary protocol stated outcome was difference in improvement between groups. The primary outcome measure was response (reduction in baseline depression scores of 50 % or more) and remission rates (a final score of less than 8) both based on the HAM-D_{17} scale and assessed after five weeks of treatment. Diagnosis of major depression was confirmed at baseline by use of the M.I.N.I. instrument (131). The SIGH-SAD scale was included to cover seasonal symptoms (132).

Saliva cortisol were collected at awakening, and after 20, 40 and 60 minutes as described by Pruessner et al (133) before start of the study, at week five, and at week nine to determine cortisol awakening profiles (CAR).

Results

In all, 102 patients were included in the study. Depression scores decreased substantially in both groups, but most in the bright light treated group. From week one and on all following assessments till week five there was a statistically significant better outcome in the bright light treated group, resulting at week five in response rates of 66.7 % versus 40.7 % and remission rates of 41.7 % versus 14.8 % in the bright versus the dim light treated group. Survival analysis showed a statistically significant higher response rate ($\chi 2 = 9.6$, $p = 0.002$) and higher remission rate for the whole five weeks study period ($\chi 2 = 12.5$, $p = 0.0004$) for the bright versus the dim light treated group.

At week nine (after light treatment had been stopped for four weeks) the results showed a response rate of 79.2 % versus 75.9 % and a remission rate of 60.4 % versus 55.6 % in the bright versus dim light treated group. The difference in depression scores seen at week five, favouring the bright-light-treated group, thus disappeared gradually in the four-week follow-up period, where antidepressant drug dosage could be adjusted, resulting in similar end-point scores (134).

In all, 63 patients collected cortisol saliva samples at baseline and at week five. The CAR value was calculated as the area under the curve (AUC) of cortisol concentrations plotted against time according to Pruessner et al (135). In this thesis, only the AUCI data are presented (area under the curve for the increase in cortisol concentration in relation to baseline). Results showed that patients responded differentially to light treatment according to their CAR levels (dichotomized to high or low about the mean). Thus, in the bright light group HAM-D_{17} scores were reduced by 15.7 (4.2) points for patients with a low CAR (below mean), and 11.4 (4.8) points for patients with a high CAR (above mean) from baseline to week five. In the dim light group the corresponding values were 11.1 (5.2) for patients with a low CAR and 11.3 (5.3) for patients with a high CAR (see figure 1.2). This interaction between CAR and treatment group was statistically significant ($p = 0.006$), (136).

Correspondingly, remission rates at week five were highest in the bright light treated group of patients with a low CAR. Thus, in the bright light group remission rates were 60.0 % for patients with a low CAR (below mean), and 20.0 % for patients with a high CAR (above mean). In the dim light group the corresponding rates were 19.0 % for patients with a low CAR and 16.7 % for patients with a high CAR. This interaction between CAR and treatment group was statistically significant ($p = 0.02$), (137).

Figure 1.2 shows HAMD-D_{17} scores according to treatment group and CAR status

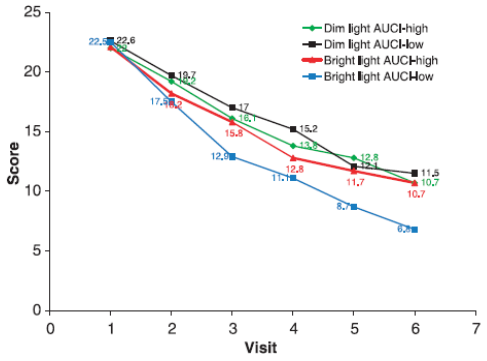


Fig. 1. Depression scores on the HAM-D_{17} from baseline to endpoint separated into treatment group and AUC_I high and low secretors.

Discussion

We could confirm the main hypothesis for the protocol of an accelerating effect of bright light therapy over a period of five weeks, but when light treatment was discontinued, the effect was lost. This is in accordance with our group's earlier work in seasonal depression where patients with SAD responding to bright light therapy relapsed after stopping light treatment (122). There are, however, other possible explanations as to why the differ-

ence between the dim light and bright light treated groups disappeared. Firstly, from a psychometric angle, the obtained scores at endpoint are very close to remission. Illustrated by the HAM-D_{17} scale, using the remission cut-off at 7 points, the patients treated with bright and dim light had a scale score of 8.1 (6.3) versus 8.5 (5.4) at week nine. Thus the limit of remission is quite close and it could be argued that even if the effect of bright light was continued, the scores in the two groups would converge toward a score level not much lower than 7 points. Secondly, the augmenting effect of bright light treatment could be transient simply because the treatment duration was too short. This is comparable with the finding that relapse is less likely when stopping medication after remission has been reached (138). In order to state with certainty that the effect of bright light therapy is transient we would need to carry out a study with a prolonged use of bright light therapy until remission was reached and then observe the effect of stopping light therapy together with unchanged dosages of medication. Thirdly, as patients' responses are highly variable, it is possible that some patients will have a lasting augmenting effect of light therapy after discontinuation whereas others will not. These subgroup differences in response to light have not been thoroughly investigated.

The results from the cortisol awakening response showed that the subgroup of patients with a high cortisol awakening response (CAR) had a significantly lower response to bright light than patients with a low CAR. This implies that patients with an over-activated HPA axis are less responsive to the antidepressant effect of light. Another important result from the light study was that the greatest difference between treatment groups was seen for the core depressive symptoms and not for the atypical symptoms covered in the SIGH-SAD scale (123) pointing to that the effect of light was not primarily working on the seasonal symptoms. Side effects of light were rare and compliance with light treatment in both groups was high.

There is no agreement at present on light treatment regimes in non-seasonal depression. Personally I would recommend using bright light until remission is reached and then tapering it off over two to three weeks. This would mean a length of minimum 10 weeks and maybe longer. The results from the chronos study have shown that such long-term light treatment is feasible (139). Our results from the cortisol data need confirmation from other research groups working with estimation of subgroup responses in relation to cortisol.

The current evidence points to an antidepressant effect of bright light treatment in non-seasonal depression even though a recent study with bipolar depressed patients failed to find any effect of bright light compared to negative air ions (140). Table 1.1 shows high quality studies from with-in the last 10 years using bright light therapy in non-seasonal depression. This sample displays one of the difficulties in assessing evidence in this field: the design, light conditions and study population differs widely between studies.

Table 1.1 Recent RCT bright light studies in non-seasonal unipolar depression.

Author	**Benedetti 2003 (141)**	**Martiny 2004 (123)**	**Søndergaard 2006 (142)**	**Wirz-Justice 2011 (112)**	**Lieverse 2011 (143)**
Dep. type	Non-seasonal	Non-seasonal	Post-stroke	Ante-partum	Non-seasonal
Design	RCT	RCT	RCT	RCT	RCT
Active: lux, color, min/day	400 green 30	10.000 white 60	10.000 white 30	7.000 white 60	7.500 blue 60
Placebo: lux, color, min/day	Deactivated ion-generator 30	50 Red 30	4.000 White 30	70 Red 60	50 Red 60
Days of study	14	35	14	35	21
Medication	citalopram	sertraline	citalopram	None	TAU*
Nb. of pt.	30	102	63	27	89
Blinding	Not blinded	Blinded	Blinded	Blinded	Blinded
Primary outcome scale	Hamilton depression rating scale	Hamilton depression rating scale	Hamilton depression rating scale	SIGH-ADS*	Hamilton depression rating scale
Result	Positive	Positive	Positive	Positive	Positive

*TAU = treatment As Usual, **Structured Interview Guide for the Hamilton Depression Rating Scale with atypical depression supplement

2. Pindolol Study

Study specifics

Protocol title: pindolol augmentation in venlafaxine treated patients with major depression (original Danish title: *"En korttids dobbeltblind randomiseret undersøgelse af pindolols indflydelse på venlafaxins antidepressive effekt"*).

ClinicalTrials.gov Identifier: NCT00159146. Abbreviation in text: "pindolol study".Principal Investigator Site: Mental Health Centre North Zealand, Research Unit, University Hospital of Copenhagen.

This chapter is based on the following paper from the study:

- Martiny K, Lunde M, Bech P, Plenge P (2012). A short-term double-blind randomized controlled pilot trial with active or placebo pindolol in patients treated with venlafaxine for major depression. *Nord J Psychiatry* 66: 147-154.

Introduction

This study examined whether the delay in onset of antidepressant drug action of four to six weeks could be shortened by augment-

ing venlafaxine treatment with pindolol in patient with major depression (144). Besides being a beta-blocker with partial beta-adrenergic receptor agonist activity, pindolol at the same time works as a partial (partial efficacy) antagonist of the presynaptic 5-ht1a somatodendritic autoreceptors.

It was artigas et al who in a pilot study from 1994 found that pindolol augmented the antidepressant effect of paroxetine and other antidepressants, and formulated the proposed mechanism of action (145). By blocking the 5-ht1a autoreceptors in the raphé nuclei in the brain stem with pindolol, the initial inhibition of the serotonergic neurons, normally seen at the beginning of antidepressant treatment with serotonin reuptake inhibitors caused by the increase in the extracellular serotonin concentration, would be aborted (146). Since the discovery of this mechanism, several randomized controlled studies have been performed. The latest reviews concluded that pindolol seemed to hasten the response to selective serotonin reuptake inhibitors (SSRIs) in depression with a timing window circumscribed to the first weeks of treatment, but with some heterogeneity between studies (147, 148, 17, 149).

This study was performed by inspiration from Per Plenge and Erling Mellerup, Neuropsychiatric Laboratory Department O, Rigshospitalet, based on their publication from 2003 (150) arguing that any acutely working augmenting effect of pindolol should work best with paroxetine or venlafaxine due to the ability of these drugs to rapidly reach a concentration in water phase giving an almost total blockage of the serotonin transporter (151). This was in line with our research effort trying to find augmenting or acceleration antidepressants agents. To the best of our knowledge, no earlier clinical randomized controlled study has examined the effect of pindolol with other than SSRI antidepressants and we opted for the use of venlafaxine on the above mentioned pharmacokinetic grounds and because we would like to investigate if the supposed added norepinephrine activity of the drug might enhance the augmentation of pindolol. However, newer studies have shown that, in humans, the 150 mg daily dosage of venlafaxine used in this study probably doesn't yield a significant norepinephrine reuptake inhibitor effect (152). That the antidepressant effect of venlafaxine, in a proper dosage, could be augmented by pindolol was suggested by a study from 2000 by Béïque et al who found that in rats treated with venlafaxine, additional treatment with pindolol potentiated the activation of postsynaptic 5-HT1A receptors, probably by blocking presynaptic somatodendritic 5-HT1A receptors (153).

In our study, pindolol was used in an extended release formulation, as it was believed to give a more stable receptor blockade than with a non-extended release tablet (154, 155). The intention was to include patients without current antidepressant medication as patients in long-term current antidepressant treatment might not exhibit an inhibition of the serotonergic presynaptic receptors, due to habituation (156). Most previous studies has likewise preferred drug naïve patients or using a drug wash-out phase; and the study by perry et al that included ssri-resistant patients in current treatment found no efficacy of pindolol augmentation (157). However, due to difficulty in recruiting patients without current antidepressant treatment we also allowed inclusion of patients in ongoing antidepressant treatment. Due to shortage of additional funding, we chose to terminate inclusion at 31 patients and not the 50 that was planned in the protocol. The number of included patients in the review by whale et al (20) is between 21 and 164 and the sample size of our study is thus at the very lowest end. The daily dosages of pindolol, in the same review ranged from 10 mg to zero (placebo) whereas we used an extended release preparation containing 20 mg pindolol.

Methods and materials

Patients were included and assessed at two sites, a specialist psychiatric practice in Copenhagen and at the Research Unit at Mental Health Centre North Zealand and were referred from psychiatric specialist practices, general practitioners, and from inpatient wards. The study design was a randomised controlled trial with double blinding. Patients were randomised into either active pindolol in an extended release formulation containing 20 mg pindolol or a matching placebo pindolol, with a block size of four. Both groups were additionally treated with venlafaxine in a 75 mg daily dosage for the first five days of the study and venlafaxine in a 150 mg daily dosage for the remaining 14 days of the study period. The total study length was thus 19 days. Assessments were done at baseline, day six, day 11 and a final assessment at day 19. Blood tests for plasma concentration of pindolol, venlafaxine, and its metabolites O -DesmethylVenlafaxine (ODV = metabolite of venlafaxine by CYP2D6) and N -DesmethylVenlafaxine (NDV = metabolite of venlafaxine by CYP2C19) were taken at day 12 and 19. Diagnosis of major depression was confirmed at baseline by use of the M.I.N.I. instrument (131) and at each visit, depression severity, subjective sleep, and side effects were assessed. The primary outcome was difference in depression severity at endpoint between groups. The primary outcome measure were the scores on the HAM-D_{17} scale (158) and the secondary outcome measure was the scores on the HAM-D_6 subscale (159) or the Bech-Rafaelsen Melancholia scale (160).

Results

In all, 31 patients were included. No statistically significant difference was found between placebo and active pindolol treatment during the 19 days' study period. When examining the patients according to their ability to metabolize venlafaxine (v) to o-desmethylvenlafaxine (odv) calculated by the ratio of plasma o -desmethylvenlafaxine /venlafaxine (odv/v), we found a statistically significant interaction with treatment group ($f = 7.1$, $p = 0.01$). Using the odv/v ration as a proxy for metaboliser status we concluded that patients with a low odv/v ratio (= poor metabolizer) had a better outcome when treated with pindolol compared with placebo than patients with a high odv/v ratio (extensive metabolizer). We could partly confirm earlier findings of a higher combined plasma concentration of venlafaxine plus odv in responders compared to nonresponders ($p = 0.04$), (161) whereas the plasma concentration of venlafaxine or odv alone was not significantly different between responders and non-responders. Pindolol concentration did not have any influence on depression outcome.

Side effects were mild. One patient left the study due to development of asthma, believed to be caused by pindolol. Venlafaxine concentration varied greatly on the same drug dosage of venlafaxine 150 mg daily. Thus, at day 19 minimum venlafaxine concentrations were 126 nmol/l and maximum concentrations 3912 nmol/l. Pindolol concentrations varied between 94 and 1819 nmol/l.

Discussion

The hypotheses stated in the protocol were "does pindolol augments antidepressant response" which we could not confirm, and

"does the rate of ODV/V, reflecting genotype, influences the effect of pindolol as an augmenting antidepressant agent" which was confirmed.
As stated in the paper, there are several limitations to the study. The interaction found between ODV/V is based on a secondary protocol hypothesis, and the study had a small sample size. Furthermore 17 of the included 31 patients were in antidepressant treatment at time of inclusion and this might have influenced results. Due to the small number of patients it is not relevant to carry out analyses on the influence of specific drug type on outcome. Most studies on pindolol augmentation have used drug naïve patients. However, we could not find any discrimination in outcome when comparing the group of patients who were in antidepressant treatment at inclusion with those that were not. Timing of pindolol administration could also influence results. In the drug naïve patient it might give a better result if pindolol were administered before the first dose of antidepressant to prevent negative feedback. The dosage of pindolol could also be an issue. In our study we used a high and extended release formulation of pindolol and this could have reduced antidepressant efficacy by blocking postsynaptic 5-HT1a receptors. Furthermore, the possible, perhaps small, norepinephrine activity of venlafaxine might also influence results compared to pure serotonergic drugs in an unknown direction.
Rabiner et al in 2004 found a difference in the preferential pindolol occupancy (difference in occupancy between autoreceptor and postsynaptic 5-HT1A receptors) between healthy subjects and depressed patients (162). Thus, the preferential occupancy was only 2.9 % in depressed patients on SSRIs compared to 22.6% in healthy volunteers, after a single 10 mg dosage of pindolol, and in the paper it is speculated whether this phenomenon is an endophenotype for depression or a result of medication. The mean pindolol autoreceptor occupancy, from another experiment in the same paper in depressed patients, was only 19.0 % on repeated dosage of 15 mg pindolol. Thus, many other factors might influence the outcome of pindolol augmentation not controlled for in this study. We have supplied data in the paper to facilitate comparison with studies that have measured plasma concentrations of venlafaxine and its metabolites or to use in future studies, in order to make possible a replication our finding of a differential effect of pindolol in slow and extensive metabolizers. Table 2.1 shows our own study in comparison with the largest four studies in the latest review by Whale et al (20) supplemented by two later studies. The outcome is equivocal and even the largest studies differ in results, suggesting that the uncertainty is not due to a type II error. In many of the studies, subgroups of depression types and biomarkers have been investigated and no clear results have crystallized. In the review by Whale neither baseline depression severity, placebo-run in, pindolol dosage or antidepressant drug type could be associated to any outcome, primarily due to too little variation between studies. The preliminary idea by Plenge and Mellerup (150) arguing for the use of paroxetine could thus not be substantiated in the review by Whale.

Table 2.1. Comparison of high quality RCT studies using pindolol as augmentation in depression.

Author	**Zanardi 1997** (163)	**Tome 1997** (164)*	**Geretsegger 2008** (165)	**Portella 2011** (149)	**Martiny 2012** (144)
Depression type	Uni- and bipolar	Unipolar	Uni- and bipolar	Unipolar	Uni- and bipolar
Design	RCT	RCT	RCT	RCT	RCT
Intervention	Fluvoxamine 20 mg Pindolol 2.5 mg*3	Paroxetine 20 mg Pindolol 7.5 mg	Paroxetine 20 mg Pindolol 2.5 mg*3	Citalopram 20 mg Pindolol 5 mg*3	Venlafaxine 150 mg Pindolol retard 20 mg
Control	Fluvoxamine 20 mg Placebo	Paroxetine 20 mg Placebo	Paroxetine 20 mg Placebo	Citalopram 20 mg Placebo	Venlafaxine 150 mg Placebo
Placebo run-in (days)	7	No information	3	Drug free	Not used
Days of study	42	42	28	42	19
Nb. of patients	155	80	53	30	31
Blinding	Double blind	No information	No information	No information	Double blind
Outcome	HDRS	MADRS	HDRS	HDRS	HDRS
Result	Positive	Negative	Negative	Positive	Negative

HDRS = Hamilton depression rating scale, MADRS = Montgomery Åsberg Depression Rating Scale
*Data retrieved from (148)

3. PEMF Study

Study specifics

Protocol title: pulsed weak electromagnetic fields (PEMF) treatment in patients with treatment-resistant major depression in on-going antidepressant drug treatment (original Danish title: *"PEMF behandling hos patienter med behandlingsresistent depression i farmakologisk antidepressiv behandling"*).

ClinicalTrials.gov Identifier: NCT00287703.
Abbreviation in text: "PEMF study"
Principal Investigator Site: Mental Health Centre North Zealand, Research Unit, University hospital of Copenhagen.

This chapter is based on the following paper from the study:

- Martiny K, Lunde M, Bech P (2010). Transcranial low voltage pulsed electromagnetic fields in patients with treatment-resistant depression. *Biol Psychiatry* 68: 163-169.

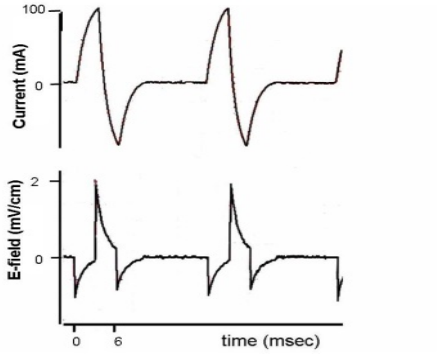
Introduction

This chapter deals with the effect on depression of weak pulsating electromagnetic fields (PEMF) as investigated in our randomized controlled trial (166). The influence of PEMF on biological systems has been the subject of investigation for some time (167), done in a number of different plants, species and organ systems going from germination of seeds (168) to blood pressure (169). The

broad subject "electromagnetic fields" has a long and colourful history within science and (science-) fiction (170) often giving a connotation of something fantastic and even spiritual. Thus, it is important to state that the supposed mechanism of action of PEMF is through the induced electrical currents in the brain due to a changing electromagnetic field.

The principle of PEMF, as used in this study, is the following: a pulsed current (in mA) generated in a coil creates a time-varying magnetic field according to faradays law. In the PEMF system, the resultant time-varying magnetic field is imposed on ions and charged proteins in the cerebral cortex where it creates a time-varying electrical field (171). As illustrated in figure 3.1 the induced electrical field is proportional to the changes in currents running through the coils.

Figure 3.1 time relation between current in coils and the resultant electromagnetic field.



It is important to note that the electrical field imposed on the cerebral cortex using this technology is very small and amount to approximately 30 μV/cm at 10 cm from the coil (166). The transmembrane electrical potential is approximately -70 mV across a cell membrane 5 nm wide equivalent to and electrical gradient of 1.4 *104 V/cm, and thus very much larger than the PEMF induced electrical field. The threshold potential is about -55 mV. Thus, the stimulus from the PEMF equipment is fundamentally different from, for example, the principle of repetitive Transcranial Magnetic Stimulation (TMS) in which potential changes during treatment are just below the threshold for opening of Na+ channels and therefore close to being able to elicit action potentials. Recommended intensity in rTMS is between 90 % and 120 % of the motor threshold (172).The pulse patterns of the PEMF generator were designed to mimic, in magnitude and frequency, the electrical fields occurring outside nerves and muscles due to their own propagation of action potentials.

There is no evidence that humans can consciously register a changing electromagnetic field or the ultra-low electrical currents induced by the PEMF technology. However, very low-level, environmental-strength electromagnetic fields have been shown to have a *biological* impact in humans (173). In animals, birds can detect weak electromagnetic signals and act upon them when setting a flying trajectory, and sharks use electrical sensors when seeking out prey by being able to sense electrical signals from preys heart activity in the range below 5 nV/cm (174, 175) which is lower than the calculated PEMF generated electrical field in the brain. In animals, the receptor system for weak electromagnetic fields has been proposed to be located in specialized cells where interaction between the changing electrical field and glycoproteins bound to ion channels gates would then mediate an intracellular signal (176). The existence of low electrical field receptors in the human brain is, however, debated.

PEMF stimulation has been shown to cause activation of tyrosine kinase related cellular signaling in endothelial cells, glial cells and up-regulation of m-RNA for BDNF and angiogenesis (177). Clinical studies of PEMF have so far been restricted to non-psychiatric indications such as osteoarthritis (178, 179), microcirculatory effects (180), neuron growth (181) and others. Currently, in all, 26 clinical studies are listed on clinicaltrials.gov homepage involving the use of PEMF technology with different indications for its use (182).

Methods and materials

Patients were allocated from psychiatric specialist practices, general practitioners, psychiatric outpatient departments, a community mental health centre, and by use of advertisement (n=2) and assessed at the Research Unit at Mental Health Centre North Zealand and at a specialist psychiatric practice. Diagnosis of major depression was confirmed at baseline by use of the M.I.N.I. instrument (131). The design was a randomised controlled trial with double blinding. Patients were randomised from a computer generated random number list into either active PEMF treatment or sham PEMF treatment with a block size of ten. The sham condition was obtained by an internal deactivation of the PEMF generator and was not discernable from the outside. Both the active and the sham PEMF were taken for 30 minutes on all weekdays at the same psychiatric research unit and specialist psychiatric practice for five weeks. The PEMF delivery system consisted of a pulse generator, receiving 220 V, and providing pulses to the applicator constructed as a plastic treatment helmet. The dimensions of the Re5 PEMF generator was (width x height x depth) 2.8 x 1.6 x 9.2 inches. The pulses provided by the generator to the coils in the helmet alternate between +50 and – 50 V. The treatment helmet incorporated, on the inner side, 2 coils in the anterior and posterior temporal region on both sides and 1 coil in the upper parietal region on both sides and 1 coil in the centre of the lower occipital region. Thus, in total, 7 coils were connected in parallel with the pulse generator. The Re5 PEMF pulse generator powers the coils with alternating bipolar square pulses, each lasting 3 milliseconds and interspersed by a 12 milliseconds pause, each pulse-sequence thus lasting 18 milliseconds (see figure 3.1) , corresponding to a pulse frequency of 56 Hz (for comparison cell phones operate in GigaHertz frequencies). The rapid change of the current in the coils from the pulse generator creates an alternating magnetic field with a calculated maximum of 19 Gauss at 0.5 cm from the coil and capable of inducing electrical fields in tissue with a magnitude of 2.2 mV/cm at a distance of 0.5 cm from the individual coil (41).The imposed electrical field decreases approximately exponentially with distance and amounts to 30 μV/cm at 10 cm from the coil.

Primary inclusion criteria were current major depression according to the DSM-IV system and with a minimum treatment resistance level of three according to Sackheim (183). To assess blinding, patients were asked after completion of the study, to indicate which treatment they had been given (active or sham). PEMF generators were consecutively numbered by the monitoring company Remedium Aps (184) according to the randomisation list.

The study was approved by the Regional Scientific Ethical Committee, and the Danish Data Committee. All patients were assessed weekly with depression scales, a cognitive speed test (AQT), sleep log, side effects scale, and PEMF treatment logs, for five weeks. Medication was unaltered during the five weeks study period and four weeks prior to inclusion. Primary outcome as

stated in the protocol was difference in improvement between groups at endpoint. The primary outcome measure was reduction in scores on the Hamilton depressions rating scale (HAM-D_{17}) and secondary outcomes were response and remission rates based on the Hamilton depression rating scale according to the usual criteria.

Results

In total, 50 patients were included and all entered the statistical analysis. The mean duration of current depressive episode was 31.3 (34.3) months in the active PEMF group and 34.7 (55.0) month in the sham treated group; number of previous depressive episodes were 6.4 (5.3) and 6.4 (5.5) in respective groups. The blinding test, carried out at the final assessment, showed that patients were not able to determine whether they had received active or sham treatment. At inclusion into the study, patients were treated with one or more psychotropic drugs: SSRI, SNRI, NaSSA, tetracyclic, tricyclic, NaRI, MAO inhibitors, mood stabilizers, antipsychotics, and hypnotics. All patients had major depression and in a greater proportion with melancholic features. Two patients were suffering from bipolar depression, 10 patients had comorbid panic disorder, nine had social phobia, and five had agoraphobia. No patients had any previous or present psychotic disorders. The patients' treatment expectancy was low with a score around 5.0 (2.4) in the active treated group and 5.4 (1.7) in the sham treated group (0 = no expected improvement, 10 = maximum expected improvement). Baseline HAM-D_{17} scores were 21.1 (4.1) in the group treated with active PEMF and 20.9 (3.3) in the group treated with sham PEMF treatment. Patients were assessed at baseline and weekly for 5 weeks. The active PEMF treated group had the largest reduction in depression scores and this reached statistical significance from week one and on all the following assessments ($p < 0.01$). On the HAM-D_6 a statistical significance was found from week two and on and on the MES from week one. Response at endpoint was 61.0 % in the group treated with active PEMF and 12.9 % in the sham treated group ($p < 0.01$). Remission was obtained in 33.9 % in the active group and 4.1 % in the sham treated group ($p < 0.05$). Side effects were similar between groups and were mild. A further analysis from the same study focusing on self-assessment (HAM-D_6 self-rating, WHO-5 Quality of life and UKU side effect) found comparable results (185).

Discussion

The hypotheses stated in the protocol "does active PEMF treatment reduce depression scores more than sham PEMF" and "does active PEMF treatment increase response and remission rates more than sham PEMF" were both confirmed. The placebo response in the sham treated group was very low, as seen in clinical studies in patients with treatment resistant depression. The present study was designed to investigate whether any signal of effect could be found for the PEMF treatment and was not designed to estimate the full magnitude of antidepressant effect. With the obtained endpoint remission rates of 33.9 % in the active PEMF treated group and 4.1 % in the sham treated group after 5 weeks of therapy it would be interesting to investigate whether a longer treatment period would induce larger remission rates. In the latest PEMF study, in patients with depression, investigators used a design with one versus two treatments per day, and found remission rates after 8 weeks of therapy of 73.5 % versus 67.7 % (186).

The mechanism by which the PEMF treatment works as an antidepressant augmenter is unknown. Even though we know some of the biological effects of PEMF on living tissue it is premature to suggest any specific antidepressant effect. The challenge will be to find out how such weak alternating electrical currents are able to translate into a large antidepressant effect. Brain imaging studies, in a sham controlled trial design, should be able to find changes in brain functioning in areas believed to be of interest as mediators of antidepressant effect. This will require the use of different neuroimaging techniques and biomarkers. The exact molecular effect will probably require neurophysiological studies of candidate receptors or intracellular messengers; this is currently being investigated by Professor Steen Dissing and his group. This group hypothesizes that activation of brain endothelial cells (blood brain barrier) contributes to the beneficial effects of PEMF. Recently researchers have focused on the relation between the pulsed nature of electrical brain stimulation therapies, including PEMF and their potential to entrain brain oscillatory activity (187). Perhaps the zeitgeber ability of light and the electrical oscillation from the PEMF generator both works through entrainment of brain circuitry.

As mentioned in the general introduction to this thesis, a number of noninvasive brain stimulation (NIBS) based therapies have been developed for the treatment of depression: ElectroConvulsive Treatment (ECT), Magnetic Seizure Therapy (MST), repetitive and synchronized Transcranial Magnetic Stimulation (rTMS and sTMS), Direct Current Stimulation (tDCS), and Vagus Nerve Stimulation (VNS) (188, 189). ECT is a well-established method with high efficacy, but with a tendency to relapse after end of treatment and cognitive transient side effects. MST probably has the same efficacy as ECT and maybe with less cognitive side effect but, like ECT, requires anesthesia. TDCS has only been used in a few studies, some showing promising effect and low side effect rate but the real efficacy and indication for this treatment remains uncertain. rTMS has been extensively investigated and recent reviews has found a moderate efficacy and low side effects but rTMS requires daily or frequent treatments in hospital settings. sTMS where the magnetic stimulus is synchronized to the individual patient's alpha waves is purely experimental. The efficacy of VNS is unsettled, the antidepressant effect might be delayed until one year, and stimulus intensity and properties of the implanted stimulator including the mechanical contact between the electrical wire and the vagal nerve is still under development. The PEMF technology is simple, easy to use, the latest study used a home stimulation regime, and thus requires no assistance, and side effects were very mild. More randomised controlled trials needs to be done, by other research groups, to establish efficacy in different subtypes of depression and for maintenance or relapse prevention.

Table 3.1 shows our own study in comparison with different NIBS therapy studies using, ECT, Transcranial Magnetic stimulation, Direct Current Stimulation, Magnetic Seizure Therapy, and Vagus Nerve Stimulation.

These studies were designed as sham controlled RCT's apart from the VNS study using a dose-response design. The stimulus received at brain tissue level is difficult to compare as the means of delivery are specific for every treatment method.

Table 3.1. RCT studies using NIBS as augmentation in depression.

Author	Brandon	Klein 1999 (191)	Loo 2010 (192)	Martiny 2010 (166)	Kayser 2011 (193)	Aaronson

	1984 (190)					2013 (194)
Therapy	ECT	TMS	tDCS	PEMF	MST	VNS
Depression type	Unipolar	Uni- and bipolar	Unipolar	TRD	TRD*	Chronic
Design	RCT	RCT	RCT	RCT	RCT	RCT
Active interv.	ECT	TMS	tDCS	PEMF	MST	3 intensities
Active applicat.	Bitemporal	Right prefrontal	Left DLPFC	Multifocals	Twin coil	Implanted VNS
Frequency (Hz)	No info.	1	Continuous	50	100	10-20
Wave form	Chopped sine wave	Mono- or biphasic	None	Bipolar square pulse	Dampened cosine	No information
Pulse width	No info.	100 µs	None	3 ms	No info	130-250 µs
Control interven	Sham ECT	Sham TMS	Sham tDCS	Sham PEMF	ECT	3 intensities
Control application	Bitemporal	Right prefrontal	Left DLPFC	Multifocal 8 coils	Right unilateral	Implanted VNS
Medication	None	Continued	Continued	Continued	Continued	Continued
Days	28	14	9	35	42	22+28 w
Nb. of pt.	95	70	35	50	20	331
Blinding	No info.	Rater blind	Double blind	Double blind	Open label	Open label
Scale	HDRS	Respons	MADRS	HDRS	MADRS	IDS-C
Side eff.	No info.	No info.	Minor	None	Minor	No info.
Result	Active ECT better	Active TMS better	No difference	Active PEMF better	No difference	High intensity best

HDRS = Hamilton depression rating scale, MADRS = Montgomery Åsberg Depression Rating Scale, IDS-C = Inventory of Depressive Symptomatology, TRD =Treatment Resistant Depression.

4. Chronos Study

Study specifics

Protocol title: Chronos, the use of chronotherapeutic treatment in depression (original Danish title: "*Kan den af søvndeprivation inducerede antidepressive effekt hos patienter med major depression i duloxetin-behandling vedligeholdes ved hjælp af vedvarende stabilisering af døgnrytmen og langtidslysbehandling?*").ClinicalTrials.gov Identifier: NCT00149110.
Abbreviation in text: "chronos study"
Principal Investigator Site: Mental Health Centre North Zealand, Research Unit, University Hospital of Copenhagen.

This chapter is based on the following papers from the study:

- Martiny K, Refsgaard E, Lund V, Lunde M, Sørensen L, Thougaard B, Lindberg L, Bech P (2012). Nine weeks randomised trial comparing a chronotherapeutic intervention (wake and light therapy) to exercise in major depression. *J Clin Psychiatry* 73: 1234-1243.
- Martiny K, Refsgaard E, Lund V, Lunde M, Sørensen L, Thougaard B, Lindberg L, Bech P (2013). The day-to-day acute effect of wake therapy in patients with major depression using the HAM-D_6 as primary outcome measure: results from a randomised controlled trial. *PLoS One* 28;8: e67264.
- Martiny K, Refsgaard E, Lund V, Lunde M, Thougaard B, Lindberg L, Bech P (2015). Maintained superiority of chronotherapeutics vs. exercise in a 20-week randomized follow-up trial in major depression. *Acta Psychiatr Scand* 131: 446-457.

Introduction

In this thesis, and in our own papers, the term 'wake therapy' is used in preference to sleep deprivation. Wake therapy when used as in the present regime, does not cause a major sleep debt but more a rearrangement of the sleep schedule. The practical inspiration to work with wake therapy came from Professor Francesco Benedetti and his research group at Hospital San Raffaele in Milano (195) who had been working with wake therapy, mainly in patients with bipolar depression, for a number of years (196), and from the members of the Committee of Chronotherapeutics of the International Society for Affective Disorders (ISAD) (197). Our chronos research team visited Hospital San Raffaele in Milano in 2004. We had the opportunity to experience how wake therapy was performed, from observing a patient who went through the procedure, and confer with Dr. Francesco Benedetti and his staff about their experiences with the use wake therapy. In this way we learned how to carry out this treatment method. Professor Anna Wirz-Justice from Basel, and Professor Francesco Benedetti had, in collaboration, developed the protocol used at San Raffaele, and this was adopted in a slightly modified version into the chronos study. The procedures for the management of wake therapy in this study were thus adopted as they encompass the evidence and experience collected through several decades and include recent findings from studies combining wake therapy with bright light therapy and sleep phase advance.
The chronos study can be regarded as an extension of the bright light study based on a theoretical framework from chronobiology and from corresponding chronotherapeutic treatment regimens. In the chronos study we added three chronotherapeutic principles to bright light therapy: wake therapy, sleep phase advance, and sleep time stabilisation.

The antidepressant effect of sleep deprivation has been known for a long time, already mentioned in Johann Christian August Heinroths *Textbook of Psychiatry* from 1818 (198). Sleep deprivation was later mentioned in a case-report from Schulte in 1966 (199), and in 1973 Pflug investigated sleep deprivation in his *Habilitationsschrift (thesis)* (200). Pflug was thus the first to establish clinical evidence for an acute antidepressant effect of sleep deprivation. Pflug and Tölle wrote extensively on the subject in the following years (35, 201, 202). Studies and reviews have been published by a number of authors from different European countries and from the US in the following decades (203, 204, 205, 206, 207, 208). The great majority of studies, except for an adjuvant study using trimipramine, confirmed the acute antidepressant effect of wake therapy in a major proportion of patients (209), including the tendency to relapse after recovery sleep, but also documented that a subset of patients have a lasting antidepressant effect of wake therapy treatment even though this subset is not clearly characterized. No clear relation has been found between the numbers of wake therapies in a treatment algorithm and outcome, and studies have used very different number of wake therapies from a single up to more than ten (205). However, in the study by Kuhs et al (210) using amitriptyline and repeated PSD, the effect of additional nights with partial sleep deprivation was only evident after the fourth PSD in weeks 3/4. Total wake therapy (the whole night) is probably more effective that partial wake therapy (211). The timing of the partial wake therapy (early or late night) is probably not of great importance to effect, however, we need more investigation into this topic (212). Patients with bipolar illness have been found to have a superior response compared to unipolar depressed patients (213) and switch to mania is rare provided bipolar patients are in mood stabilizing drug treatment (214). Diurnal variation (morning worst), and the magnitude of daily and day-to-day mood fluctuations, have consistently been found to predict a better response to wake therapy (215). Naps in the daytime after wake therapy has been found to induce relapse in some patients (216). No increase in suicidal ideation has been found in relation to wake therapy procedures (217, 218). Nearly all patients in clinical studies have been treated in hospital settings with a few exceptions (219, 220).

The use of wake therapy regimens and the research database is described in detail in the manual written by Anna Wirz-Justice, Francesco Benedetti and Michael Terman (31) and in the Handbook of Clinical Neurology (221).

Wake therapy has been used continually in psychiatric clinics mainly in Germany, Holland and Italy. Wake therapy is recommended in the WFSBP guideline for unipolar depression as an option for unmedicated depressed patients, or to be started at the same time as an antidepressant medication with the goal of accelerating the response to medication or to be added as a strategy to potentiate an ongoing antidepressant drug therapy (18), and in the CANMAT guideline as an adjunctive treatment in the acute management of mild to moderate MDD, and with some limited support for its use in seasonal, antepartum and postpartum major depressive disorder (222).

Research in chronobiology and chronotherapy for mood disorders has increased in recent years. Based on findings, in both animal and human research, a clear connection has been found between circadian clock disturbance and mood disorders (223, 71). Data now suggests disrupted circadian synchronisation within regions of the brain itself: circadian transcription of a number of genes is out of phase between different brain regions in patients with depression in contrast to normal controls (224). The exact mechanism(s) behind the acute antidepressant action of wake therapy and sleep phase advance is not understood. It is proposed to work differently from traditional antidepressant drug therapy due to the observed very rapid acute effect over hours. Several possibilities have been considered:

1. Increased activity of the raphe nuclei. From animal research we know that the serotonergic activity from the dorsal raphe nuclei (DRN) is reduced during REM and slow wave sleep (225). In cats, total sleep deprivation (TSD) has been found to increase serotonergic activity from the DRN (recorded through stereotaxically implanted electrodes) and found to diminish neuronal inhibition produced by administration of a selective 5-HT1A selective agonist (226). In the same way, a decreased sensitivity of the inhibitory effect of citalopram on 5-HT neuronal firing was found in sleep deprived rats (227). These findings point to that TSD could also work, by decreasing 5-HT1A autoreceptor sensitivity thus enhancing serotonergic transmission.

The role of the DRN is substantiated by the clinical finding that, selectively waking patient with depression during REM sleep or during slow wave sleep phases, elicits an antidepressant response (228, 229). Conversely, daytime napping in patients responding to sleep deprivation has been found to induce relapse into depression and more so if naps were placed in the morning (230). Wake therapy might thus work by a combination of desensitisation of the 5-HT1A autoreceptor and by removing the dampening effect on the DRN by REM and slow wave sleep.

2. Psychological/placebo mechanisms. It is unlikely that this effect can be explained by a psychological effect. No known psychotherapeutic method has ever shown acute improvement in a few hours as seen with wake therapy. Placebo responses are also not likely to be of importance, as patients when introduced to wake therapy feel that it is counterintuitive as they already have difficulty sleeping.

3. Serotonergic, noradrenergic and dopaminergic mechanisms might be involved. A number of treatments with 5-HT-related treatment modalities have been shown to potentiate wake therapy or prevent relapse after wake therapy: pindolol, bright light, lithium, SSRI's and TCA antidepressants (231, 232, 233, 234, 210). This is substantiated by the finding of a differential response to wake therapy from patients with polymorphism within the promoter of the serotonin transporter gene, with a superior response seen for homozygotes for the long alleles (235). However, one study showed that tryptophan depletion had no effect on response to wake therapy, whereas it unexpectedly did prevent relapse after recovery sleep (236). One study investigated the effect of a Val/Met polymorphism in the Catechol-O-methyltransferase (COMT) enzyme. COMT works by inactivating, among other, norepinephrine and dopamine. This investigation showed that patients who were homozygotic for the Val/Val variant had a smaller acute antidepressant effect of wake therapy than patients who were hetetozygotic (Val/Met) and homozygotic (Met/Met) for the Met variant (237). In a SPECT study by Ebert et al (238) with sleep deprived depressed patients they found a decrease of relative basal ganglia D2 receptor occupancy after TSD in responders compared to nonresponders. In the study by Gessa et al, administration of haloperidol to sleep deprived rats inhibited behavioral activation, with shortening of the sleep latency (239). These results suggest dopaminergic involvement in the therapeutic action of wake therapy and might explain why antipsychotic drugs abolish the effect of wake therapy (240).

4. *Internal coincidence hypothesis.* In *forced desynchrony* protocols the influence of process S (the homeostatic sleep drive) and

process C (the circadian drive for arousal) on mood and other variables can be separated by, in a rigid protocol, submitting patients to artificial daylength schedules outside the range of entrainment of the human circadian system (more than 28 hours or less than 22 hours). This way the sleep-wake cycle follows the imposed daylength but the circadian system will be out of synchrony with sleep schedule, resulting in different relationships between the two processes. These investigations have shown that a nonlinear interaction between the circadian rhythm and the sleep-wake cycle determines daily patterns of mood, sleepiness, alertness and other cognitive symptoms (241). The internal coincidence hypothesis poses that the phase angle (time-misalignment) between the sleep-wake cycle and the circadian system (internal desynchrony) is causing depression (e.g. is depressogenic). Patients with depression may be sleeping out of alignment with their inner circadian rhythm, like a person with jetlag or shiftwork. Wake therapy is thought to function by avoiding sleeping in a depressogenic phase (the second half of the night) and by realigning the circadian and the sleep-wake cycle during recovery sleep nights. Thus, it is possible that therapies working on synchronising the circadian system with the sleep-wake cycle will also have a correcting impact on between-region difference in the brain of clock gene expression and in this way influence mood (242).

5. *Sleep-phase-advance*. Most wake therapy schedules include a slight sleep-phase advance by adjusting the recovery nights to an earlier time schedule and maintaining this as long as possible. The idea that sleep-phase advance would be an antidepressant comes from the work of Tom Wehr and coworkers (243) claiming that REM sleep (patients with depression have short REM latency) and other circadian rhythms are phase-advanced relative to the sleep-wake cycle and that correction of this circadian misalignment has an antidepressant effect. These finding have been replicated by a number of researchers (91, 207). The added benefit of bright light therapy, in wake protocols, is probably partly caused by a reinforcement of the stability of the sleep-wake cycle with an inbuilt sleep phase advance or at least an avoidance of oversleeping.

6. *The S deficiency model.* In the two process model of sleep regulation (244) sleep is supposed to be regulated by two processes: process S, the need for sleep, a process postulated to be caused by the build-up of sleep pressure, for example, a chemical substance such as adenosine. Process S increases with time spent since last slept and is reflected in an increased subsequent amount of delta sleep in recordings from recovery sleep after a night awake (245). The other component is process C, the circadian component driven by the central circadian pacemaker in the SCN. In the evening, process S is high and coincides with fall in the circadian signal for wakefulness, which is mirrored by the increasing melatonin level, and as a result sleep is possible. In the morning, process S is low due to the time slept, and coincides with a rise in the circadian wake signal, and this makes awakening possible. The S deficiency model poses that the built-up of sleep need in depression is insufficient and wake therapy is as an intervention that causes a momentary large increase in sleep need (246).

7. *Resetting of abnormal clock genes*. Various clock gene expressions are disturbed in depression and the hypothesis is that wake therapy restores them to a normal level, specifically the BMAL1/CLOCK genes are supposed to be involved and to interact with sleep homeostasis (247,248).

9. *Overarousal hypothesis.* Depression can be understood as a state of physiological overarousal and in this hypothesis wake therapy is supposed to reduce this state. This is based on observations of higher baseline motor activity in responders to wake therapy than in nonresponders (249). This is also supported by sleep abnormalities in depressed patients mimicking disturbed sleep as seen in stress disorders.

Brain imaging studies have investigated a number of regions of interest (ROI) for depressive disorders. We would expect changes in activity of the anterior cingulate and dorsolateral prefrontal regions and in the connection between these areas, as this have been found to correlate with an improvement in depression symptoms. In a resting-state fMRI study in healthy subjects by Bosch et al (250), it was found that sleep deprivation reduced connectivity between posterior cingulate cortex and bilateral anterior cingulate cortex and enhanced connectivity between dorsal nexus (an area within the dorsal medial prefrontal cortex that serves as an intersection point for multiple brain networks) and areas in dorsolateral prefrontal cortex suggestive of restoring of a dysfunctional brain network.

The limbic system has been investigated in a few studies. In an fMRI study, Clark et al (251) found, in unmedicated depressed patients, a greater baseline amygdalar perfusion in responders to partial sleep deprivation (PSD) than in nonresponders. In the right amygdala, perfusion increased in nonresponders and decreased in responders after wake therapy compared to baseline whereas the left amygdala did not show any significant change between baseline and PSD conditions.

Correspondingly, in a PET study by Wu et al (252) it was shown that depressed patients responding to sleep deprivation had higher baseline relative metabolic rates in medial prefrontal cortex, ventral anterior cingulate and posterior subcallosal gyrus compared to depressed patients who did not respond to sleep deprivation, and to normal subjects. After sleep deprivation a decrease in metabolic rates was found in the medial prefrontal cortex and frontal pole in patients responding to sleep deprivation. A subsequent PET study from the same group found positive correlations (defined as reduced HDRS scores associated with areas having reduced relative cerebral glucose metabolism after TSD) in the inferior frontal gyrus and inferior frontal/orbital frontal cortex. Negative correlations (defined as reduced HDRS scores associated with areas of increased relative cerebral glucose metabolism after TSD) were found in the dorsolateral prefrontal cortex (253). An fMRI study in healthy individuals by Gujar et al (254) showed that sleep deprivation amplified reactivity in mesolimbic reward brain networks in response to pleasure-evoking stimuli. Dopamine turnover was discussed by Ebert et al (255) who argued that administration of psychostimulants decreases limbic metabolism similar to what is seen in wake therapy responders. Benedetti et al (256) have performed single proton MRI investigations in patients with depression undergoing sleep deprivation. They investigated the excitatory neurotransmitter glutamate, which is believed to play a role in the pathophysiology and treatment of mood disorders, in bipolar depressed patients who were treated with wake therapy. Changes in the brain glutamine/creatine ratio followed a general trend toward decrease, with individual variability that correlated with improvement of depression (257). Benedetti et al (258) performed another MRI study in bipolar depressed patients doing wake therapy and tested moral valence decision at four time points before and after wake therapy. The results from the MRI studies showed that in regions normally associated with cognitive generation of affect such as the anterior cingulate cortex, the dorsolateral prefrontal cortex, the insula, and in the parietal cortex, responders to sleep deprivation changed their blood oxygen level–dependent responses (BOLD) to emotional stimuli in a pattern opposite to that in nonresponders. As an example, the authors found that, for negative stimuli, BOLD

activation in the right anterior cingulate cortex was *reduced* in responders to wake therapy but *increased* in non-responders to wake therapy.

The results from neuroimaging studies does not point to a single mechanism of action of wake therapy but certainly to a differential pattern of activity in brain regions according to responder status and to resolution of a dysfunctional brain network. The differential effect of brain functioning in relation to response to wake therapy might point towards the existence of different depression subtypes with distinctly different underlying psychopathology.

Animal investigation has shown, in a wake therapy model, that an antidepressant-like effect was dependent on astrocyte-dependent adenosine mediated signaling (259). Adenosine builds up in the brain with increasing sleep pressure (the need to sleep). Profound changes in neurotransmitter receptor expression has been found to happen throughout the brain in sleep deprivation (260) and adenosine might be involved in the antidepressant effect of sleep deprivation.

A number of biochemical and hormonal changes in cytokines (261), cortisol (262), growth hormone, and thyroid secretion are influenced by wake therapy (263). A study of plasma metabolomics in normal controls showed a more than 40 % increase in serotonin, and also increases in tryptophan and taurine during sleep deprivation compared to sleep (264).

The supposed mechanism of the antidepressant action of bright light is given in the bright light study section and summarized in the book chapter by Terman et al (265): bright light acts as an acute energizer, a circadian rhythm phase shifter with phase direction depending on timing, and impacts on the level of neurotransmitters, all of which are important elements in the chronos study. Light exposure upon awakening reduces early insomnia (difficulty falling asleep), stabilizes irregular sleep patterns, discourages oversleeping and reduces sleep inertia post-awakening. Sleep, when taken in a vulnerable phase after wake therapy, such as when oversleeping in the morning, can induce a depressive relapse. Morning light therapy and earlier bedtime are thus protective factors against relapse into depression after wake therapy. This is why the regimens used in the chronos protocol deliberately induced a mild form of sleep phase advance on the recovery sleep nights and psychoeducated patients on sleep time stabilisation to avoid oversleeping. The crucial hypothesis in the chronos study was *not* to achieve an antidepressive response to wake therapy. This has been shown in a great number of trials. What was important was to use chronotherapeutic principles to avoid relapse and deterioration between wake therapies on recovery nights and in the weeks after the intervention. To be able to measure whether this was the case we employed a large number of scales and day-to-day assessments in the intervention week.

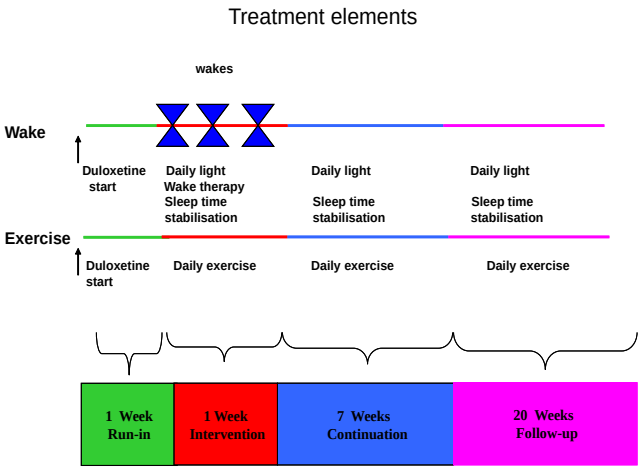
Methods and materials

Design of study

The chronos study was designed as a randomised controlled trial with rater blinding. Patients were randomised, with a computer generated block size of four, into either a *wake group* or an *exercise group*. The wake group included wake therapy, sleep phase advance and sleep time stabilisation with continuous light therapy. The exercise group included individually tailored daily exercise of moderate intensity for at least 30 minutes. The study was divided into four parts (figure 1): a one-week outpatient *run-in phase*, a one-week inpatient *intervention phase*, a seven-week outpatient *continuation phase* and a 20-week outpatient *follow-up phase*. Randomisation took place prior to the run-in phase.

The exercise group was designed to act as an active control. To avoid any placebo response from the inpatients chronotherapeutic interventions we used a design where patients in the exercise group were also admitted to open psychiatric wards for the same time period. A description of the different treatment elements is given below in figure 4.1.

Figure 4.1 Treatment elements in the chronos study



In the one-week outpatient ***run-in phase*** all patients were started up on 60 mg of duloxetine and self-assessed their mood 7 times a day over a consecutive six day period.

In the one-week ***intervention phase*** patients in the *wake group* went through the wake therapy regime including a one week inpatient intervention with total sleep deprivations on Mondays, Wednesdays and Fridays interspersed with recovery sleep nights on Tuesdays, Thursdays and Saturdays and these were scheduled with an early bedtime (8 pm at latest) and an early rise time (according to light therapy timing but at 8 am at the latest) to achieve a slight sleep phase advance. Light therapy was used daily from the start on Mondays and continued for the whole of the study period. Patients randomised to the *exercise group* started daily exercise from Mondays and continued daily for the whole of the study period.

Patients in the *wake group* were orally informed and given written instructions on sleep hygiene, wake therapy, timing and use of light therapy.light therapy was started on tuesday morning based on an algorithm derived from the scores of the morningness-eveningness questionnaire (MEQ= measuring the level of morningness or eveningness based on preference of tasks and sleep timing) as published by Michael Terman (90). Sleep time stabilisation was secured, in the wake group, by daily consultations with the patients at the ward with a focus on giving guidance on how to administer the sleep on the recovery nights and sleep on the nights after discharge. Warnings were given, especially against morning napping due to the propensity for relapse induction (230, 266).

Patients in the *exercise group* were orally informed and given written instructions regarding exercise, contact information for their personal physiotherapist, exercise logs, a basic exercise manual, and the Borg scale to self-assess degree of exertion. They started up on the individual exercise program on Mondays, instructed by physiotherapists who were part of the research team.

No guidance on sleep was given to patients in the exercise group and they followed the normal sleep schedule of the ward.
All patients were discharged on a Saturday and assessed at the research unit on the following Monday. A description of treatment elements in the intervention-phase is shown in figure 4.2.

Figure 4.2. Nomenclature and structure of the intervention phase

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

In the seven-week outpatient ***continuation-phase*** all patients were kept on an unchanged dosage of 60 mg duloxetine. Patients in the wake group continued with daily bright light therapy and sleep time stabilisation and patients in the exercise group continued with daily exercise. Patients were assessed weekly.
In the 20-week outpatient ***follow-up phase*** all therapy elements were carried out as in the seven-week continuation-phase. Patients were assessed every four weeks.
To attain blinding of assessment, patients were told not to reveal group allocation to assessors at rating sessions. Instructors of wake therapy, bright light therapy, and exercise were unblinded.
The study was monitored (GCP unit Copenhagen) and approved by the Regional Scientific Ethical Committee, the Danish Medicines Agency and the Danish Data Committee.
Wake therapy procedures

On wake nights patients were instructed to stay up the entire night and were not to sleep on the following day until 8 pm. Patients filled in the Stanford Sleepiness Questionnaire (267), for every hour on the wake nights. Patients were, during the wake period, allowed to walk freely in and outside the ward, to use the facilities and were instructed to avoid darkness. The light intensity during the wake period was thus ambient evening level. The ward staffs was instructed not to press patients to stay awake and patients were informed that no substantial help could be expected from ward personal to stay awake. On recovery nights patients were scheduled to go to sleep at 8 pm and to wake up no later than 8 am (a milder version of a sleep phase advance). Patients were allowed to take a maximum of two additional separate wake therapies from week four to seven if they had not attained an adequate response (Hamilton score $\geq$ 7).

Light therapy procedures

Patients took 30 minutes of light therapy at 4 am on each wake nights to alleviate tiredness. Daily morning light therapy was started on the morning after the first wake night, and continued for the remaining study period (at home). Light was administered from a SMIFA Biolamp (colour temperature 5500 K, 10000 lux white light at a 40 cm distance from screen), for a duration of 30 minutes. Timing of light therapy was scheduled from an algorithm based on the Morningness-Eveningness Questionnaire (MEQ) score, with 7 o'clock in the morning as the earliest, as devised by Terman et al (90).

Sleep time stabilization procedures

Sleep logs were recorded in both groups but only in the wake group were they used to guide patients to keep a stable sleep-wake cycle and prevent oversleeping. Patients in the wake group were encouraged not to go to sleep later than midnight.

Exercise procedures

The exercise program consisted of a basic exercise program supplemented with any exercise preference of the patients like running, bicycling or gardening. Patients in this group followed the ordinary bedtime and sleep length regime in the open ward and exercise was taken between 9 am and 4 pm. At home patients could start exercise in the morning as early as they wished, but were advised not to exercise later than 7 pm due to the risk of insomnia. Patients were seen weekly for the next seven weeks, in training group/ individual instruction. At each visit the physiotherapists evaluated each patient's exercise performance. This was done by inspecting the daily entries in the exercise logs and through a questionnaire evaluating, for the preceding week, the degree of compliance with the training program (0 = none, 100 = complete and >100 more than expected) and the need for support (ranging from minimal to maximal, score 1-6). The duration and type of exercise could be adjusted at all visits according to the individual patient's motivation. Patients were also allowed extra sessions with the physiotherapist if needed. Training was for one hour in a group of three to five patients or individually.

Medication

All current antidepressants were discontinued at inclusion. study medication was a fixed dosage of 60 mg duloxetine for the first nine weeks of the study. in the follow-up period medication could be increased or changed if no improvement was seen. anxiolytics and hypnotics could be prescribed for the whole study period.

Assessment

Diagnosis of major depression was confirmed at baseline by use of the M.I.N.I. instrument (131). Primary interviewer assessment scale was the HAM-D_{17} for the weekly and 4-weeks assessments and the HAM-D6 scale for the intervention days. The HAM-D_6 scale does not contain sleep items making it appropriate for wake therapy assessments. All patients were furthermore assessed with self- assessment depression scales, sleep logs, medication logs, light timing logs, exercise logs, side effects scale, and daily depression self-assessments with the Preskorn scale (= VAS scoring from 0 = no depression to 10 = worst depression ever) used in this thesis to monitor day-to-day depression severity daily for the first nine weeks and thereafter every four weeks.

Primary outcomes as stated in the protocol were response and remission rates after two, nine and 29 weeks of therapy. Response rates were defined as a reduction in HAM-D_{17} baseline scores of 50 % or more, and remission rates as a HAM-D_{17} score of less than 8.

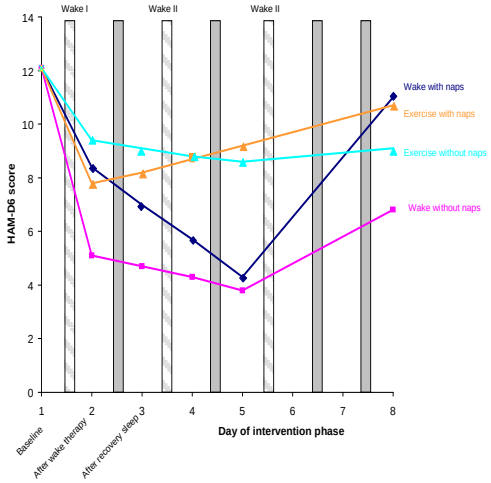
Results

The hypotheses stated in the protocol were confirmed. Patients in the wake group had an immediately better antidepressant effect than patients in the exercise group from the day after the first wake therapy as measured on the HAM-D_6 scale with response rates 58.7 % versus 13.7 ($p < 0.0001$) and remission rates 38.6 % versus 2.9 % ($p < 0.0001$). Patients were last assessed on the ward after the second recovery sleep (at day 5, having then performed the second wake therapy the night before), and response rates were then 75.0 % versus 25.1 % ($p < 0.0001$) and remission rates were 56.8 % versus 6.0 % ($p < 0.0001$) in the wake versus exercise groups.

Some deterioration in both groups was seen at the next assessment at week two (3 days later) but a statistically significant difference favouring the wake therapy group was still present on all used scales. On the HAM-D_{17} scale response rates were 41.4 % versus 12.8 % (p=0.003) and remission rates were 23.9 % versus 5.4 % (p=0.004) at week two. Similar results were found on the HAM-D_6 and MES scales. This better outcome for the wake group was sustained for the seven weeks following the intervention phase with endpoint (week nine) response rates of 71.4 % versus 47.3 % (p = 0.04) and endpoint (week nine) remission rates of 45.6 % versus 23.1 % (p = 0.04). In the follow-up period a continuous improvement was seen in both groups. At end of the follow-up phase (week 29) response rates were similar between groups with 74.6% in the wake versus 64.4% in the exercise group (p = 0.22). Remission rates were statistically significantly higher in the wake group with 61.9% versus 37.9% in the exercise group (p = 0.01). HAM-D_{17} endpoint scores were statistically lower in the wake group with endpoint scores of 7.5 (SE = 0.9) vs. 10.1 (SE = 0.9) in the exercise group (p = 0.02).

In a further analysis from the one-week intervention phase, we found that patients in the wake group who had been napping in the discharge period (Saturday, Sunday and Monday when discharged from the inpatient ward) had a larger deterioration of mood at the next assessment at week two compared to patients not napping in the discharge period (p = 0.02). This effect of napping was not found in the exercise group. Furthermore, patients that did nap in the discharge period had a poorer response to the first wake therapy compared to patients not napping in this period. Probably they were sleepier, not able to resist napping, which could also have affected the course of their wake therapy (microsleep). Figure 4.4 shows the effect of napping.

Figure 4. Effect of napping on depression level



The diurnal variation of mood was assessed in the week prior to the intervention week, with 7 self-ratings during six days, by the Preskorn scale (0 = no depression, 10 = worse depression ever, range 0-10). Mood changes over the day ranged from a maximum score increase (worsening during the day) of 3.8 point to a 3.6 points score reduction (improvement during the day). In the wake group, a positive diurnal variation (improvement during the day) was associated with a better outcome (examined by the HAM-D_6), after the wake therapies, compared to a negative diurnal variation (worsening during the day). In the exercise group, the reverse was found, as a positive diurnal variation (morning worst) was associated with worse outcome compared to a negative diurnal variation. This interaction between group and diurnal variation was statistically significant (p=0.0004).

Patients in the exercise group performed exercise with a mean of 63.0 minutes/day (55.3) for the first eight weeks and 41.9 (40.2) min/day in the follow-up period.

Sleep diaries, from the intervention phase, showed that patients in the wake group slept a total of 49:45 (6:03) hours: minutes versus an average of 60: 02 (7:45) hours: minutes in the exercise group during the intervention week (excluding naps). Patients in the wake group thus lost app. 10 hours of sleep during this week relative to the exercise group. The reason that the sleep debt was relatively small was due to a partial compensation on the long recovery nights. In the wake group patients slept 10:35 (1:11), 10:14 (1:41), and 9:51 (1:58) hour: minutes on the I and II and III recovery night. Patients in the exercise group, on the corresponding nights, slept 7:17 (1:20), and 7:47 (1:35) and7:14 (1:48) hour: minutes. This difference between sleep duration for the groups was statistically significant for each of the three days (p < 0.0001).

Sleep diaries, from the continuation phase, show that sleep was phase advanced in the wake group compared to the exercise group as illustrated by a sleep midpoint in the wake group / exercise group of 3:34 AM (1:41) / 3:28 AM (1:51) at baseline and 3:02 AM (1:06) / 3:43 AM (1:47) at week nine (wake group p < 0.001; exercise group p = 0.08). The day-to-day variation of all sleep parameters (sleep onset, sleep offset and sleep midpoint) was significantly smaller in the wake group compared to the exercise group (for sleep midpoint p < 0.01) in the first 9 weeks of the study. In the follow-up period the advance of the sleep-wake cycle seen in the continuation phase was only partially maintained with sleep onset at 23:19 (SE = 0:05) in the wake group and at 23:42 (SE = 0:04) in the exercise group and sleep offset at 7:39 (SE = 0:07) in the wake group and at 7:37 (SE = 0:06) in the exercise group, at week 29.

At baseline, patients were asked whether they in their current depressive episode had experienced mood drops after day-time sleep. This was thought to be a predictor for relapse after wake therapy. Data showed that 47.1 % per cent of patients had experienced this phenomenon with a mean duration of the mood drop of 92.7 (69.5) minutes with no significant differences between groups. This presence of mood drop was associated with higher depression scores in the intervention week (p =0.05) without any difference between groups.

During the first 9 weeks of therapy seven patients dropped out of the wake group and four patients of the exercise group, in the follow-up phase the dropout was six versus four patients.

Sensitivity analyses from the follow-up phase showed that the continued difference between groups at endpoint was robust and that drop-out rates, depression severity at drop-out, time in study, and causes for drop-out did not differ across the two groups.

Discussion

The hypotheses stated in the protocol were: “does a chonotherapeutic intervention yields a greater response and remission rate than exercise?”, and ”is daily exercise duration of minimum 30 minutes attainable in patients with major depression?”, and “does diurnal mood variation predict response to wake therapy”, all of which was confirmed.

The primary endpoint, response and remission, showed statistically and clinically meaningful greater response and remission

rates in the wake group, at the end of the intervention-phase, after the end of the continuation-phase and, regarding remission, after end of the follow-up phase. Patients' completion and compliance with wake therapy procedures, light therapy and exercise were good. Patient evaluations from semi-quantitative questionnaires were positive regarding all treatment elements. Wake therapy was however, in a few patients associated with anxiety attacks (four patients). None of neither these nor any other of the patients experienced delusions, that have been reported to worsen during wake therapy (268), probably due to the exclusion of patients with psychotic depression. Even though the procedures were able to successfully avoid relapse between wake therapies, some patients did experience worsening after discharge, probably due to being unable to resist napping. One of the possible adverse effects of our intervention was the use of a dosage of bright light late at night, aimed to alleviate tiredness. This might have shifted patients' circadian phase in an unknown direction. According to the PRR, light given at the most sensitive phase of the circadian system, as we did, using a light pulse at 4 AM, could either phase advance or phase delay sleep. If light therapy phase delayed sleep this would induce increased sleep inertia when trying to get up in the days after discharge and thus a tendency to nap during the day and provoking mood drops. Probably light therapy (as a thirty minute 10'000 lux light pulse) during the night should be avoided during wake therapy, or rather, to keep patients more alert, the general lighting intensity throughout the whole night could be enhanced to about 500-600 lux. This might counteract the sleepiness, and because it is spread across the whole night, less phase shifting would be induced.

Caution should be taken when interpreting how much the individual patient experienced study procedures as a burden. Clinical trials are an artificial situation in many ways (e.g., researcher enthusiasm, patients seeking the "last treatment option", higher service level during study period) and the real balance between treatments will only show itself in daily clinical practice. We do believe that the procedures in both the treatment groups in the chronos study required a substantial investment from a depressed patient and also required careful consideration and support from clinicians and staff.

Hamilton scores of 9.0 (SE=0.8) at week 9 and 7.5 (SE=0.9) at week 29 in the wake group, and 12.0 (SE=0.8) at week 9 and 10.1 (SE=0.9) at week 29 in the exercise group are very close to remission. Why did patients in both groups respond so well to treatment? The substantial effort that we put into sleep regulation and sleep guidance in the wake group possible helped. At least research data seems to support that restriction of napping in daytime is beneficial as napping has a significant impact on thermoregulatory processes linked to sleep inertia (269) and, as our data has shown, napping induced mood drops in a high percentage of the patients. As recent studies have found exercise to have an effect on depression, the exercise probably did act as an active intervention. This means that the "true" effect of the chronotherapeutic intervention, in this study, is under-evaluated.

The hierarchy of treatment options for a depressed patient is by no means clear and depends on patient and illness characteristics, level of psychiatric service and skills, and previous experiences of the individual clinician. The use of a wake therapy regimen in its current form should be restricted to centres with special interest and experience in chronotherapeutics. These centres should build up a database collecting predictors of response in order to tune in on which patients to offer this kind of treatment. Table 4.5 shows a comparison of RCT studies using wake therapy in combination with other chronotherapeutic methods and/ antidepressants. Both design and study period vary considerably between studies making comparisons very difficult.

Table 4.5. Comparison of studies using wake therapy with drugs or other chronotherapeutic methods.

Author	Holsboer-Trachsler 1994 (209)	Kuhsl 1996 (210)	Neumeister 1996 (232)	Smeraldi 1999 (231)	Wu 2009 (204)	Martiny 2012 (270)
Type	Bi- and unipolar	Bi-and uniplar	Bi- and uniplar	Bipolar	Bipolar	Bi- and unipolar
Setting	Inpt.	Inpt.	Inpt.	Inpt.	Outp	Outpt
Design	RCT	RCT	RCT	RCT	RCT	RCT
Blinding	No info.	None	Rater blind	Double blind	None	Rater blind
AD	Trimipramine	Amitriptyline	Continued AD	None	Sertraline/ other	Duloxetin
Active intervention	AD + BL or AD + Wake	PSD+AD	PSD responders: BL + AD	Wake + active pindolol	Wake + SPA + BL + AD + MS	AD + wake + BL + SPA
Wake type	PSD 01:30 AM	PSD 01:30 AM	PSD 01:30 AM	TSD	TSD	TSD
Nb. of wakes	6	6	1	3	1	3 (+2)
Days betw. wakes	1 and 6	4-5	-	1	-	1
Control intervention	AD	AD	PSD response: DL + AD	Wake + placebo pindolol	AD +MS	AD + Exercise
Dur.	42 d	4 w	7 d	10 d	7 w	29 w
Nb. Pt.	42	51	20	40	49	75
Scale	HDRS 17	HDRS 21	HDRS 21	HDRS 21	HDRS 19	HDRS 17
Result	Negative	Positive	Positive	Positive	Positive	Positive

AD = antidepressants, MS = mood stabilizer, HDRS = Hamilton depression rating scale, MADRS = Montgomery Åsberg Depression Rating Scale, SPA = sleep phase advance, TSD = total sleep deprivation, PSD = partial sleep deprivation, BL = bright light, DL = dim light, w= week, d = day.

5. General conclusion

General results

In the bright light study, the PEMF study and the chronos study we found an accelerating effect of the active interventions and a larger reduction in depression severity at endpoint.

In the Pindolol study the main outcome showed no difference between groups. Analysis pre-specified in the protocol as a secondary outcome showed an interaction between metabolizer status of venlafaxin and the effect of pindolol on depression scores.

Table 5.1 shows the trial designs of all four studies. All studies are RCTs with control groups using placebo or sham treatment or an alternative treatment. Study length varied from 19 days to 29 weeks. All primary outcomes were based on scores from the Hamilton Depression Rating Scale.

Table 5.2 shows common sociodemographic data from al studies. Age was comparable between studies, and numerically a little higher in the PEMF study. A higher percentage of females was seen in all studies. The duration of the current depressive episode was long, from 12.0 (15.8) months to 34.7 (55.0) month. The large SD values of illness duration illustrate that the distribution of illness length is highly skewed due to outliers. This is a common phenomenon caused by some patients having suffered from depression for decades. The number of previous depressive episodes was between 1.5 (2.0) and 8.7 (11.0) and somewhat higher in the PEMF and chronos studies. A major part of the patients were in antidepressant treatment at inclusion. Percentages of bipolar patients were low in all studies.

Table 5.3a shows baseline depression levels as measured on the HAM-D_{17}, HAM-D_6, MES, SIGHSAD, and WHO-5. Severity varies with scores from 20.9 (3.3) to 24.3 (5.4), corresponding to moderate depression ($18 \leq$ HAM-$D_{17} \leq 24$). Values were numerically but statistically insignificantly higher in intervention groups.

Table 5.3b shows endpoint scores on the HAM-D17, HAM-D_6, MES, SIGHSAD, and WHO-5 scales.

Endpoint scores in the active groups of the light and chronos studies approached remission both on the HAM-D_{17} (<8) and the HAM-D_6 (<4) after five, nine and 29 weeks. In the chromos study the WHO-5 score at week 29 was within the normal level of the general Danish population (271, 272).

Table 5.4 shows response and remission rates at endpoint on the HAM-D_{17} scale. Response rates in the active groups vary from 41.4 % to 74.6 % and in the placebo groups from 12.8 % to 64.4 %.

Remission rates in the active groups vary from 14.1 % to 61.9 % and in the placebo groups from 4.1 % to 37.9 %.

Table 5.5 shows effect sizes, based on Cohen's d, with values between 0.39 and 0.87 (moderate-high effect size) on the HAM-D_{17}, between 0.45 and 0.91 on the HAM-D_6, and between 0.49 and 1.06 on the MES.

The outcomes scales, used in the included studies in this thesis, have been shown to have very high interrater reliability with intra-class coefficients of 0.93 (HAM-D17), 0.89 (HAM-D6), and 0.91 (MES) (273).

Side effects were measured by use of the UKU scale. Specific items were selected from the full UKU instrument for the different studies according to expected side effects from the psychotropic drugs used. Expected or suspected side effects of augmentation methods were also recorded, as were any adverse events.

The UKU instrument contains side effects items categorized as psychiatric, neurological, autonomic and miscellaneous. In the four studies we used the following items:

Psychiatric = concentration, sedation, memory disturbance, inner tension, increased sleep, reduced sleep, increased dreaming, nightmares (pindolol study), emotional indifference.

Neurological = tremor, paresthesia

Autonomic = reduced salivation, nausea, diarrhoea, constipation, voiding problems, orthostatic hypotension, palpitations, increased sweating, cold extremities (pindolol study)

Miscellaneous = weight gain, reduced sexual libido, erective dysfunction, orgasmic dysfunction, headache, irritation of the eyes (light study)

Items were scored according to the manual as: score 0, no side-effects; score 1, mild side-effects that do not interfere with the patient's performance; score 2, side-effects that interfere moderately with the patient's performance; score 3, side-effects that interfere markedly with the patient's performance.

In the bright light *study* we published side effects as "treatment emergent side effects" defined as side effects that increased from baseline at some time point during the study duration. These were nausea/vomiting (both groups), diarrhoea (both groups), headache (both groups) and eye irritation (bright light group). All side effects were rated as mild and did not interfere with daily life. The rest of the rated UKU items were either unchanged or reduced from baseline.

In the *pindolol study* the rated UKU item scores were moderate with decreasing scores from baseline and without significant differences between groups. A larger reduction from baseline of the items tenseness/nervousness and impaired memory were seen in the in the placebo group compared to the pindolol group.

In the *PEMF study* we published "treatment emergent side effects" and reported those UKU items where the number of patients with treatment emergent side effects in the active PEMF group was double the number of patients in the sham group who developed symptoms. This was the case for increased dream activity, suicidal ideation, tremor, paresthesia, dizziness, constipation, stranguria/voiding problems, increased sweating, helmet felt heavy, flu-like symptoms, lower back pain, stabbing pain in the head. The number of patients in the active PEMF group experiencing treatment emergent side effects was below 3 for any side effect. One patient receiving active PEMF treatment developed mild suicidal ideation lasting for two days due to a social incident. No intervention was necessary and the patient continued in the study.

In the c*hronos study* side effects reached a maximum of 2 or less, corresponding to a moderate interference with daily activities in both groups. Four patients developed anxiety attacks related to wake therapy. One patient with insulin dependent diabetes developed hypoglycaemia during a wake therapy night, which was relieved by administration of oral glucose. One patient experienced watering eyes due to light therapy and one patient developed substantial pain in the Achilles tendon due to exercise. Blood pressure and weight were unchanged from baseline to endpoint (nine weeks).

General discussion

All augmentation strategies were well tolerated and except for the pindolol study active groups were superior to placebo/sham interventions. The proposed mechanism of action of the antidepressant augmentation involves a variety of systems: gene expression of circadian clocks, internal and external circadian

rhythms entrainment and synchronisation, sleep time stabilisation and changes to sleep architecture, direct sensory stimulation from retinal receptors to a variety of changes in brain areas including the limbic system, autoreceptor blockage or desensitisation (pindolol and wake therapy), electrical stimulation of hypothesized electrical neural sensors, activation of intracellular second messengers, regulation of brain stem nuclei and resultant changes in neurotransmitters.

There is no obvious final common pathway that can be deduced from these mechanisms of action. The psychopathology of depression points to that depressive illness involves a multitude of cortical, subcortical and brainstem dysfunctions, presenting clinically as changes in mood, anhedonia, loss of appetite, loss of sexual interest, reduced concentration, sleep disturbances and many other symptoms and signs. Therefore it is not surprising that antidepressant agents can work through targeting different areas of the brain and working on different parts of the neural machinery.

In the three studies where the active treatment was superior to control treatment, patients had a reduction in HAM-D_{17} / HAM-D_6 scores from a baseline range of 21.4-24.3 / 12.6-13.1 (moderate/severe depression) to an endpoint range of 7.5-11.0 / 4.1-6.7 (questionable to mild depression). Response rates in the three studies reached a range of 72.9 % - 74.6 % and remission rates 33.9 % - 61.9 %. The studies thus show that it is possible to augment the effect of antidepressant treatment and with a clinically meaningful magnitude.

The four studies are very different in their set-up and from an administrative and economical viewpoint light therapy is the easiest and most cost-effective modality. PEMF requires rather expensive equipment, but once this is purchased, it is viable for years. The latest PEMF study used home treatment, making it much easier to administer (186). The chronos study is the most labour intensive study to carry out primarily due to safety precautions for the wake therapy. However, as no serious adverse events appeared in the study due to wake procedures and as a there are now several rapports of successful home-treatments with wake therapy (219), this treatment can probably be administered in a more cost-effective way, at least for some of the patients. The chronos study encompasses as an important part, a high degree of psychoeducation on sleep, and this is readily useful. Caution should however be taken as we do not know to what extent the sleep stabilisation was effective compared to the other elements in the chronos study.

Table 5.1 Design of studies

Study	Design	Experimental intervention	Control intervention	Duration	Primary outcome and scale
Light	RCT	Bright white light	Dim red light	9 weeks	Improvement HAM-D_{17}
Pindolol	RCT	Active pindolol and active venlafaxine	Placebo pindolol and active venlafaxine	19 days	Response rate HAM-D_{17}
PEMF	RCT	Active PEMF stimulation	Sham PEMF stimulation	5 weeks	Improvement HAM-D_{17}
Chronos	RCT	Wake therapy, sleep time stabilisation, bright light therapy, duloxetine	Exercise and duloxetine	29 weeks	Response / Remisson rates HAM-D_{17}

Table 5.2 Sociodemographics

Parameter	Group	Light	Pindolol	Pemf	Chronos
Age, years, mean (SD)	Active	43.1 (15.8)	48.5 (15.7)	56.4 (13.7)	46.9 (12.6)
	Control	45.9 (16.1)	45.3 (13.7)	49.7 (11.4)	48.5 (11.2)
Female gender, per cent	Active	70.8 %	60.0 %	68.0 %	64.9 %
	Control	66.7 %	31.3 %	72.0 %	52.6 %
Duration of present Depressive episode, Month, mean (SD)	Active	12.0 (3-24)*	12.0 (15.8)	31.3 (34.3)	24.9 (29.0)
	Control	10.0 (3-24)*	18.8 (14.3)	34.7 (55.0)	21.3 (54.3)
Mean number of depressive episodes in lifetime (SD)	Active	3.7 (5.9)	2.3 (4.3)	6.4 (5.3)	8.7 (11.0)
	Control	4.3 (6.3)	1.5 (2.0)	6.4 (5.5)	6.2 (7.5)
Antidepressant treatment at inclusion, per cent	Active	45.8 %	53.3 %	100 %	83.4 %
	Control	29.6 %	57.1 %	100 %	84.2 %
Patients with bipolar Disorder, per cent	Active	2.3 %	6.7 %	8.0 %	16.2 %
	Control	0 %	6.3 %	0 %	15.8 %

* Median with 25th and 75th quartiles

Table 5.3a Baseline depression severity

Group / scale	Light (SD)	Pindolol (SD)	Pemf (SD)	Chronos (SD)
Active Ham-D_{17}	22.4 (4.4)	24.3 (5.4)	21.1 (4.1)	23.9 (4.3)
Control Ham-D_{17}	22.1 (3.5)	23.4 (4.8)	20.9 (3.3)	22.3 (3.8)
Active Ham-D_6	12.6 (1.9)	13.1 (2.5)	12.6 (2.1)	13.1 (1.7)
Control Ham-D_6	11.7 (1.4)	12.3 (2.3)	12.1 (2.1)	12.6 (2.0)
Active MES	21.6 (3.5)	23.7 (4.0)	21.6 (3.0)	24.1 (3.4)
Control MES	20.9 (2.9)	22.8 (3.7)	21.0 (2.7)	22.6 (3.3)

Table 5.3b Endpoint depression severity

Group / Scale	Light W 5 (SD)	Pindolol Day 19 (SD)	Pemf W 5 (SD)	Chronos W 9 (SE)	Chronos W 29 (SE)

Active Ham-D_{17}	9.0 (4.4)	14.2 (5.9)	11.0 (5.7)	9.0 (0.7)	7.5 (0.9)
Control Ham-D_{17}	11.6 (4.3)	12.0 (5.8)	16.0 5.6)	12.0 (0.8)	10.1 (0.9)
Active Ham-D_6	5.5 (2.8)	8.4 (3.4)	6.7 (3.7)	5.1 (0.5)	4.2 (0.6)
Control Ham-D_6	7.0 (2.6)	6.8 (3.7)	9.8 (3.7)	7.3 (0.5)	5.8 (0.5)
Active MES	10.2 (5.0)	15.1 (6.1)	11.5 (5.6)	10.0 (0.9)	7.5 (1.0)
Control MES	12.2 (4.4)	12.1 (6.0)	16.9 (5.6)	12.5 (0.9)	10.6 (0.9)

W =weeks

Table 5.4 Response and remission rates at endpoint on the Ham-D_{17} scale with remission defined as a score below 8 and response at a 50 % or larger reduction from baseline.

Group	Light W 5	Pindolol Day 19	Pemf W 5	Chronos W 9	Chronos W 29
Active Resp	66.7 %	52.4 %	61.0 %	71.4 %	74.6 %
Control Resp	40.7 %	39.7 %	12.9 %	47.3 %	64.4 %
Active Remis	41.7 %	14.1 %	33.9 %	45.6 %	61.9 %
Control Remis	14.8 %	28.7 %	4.1 %	23.1 %	37.9 %

W = weeks, Resp = response, Remis = remission, Light therapy study used available data at week five and LOCF at week nine. The pindolol, pemf and chronos study used estimated scores.

Table 5.5 Cohen's unbiased effect sizes at endpoint using LOCF. The interval between 0.00 and 0.19 refers to no effect; 0.20 and 0.39 refers to a small effect; the interval between 0.40 and 0.69 refers to a medium effect; the level of 0.70 or higher refers to a large effect.

Scale	Light W 5	Pindolol Day 19	Pemf W 5	Chronos W 9	Chronos W 29
Ham-D_{17}	0.45	Na	0.87	0.39	0.13
Ham-D_6	0.66	Na	0.91	0.45	0.18
MES	0.49	Na	1.06	0.49	0.18

W = weeks

6. Future directions

Only a fraction of the activity in the brain is assessable to conscious experience. Thus, probably only a fraction of the underlying psychopathology of depressive illness will translate into discernable and valid clinical symptoms. The total biology of the disorder is thus not available for research based solely on psychometric evaluation. Furthermore, assessable symptoms fluctuate rapidly from hour-to-hour and from day-to-day. Rating scales gives us is a point-in-time measurement of surfacing symptoms of the disorder. However, as the rating scales used in this thesis have been constructed using expert clinical global assessments as an external validator, and because the used items operate in a way fulfilling Rasch criteria (item-response theory), the sum score of the scales are a sufficient statistic of the severity of the clinical condition (274). Thus, we cannot regard the use of rating scales as reductionistic. The rating scales used in the four studies in this thesis are excellent to assess present state severity and response to treatment and in this way paves the way for new treatment methods by correctly establishing true efficacy.

The shortcoming of rating scales is that it does not automatically lead to the underlying biological dysfunction. Therefore we need to supplement rating scales with other approaches.

In response to the recent release of the DSM-5, the director of NIMH, Thomas Insel, stressed that future developments in diagnostics (and treatment development) must go from a purely symptom based system to include genetics, imaging, biomarkers, quantifiable psychopathology (retardation, diurnal variation, sleep) and cognitive science. This is named the Research Domain Criteria (RDoC) and is a research framework aiming at creating a new classification and new ways of studying mental illness. RDoC has dysfunction in basic brain mechanisms as the primary focus and studies these to understand symptoms across multiple disorders, rather than starting with clinical symptoms and working backwards. The defined Domains of functioning are organised in a matrix with: negative valence systems (aversive motivation), positive valence systems, cognitive systems, systems for social processes, and arousal/regulatory systems (including sleep and circadian systems), *as rows,* and *as columns* different classes of variables (or units of analysis) used to study the domains/constructs: genes, molecules, cells, neural circuits, physiology (e.g. cortisol, heart rate, startle reflex), behaviours, and self-reports, (275).

If this approach is used it becomes clear that the term *clinical study* will have a new meaning, as symptom clusters are not the primary focus. The problem of whom to investigate then arises. We still need to select study subjects and in the near future we will have to rely on the available diagnostic categories, possibly extending RDoC approach to healthy family relations or relying more on larger control groups (276).

In some Domains of functioning we do have specific knowledge of basic brain dysfunction, and this is the case for major parts of chronobiology where internal desynchronisation has been established between a number of markers (temperature, blood pressure) and hormones (growth hormone, thyroid hormones, melatonine) and external desynchronisation between the sleep-wake cycle and astronomical day-night. Thus, the existence of a PRC for light is an example of a domain (circadian systems) that can be investigated through circadian markers, e.g. melatonin (physiology). The circadian system is readily assessable through activity monitoring, hormone measurements, sleep recordings.

This approach is used in our actual research project (SAFE II) using psychoeducation and electronic monitoring of patients with depression discharged from hospital, in order to stabilize the sleep-wake cycle, prevent oversleeping to prevent relapse, and using melatonine profiles (DLMO) and actimetry as biological validators.
In another study, we are examining diurnal variation of mood (negative valence systems) in relation to changes in brain function through fMRI (neural circuits). The aim is to find the mechanism in the brain responsible for acute changes in mood as seen in wake therapy but without the strain of staying awake for extended periods.
Another RDoC approach would be to investigate biological changes when applying methods that have already been shown to have an antidepressant effect such as antidepressant drugs or psychotherapy. This will lead to a better understanding of the mechanism of action of antidepressant methods.
Outside the scope of the RDoC approach we are focusing on the living conditions of patients who develop depression and people in general. Depression is a disease highly susceptible to environmental stressors (277) and modulation of factors in daily living might prevent depression, reduce severity of actual depressive episodes, improve treatment of a depressive episode, and reduce relapse or recurrence of depression. One possibility is to focus on known antidepressant agents such as exercise and lighting conditions. *Home mapping* could be a new investigational and treatment tool to advice patients on living conditions regarding ambient luminance, sleep, daily exercise, but also researching the impact of food, and social contact on depression. By inviting researchers into their homes, patients might be able to present us with a lot of new information on the development and treatment of depression. Electronic monitoring is a way to gain real-time assessments of psychopathology and behavior. Electronic monitoring is an area with a great potential and will be incorporated in our future studies (278).
Furthermore the optimisation of lighting conditions in psychiatric wards is an area should be subjected to more research. In the program *Light in Mental health* we are initiating randomized trials to investigate the effect of optimising spectral composition and dynamic intensity of ambient light in affective disorders wards. Through the use of fMRI, assessing the function of the serotonin system, we hope to be able to optimize spectral composition of light to maximum effect on the entrainment of the sleep-wake cycle and antidepressant activity. Finally, the use of simultaneous multiple treatment modalities as in the chronos study combining several antidepressant treatment methods should be encouraged especially in treatment resistant patients. An example of this is found in the study by Krstić et al (279) applying TMS in combination with wake therapy in treatment resistant depression with good long-term results.
Through gradually improvement of individual treatment methods, the combination of these, and enhanced collaboration with patients, we will be able to help more attain remission and recovery.

Conclusion

PEMF, bright light therapy alone, and wake therapy in combination with bright light therapy plus sleep time stabilisation were able to augment antidepressant drug effect. The augmentation was clinically relevant regarding score reductions, response and remission rates. Effect sizes were moderate for bright light treatment, moderate for chronotherapy, and large for PEMF. Pindolol did not augment the effect of venlafaxine. A statistical significant interaction was found between metabolizer status and treatment group as a secondary outcome measure.
Applicability was good for all studies, with low drop-out rates and low side effect profiles. Exercise was also found to be applicable for patients with depression. These methods should be considered for use in daily clinical settings.
The results from the Chronos study should guide us towards a deeper understanding of the relation between sleep and depression and a possibility of developing new drugs that will give a more rapid and complete antidepressant effect.

7. Summary

Hypothesis

The hypotheses of all the four included studies share the common idea that it is possible to augment the effect of antidepressant drug treatment by applying different interventions and with each intervention attain a clinically meaningful better effect compared to a control condition, and with minor side effects, thus improving the short- and medium-term outcome in major depression.

Procedures

Study design

The basic study design has been the double blind randomised controlled trial (RCT).
In the light therapy study, all patients were treated with sertraline for the whole of the study duration. In the first five weeks of the study, patients were randomised to treatment with either 60 minutes of bright white or 30 minutes of dim red light (sham condition). In the four weeks follow-up period, patients were treated with sertraline alone.
In the Pindolol study, all patients were treated with venlafaxine and randomised to augmentation with either active or placebo matching pindolol tablets.
In the PEMF study patients were continued on ongoing medication and randomised to augmentation with active or inactive (sham) 30 minutes daily PEMF treatment on weekdays.
In the Chronos study all patients were treated with duloxetine and randomized to either a combination of three wake therapies with daily bright light treatment and sleep time stabilisation (wake group) or to daily exercise of minimum 30 minutes as an active control intervention (exercise group). The Chronos study was divided into: (1) a one-week run-in phase where duloxetine were started (and continued for the whole 29 week study period), (2) a one-week inpatient intervention phase where patient in the wake group did three wake therapies (sleep abstinence for the whole night and the following day until evening) in combination with daily light therapy and guidance on sleep time stabilisation and patients in the exercise group started a daily exercise program, (3) a seven week continuation phase where patient in the wake group continued light therapy and sleep time stabilisation and patients in the exercise group continued an individual exercise program, and (4) a 20 week follow-up phase with the same treatment elements but where duloxetine dosage could be adjusted or changed to other antidepressants.

Recruitment

Patients recruited for these studies were allocated from general practitioners, psychiatric specialist practices and for the lesser part from open psychiatric wards. Only a few patients were recruited through advertisements (in the PEMF and Chronos studies).

Inclusion criteria
Inclusion criteria were major depression according to the DSM-IV, including a depressive episode as part of a bipolar disorder. For the PEMF study, treatment resistance was a specific inclusion criterion.

Duration of studies
Study duration was nine weeks for the light therapy study, 19 days for the Pindolol study, five weeks for the PEMF study, and 29 weeks for the Chronos study.

Assessments
In all studies, assessments were done with clinician rated scales, patient self-assessment scales, including quality of life scales and a side effect scale. As clinician rated scales we used the Hamilton depression rating scale: the HAM-D_{17} and its 6 item subscale: the HAM-D_6, the Bech Rafaelsen Melancholia scale (MES), and the Bech Rafaelsen Mania scale (MAS). As self-assessment scales we used the Major Depression Inventory (MDI), the Symptom Checklist (SCL-92), and the Preskorn scale. For side effects we used the UKU scale. Further scales used are mentioned in the specific study sections. Assessments in the light therapy study were done weekly for the first six weeks and finally after nine weeks; at four time points in the Pindolol study (baseline, days 6, 11 and 19), weekly for five weeks in the PEMF study and weekly for the first nine weeks of the Chronos study and thereafter every four weeks. The clinical setting for evaluation has been the Psychiatric Research Unit at Mental Health Centre North Zealand. For the Bright Light study, Pindolol and PEMF study patients were also seen at a psychiatric specialist practice in Copenhagen.

Biochemical measures
In the Light therapy study saliva cortisol was collected at baseline before start of light therapy and sertraline and blood was drawn for thyroid analysis. In the Chronos study saliva and 24 hour urine cortisol was collected in the patients randomised to the exercise group.

Main results
The main results from the Bright Light study covering the first five weeks of the study are given in the PhD thesis "Adjunctive bright light in nonseasonal major depression" defended and awarded on the 18 November 2004 at the University of Copenhagen. Results from the cortisol measurement and for the four weeks extension period were published in separate papers after the PhD thesis and are included in this thesis.

Results from the Bright Light study
Analysis of the saliva cortisol measurements taken at baseline of the study as cortisol awakening profiles (CAR) showed that patients responded differentially to light treatment according to their CAR levels (dichotomized to high or low about the mean). Thus, in the bright light group HAM-D_{17} scores were reduced by 15.7 (4.2) points for patients with a low CAR (below mean), and 11.4 (4.8) points for patients with a high CAR (above mean). In the dim light group the corresponding values were 11.1 (5.2) for patients with a low CAR and 11.3 (5.3) for patients with a high CAR. This interaction between CAR and treatment group was statistically significant (p = 0.006).
Survival analysis, for the first five weeks of the study period, showed a statistically significant higher response rate (χ2= 9.6, p =0.002) and higher remission rate (χ^2 = 12.5, p = 0.0004) for the bright light treated group versus the dim light treated group. At end of the five weeks of light treatment response rates were 66.7% versus 40.7 % and remission rates were 41.7 % versus 14.8 % for the bright versus dim light treated group. In the subsequent publication that covered the four weeks extension period where light treatment was discontinued, data showed that the attained differences in response and remission rates between groups were *not* sustained. The offset of effect was nearly complete after four weeks of continued treatment on sertraline only. Thus, at endpoint, response rates were 79.2 % versus 75.9 % and remission rates were 60 .4 % versus 55.6% in the bright versus dim light groups. The conclusion reached was that bright light in non-seasonal depression should be used to achieve an earlier antidepressant response and that light therapy probably should be of longer duration.

Results from the Pindolol study
The results from the Pindolol study showed that pindolol did not augment the effect of venlafaxine for the whole sample. However, for those patients classified as slow metabolizers, based on their O-desmethylvenlafaxine/venlafaxine ratio (ODV/V), pindolol did augment the antidepressant effect. For patients classified as fast metabolizers, pindolol worsened the outcome. This interaction between ODV/V ratio and treatment group was statistically significant (p = 0.01).

Results from the PEMF study
The results from the PEMF Study showed that treatment with active versus sham PEMF augmented the effect of the ongoing antidepressant medication treatment. Thus, patients in the active PEMF group attained a statistically significant greater score reduction from week one and at all subsequent assessments compared to the sham treated group (p < 0.01). Response and remission rates in the active PEMF group were also larger than in the sham treated group with response rates at endpoint of 61.0 % versus 12.9 % (p < 0.01) and remission rates of 33.9 % versus 4.1 % (p < 0.05).

Results from the Chronos study
The Chronos study, published in three papers, covers a one-week intervention phase, a seven weeks continuation phase, and a 20 weeks follow-up phase.
Results from the intervention week showed that patient treated in the wake group, from the day after the first wake therapy, had en clinically and statistically significant better antidepressant effect compared to the exercise group. On the HAM-D_6 scale (which does not contains sleep items), patients in the wake group had a response rate after the first wake therapy of 58.7% versus 13.7% i the exercise group (p <0.0001) and a remission rate of 38.6% versus 2.9% (p <0.0001). After the second recovery sleep (the night after the second wake therapy = dag 5) patients in the wake group had a response rate of 75.0% versus 25.1% in the exercise group (p <0.0001) and remission rates of 58.6% versus 6.0% (p <0.0001).
Results from the continuation phase showed, on the HAM-D_{17} scale which was used at all the follwing assessments, at week two response rates of 41.4% in the wake group and 12.8% in the exercise group (p = 0.003) and remission rates of 23.9% versus 5.4% (p = 0,004). This clinically relevant and statistically significant difference between the wake and exercise groups was maintained at all the subsequent assessments with response rates of 71.4% versus 47.3% (p = 0.04) and remission rates of 45.6% versus 23.1% (p = 0.04), at week nine.

Results from the 20 weeks follow-up phase showed a continued better effect in the wake group at all visits with HAM-D_{17} depression scored at week 29 of 7.5 (SE = 0.9) in the wake group versus 10.1 (SE = 0.9), (p = 0.02) in the exercise group. Remission rates were higher in the wake group with endpoint rates of 61.9% versus 37.9% (p = 0.01) in the exercise group. Response rates was only numerically, but not statistically, higher in the wake group with 74.6% versus 64.4% in the exercise group (p = 0.22).
The sleep diary data showed a statistically smaller day-to-day variation in sleep onset, sleep midpoint, sleep offset and sleep duration in the wake group compared to the exercise group as a sign of better day-to-day sleep-wake cycle control in the wake group (p < 0.01). In the first nine weeks of the study patients in the wake group had a moderate sleep phase advance that diminished during the follow-up period.
The hypothesised predictors for response to wake therapy were confirmed. Thus, in the wake group, a positive diurnal variation (morning worst, evening best) was associated with a better outcome, after the wake therapies, compared to a negative diurnal variation (morning best, evening worst). In the exercise group, the reverse was found, as a positive diurnal variation was associated with worse outcome, compared to a negative diurnal variation. This interaction between group and diurnal variation was statistically significant (p = 0.0004).
The positive predictive value of response to the first wake therapy (i.e. maintaining response also at week two) was 56.3 % and the negative predictive value of non-response to the first wake therapy (i.e. maintaining no response also at week two) was 75.0 %.
The impact of naps on depression severity was examined. In the wake group, patients who napped on the days after wake therapy compared to those patients not napping, had a more severe deterioration at the following assessment at week two (p = 0.02).
Patients in the exercise group were able to perform exercise with a mean of 63.0 minutes/day (55.3) for the first eight weeks.

REFERENCES

[1] American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders*,
4th ed. text revised Washington, DC: American Psychiatric Association.

[2] World Health Organization (1992). *ICD-10 Classification of Mental and Behavioral Disorders: Clinical descriptions and diagnostic guidelines,* Geneva: World Health Organisation.

[3] Paykel ES (2008). Basic concepts of depression. *Dialogues Clin Neurosci* 10: 279-289.

[4] Möller HJ, Riedel M, Seemüller F (2011). Relapse or recurrence in depression: why has the cutoff been set at 6 months? *Medicographia* 33: 125-131.

[5] Rush AJ, Kraemer HC, Sackeim HA, Fava M, Trivedi MH, Frank E, Ninan PT, Thase ME, Gelenberg AJ, Kupfer DJ, Regier DA, Rosenbaum JF, Ray O, Schatzberg AF; ACNP Task Force (2006). Report by the ACNP Task Force on response and remission in major depressive disorder. *Neuropsychopharmacology* 31: 1841-1853.

[6] Kessing LV, Andersen PK (1999). The effect of episodes on recurrence in affective disorder: a case register study. J Affect Disord 53: 225-231.

[7] Gaynes BN, Rush AJ, Trivedi MH, Wisniewski SR, Spencer D, Fava M (2008). The STAR*D study: treating depression in the real world. *Cleve Clin J Med* 75: 57-66.

[8] Carvalho AF, Berk M, Hyphantis TN, McIntyre RS (2014). The integrative management of treatment-resistant depression: a comprehensive review and perspectives. *Psychother Psychosom* 83: 70-88.

[9] Kennedy N, Foy K (2005). The impact of residual symptoms on outcome of major depression. *Curr Psychiatry Rep* 7: 441-446.

[10] Sokero TP, Melartin TK, Rytsälä HJ, Leskelä US, Lestelä-Mielonen PS, Isometsä ET (2005): Prospective study of risk factors for attempted suicide among patients with DSM-IV major depressive disorder. *Br J Psychiatry* 186: 314-318.

[11] Szegedi A, Jansen WT, van Willigenburg AP, van der Meulen E, Stassen HH, Thase ME (2009). Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. *J Clin Psychiatry* 70: 344-53.

[12] Kelsey JE. Treatment strategies in achieving remission in major depressive disorder (2002). Acta Psychiatr Scand Suppl.415: 18-23.

[13] Fava M, Rush AJ (2006). Current status of augmentation and combination treatments for major depressive disorder: a literature review and a proposal for a novel approach to improve practice. *Psychother Psychosom* 75: 139-153.

[14] Trivedi MH, Greer TL, Grannemann BD, Chambliss HO, Jordan AN (2006). Exercise as an augmentation strategy for treatment of major depression. *J Psychiatr Pract* 12: 205-213.

[15] Healy D (1999): The Three Faces of the Antidepressants: A Critical Commentary on the Clinical-Economic Context of Diagnosis. *Journal of Nervous & Mental Disease* 187: 174-180.

[16] Leucht C, Huhn M, Leucht S (2012). Amitriptyline versus placebo for major depressive disorder. *Cochrane Database Syst Rev* 12;12: CD009138.

[17] Connolly KR, Thase ME (2011). If at first you don't succeed: a review of the evidence for antidepressant augmentation, combination and switching strategies. *Drugs* 71: 43-64.

[18] Bauer M, Pfennig A, Severus E, et al (2013). World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders. *The World Journal of Biological Psychiatry* 14: 334–85.

[19] National Institute for Health and Care Excellence (2009) [DEPRESSION: THE TREATMENT AND MANAGEMENT OF DEPRESSION IN ADULTS (update)]. [CG90]. London: National Institute for Health and Care Excellence.

[20] Whale R, Terao T, Cowen P, Freemantle N, Geddes J (2010). Pindolol augmentation of serotonin reuptake inhibitors for the treatment of depressive disorder: a systematic review. *J Psychopharmacol* 24: 513-520.

[21] Aronson R, Offman HJ, Joffe RT, Naylor CD (1996). Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. *Arch Gen Psychiatry* 53: 842-848.

[22] Papakostas GI, Shelton RC, Zajecka JM, Etemad B, Rickels K, Clain A, Baer L, Dalton ED, Sacco GR, Schoenfeld D, Pencina M, Meisner A, Bottiglieri T, Nelson E, Mischoulon D, Alpert JE, Barbee JG, Zisook S, Fava M (2012). L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized,

double-blind, parallel-sequential trials. *Am J Psychiatry* 169: 1267-1274.
[23] Bloch MH, Hannestad J (2012). Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. *Mol Psychiatry* 17: 1272-1282.
[24] Parker G, Brotchie H (2011). Mood effects of the amino acids tryptophan and tyrosine: 'Food for Thought' III. *Acta Psychiatr Scand* 124: 417-426.
[25] Papakostas GI, Cassiello CF, Iovieno N (2012). Folates and S-adenosylmethionine for major depressive disorder. *Can J Psychiatry* 57: 406-413.
[26] Videbech P (2012). Modafinil in the treatment of depression. *Ugeskr Laeger* 174: 348-351.
[27] Abbasowa L, Kessing LV, Vinberg M (2013). Psychostimulants in moderate to severe affective disorder: a systematic review of randomized controlled trials. *Nord J Psychiatry* 67: 369-382.
[28] Lawvere S, Mahoney MC (2005). St. John's wort. *Am Fam Physician* 72: 2249-54.
[29] Linde K, Berner MM, Kriston L (2008). St John's wort for major depression. *Cochrane Database Syst Rev* 8;4:CD000448.
[30] Benedetti F (2012). Antidepressant chronotherapeutics for bipolar depression. *Dialogues Clin Neurosci* 14: 401-411.
[31] Wirz-Justice A, Benedetti F, Terman M (2013). *Chronotherapeutics for Affective Disorders: A Clinician's Manual for Light and Wake Therapy, 2nd ed. Basel: S. Karger AG.*
[32] Pail G, Huf W, Pjrek E, Winkler D, Willeit M, Praschak-Rieder N, Kasper S (2011). Bright-light therapy in the treatment of mood disorders. *Neuropsychobiology* 64: 152-162.
[33] Terman M, Jiuan Su Terman (2010). Circadian rhythm phase advance with dawn simulation treatment for winter depression. *J Biol Rhythms* 25: 297-301.
[34] Echizenya M, Suda H, Takeshima M, Inomata Y, Shimizu T (2013). Total sleep deprivation followed by sleep phase advance and bright light therapy in drug-resistant mood disorders. *J Affect Disord* 144: 28-33.
[35] Pflug B, Tölle R (1971). Therapy of endogenous depressions using sleep deprivation. Practical and theoretical consequences. *Nervenarzt* 42: 117-124.
[36] Swartz HA, Frank E (2001). Psychotherapy for bipolar depression: a phase-specific treatment strategy? *Bipolar Disord* 3: 11-22.
[37] Lanfumey L, Mongeau R, Hamon M (2013). Biological rhythms and melatonin in mood disorders and their treatments. *Pharmacol Ther* 138: 176-184.
[38] George MS, Taylor JJ, Short EB (2013). The expanding evidence base for rTMS treatment of depression. *Curr Opin Psychiatry* 26: 13-18.
[39] Berlim MT, Van den Eynde F, Daskalakis ZJ (2013). Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *J Psychiatr Res* 47: 1-7.
[40] Martin JL, Martín-Sánchez E (2012). Systematic review and meta-analysis of vagus nerve stimulation in the treatment of depression: variable results based on study designs. *Eur Psychiatry*. 27: 147-155.
[41] Rahbek UL, Tritsaris K, Dissing S (2005). Interactions of low frequency, pulsed electromagnetic fields with living tissue: biochemical responses and clinical results. *Oral Biosci Med* 2: 29-40.
[42] Allan CL, Ebmeier KP (2011). The use of ECT and MST in treating depression. *Int Rev Psychiatry* 23: 400-412.
[43] Terman M, Terman JS (2006). Controlled trial of naturalistic dawn simulation and negative air ionization for seasonal affective disorder. *Am J Psychiatry* 163: 2126-2133.
[44] Rimer J, Dwan K, Lawlor DA, Greig CA, McMurdo M, Morley W, Mead GE (2012). Exercise for depression. *Cochrane Database Syst Rev*11;7: CD004366.
[45]Gyllensten AL, Ekdahl C, Hansson L (2009). Long-term effectiveness of Basic Body Awareness Therapy in psychiatric outpatient care. A randomised controlled study. *Advances in* Physiotherapy 11: 2-12.
[46] Smith CA, Hay PP, Macpherson H (2010). Acupuncture for depression. *Cochrane Database Syst Rev* 20;1: CD004046.
[47] Partonen T, Magnusson A (2001). Seasonal Affective Disorder: Practice and Research, Oxford, England, Oxford University Press.
[48] Mouat FJ (1881). On hospitals: their management, construction, and arrangements in relation to the successful treatment of disease, with remarks on the organisation of medical relief in the metropolis. Lancet 117: 979-982.
[49] Retrieved at: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1903/index.htmlon 18 January 2015.
[50] Foster RG, Kreitzman L, (2005). *Rhythms of life*, New Haven and London: Yale University Press.
[51] Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP (1980). Light suppresses melatonin secretion in humans. *Science* 210: 1267-1269.
[52] Arendt J (2006). Melatonin and human rhythms. *Chronobiology Int* 23: 21-26.
[53] Czeisler CA, Duffy JF, Shanahan TL, Brown EN, Mitchell JF, Rimmer DW, Ronda JM, Silva EJ, Allan JS, Emens JS, Dijk DJ, Kronauer RE (1999). Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science* 284: 2177-2181.
[54] Huang W, Ramsey KM, Marcheva B, Bass J (2011). Circadian rhythms, sleep, and metabolism. *J Clin Invest* 121: 2133-2141.
[55] Tosini G, Pozdeyev N, Sakamoto K, Iuvone PM (2008). The circadian clock system in the mammalian retina. *Bioessays* 30: 624-633.
[56] Hattar S, Kumar M, Park A, Tong P, Tung J, Yau KW, Berson DM (2006). Central projections of melanopsin-expressing retinal ganglion cells in the mouse. *J Comp Neurol*. 497: 326-349.
[57] Dai J, Van der Vliet J, Swaab DF, Buijs RM (1998). Human retinohypothalamic tract as revealed by in vitro postmortem tracing. *J Comp Neurol*. 397: 357-370.
[58] Berson DM, Dunn FA, Takao M (2002). Phototransduction by retinal ganglion cells that set the circadian clock. *Science* 295: 1070–1073.
[59] Pando MP, Sassone-Corsi P (2001). Signaling to the mammalian circadian clocks: in pursuit of the primary mammalian circadian photoreceptor. *Sci STKE* 107:re16.
[60] Borjigin J, Zhang LS, Calinescu AA (2012). Circadian regulation of pineal gland rhythmicity. *Mol Cell Endocrinol*. 349: 13-19.
[61] Provencio I, Rodriguez IR, Jiang G, Hayes WP, Moreira EF, Rollag MD (2000). A novel human opsin in the inner retina. *J Neurosci* 20: 600-605.
[62] Münch M, Kawasaki A (2013). Intrinsically photosensitive retinal ganglion cells: classification, function and clinical implications. *Curr Opin Neurol* 26: 45-51.
[63] Hannibal J, Fahrenkrug J (2006): Neuronal input pathways to the brain's biological clock and their functional significance. *Adv Anat Embryol Cell Biol* 182: 1-71.
[64] Hattar S, Lucas RJ, Mrosovsky N, Thompson S, Douglas RH, Hankins MW, Lem J, Biel M, Hofmann F, Foster RG and Yau KW

(2003). Melanopsin and rod-cone photoreceptive systems account for all major accessory visual functions in mice. *Nature* 424: 76-81.
[65] Do MT, Yau KW (2010): Intrinsically photosensitive retinal ganglion cells. *Physiol Rev* 90: 1547-1581.
[66] Hattar S, Kumar M, Park A, Tong P, Tung J, Yau KW, Berson DM J (2006). Central projections of melanopsin-expressing retinal ganglion cells in the mouse. *Comp Neurol 4*97: 326-49.
[67] Edelstein K, Amir S (1999). The role of the intergeniculate leaflet in entrainment of circadian rhythms to a skeleton photoperiod. *J Neurosci* 19: 372-380.
[68] Miller AM, Miller RB, Obermeyer WH, Behan M, Benca RM (1999). The pretectum mediates rapid eye movement sleep regulation by light. *Behav Neurosci* 113: 755-765.
[69] Rath MF, Rohde K, Fahrenkrug J, Møller, M (2013). Circadian clock components in the rat neocortex: daily dynamics, localization and regulation. *Brain Struct Funct* 218: 551-62.
[70] Edgar N, McClung CA (2013): Major depressive disorder: A loss of circadian synchrony? *Bioessays* 35: 940-944.
[71] McClung CA (2013). How might circadian rhythms control mood? Let me count the ways... *Biol Psychiatry* 74: 242-249.
[72] LeGates TA, Fernandez DC, Hattar S (2014). Light as a central modulator of circadian rhythms, sleep and affect. *Nat Rev Neurosci* 15: 443-454.
[73] Reeves GM, Nijjar GV, Langenberg P, Johnson MA, Khabazghazvini B, Sleemi A, Vaswani D, Lapidus M, Manalai P, Tariq M, Acharya M, Cabassa J, Snitker S, Postolache TT (2012). Improvement in depression scores after 1 hour of light therapy treatment in patients with seasonal affective disorder. *J Nerv Ment Dis* 200: 51-55.
[74] Rahman SA, Flynn-Evans EE, Aeschbach D, Brainard GC, Czeisler CA, Lockley SW (2014). Diurnal spectral sensitivity of the acute alerting effects of light. *Sleep* 37: 271-281.
[75] Fisher PM, Madsen MK, Mc Mahon B, Holst KK, Andersen SB, Laursen HR, Hasholt LF, Siebner HR, Knudsen GM (2014). Three-week bright-light intervention has dose-related effects on threat-related corticolimbic reactivity and functional coupling. *Biol Psychiatry* 76:332-339.
[76] Lam RW, Zis AP, Grewal A, Delgado PL, Charney DS, Krystal JH (1996). Effects of rapid tryptophan depletion in patients with seasonal affective disorder in remission after light therapy. *Arch Gen Psychiatry* 53:41-44.
[77] Carlsson A, Svennerholm L, Winblad B (1980). Seasonal and circadian monoamine variations in human brains examined post mortem. *Acta Psychiatr Scand Suppl* 280:75-85.
[78] Lambert GW, Reid C, Kaye DM, Jennings GL, Esler MD (2002). Effect of sunlight and season on serotonin turnover in the brain. *Lancet* 360:1840-1842.
[79] Rosenthal NE, Sack DA, Gillin JC, Lewy AJ, Goodwin FK, Davenport Y, Mueller PS, Newsome DA, Wehr TA (1984). Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry* 41: 72-80.
[80] Kripke DF, Mullaney DJ, M, Wolf S (1978). Circadian rhythm disorders in manic-depressives. *Biol Psychiatry* 13: 335-51.
[81] Kripke DF (1981). Photoperiodic mechanisms for depression and its treatment. In: Perris C, Struwe G, Jansson B, editors. *Biological Psychiatry,* Amsterdam: Elsevier/North Holland, pp 1249-1252.
[82] Tam EM, Lam RW, Robertson HA, Stewart JN, Yatham LN, Zis AP (1997). Atypical depressive symptoms in seasonal and non-seasonal mood disorders. *J Affect Disord* 44: 39-44.
[83] Lewy AJ, Sack RL, Singer CM, White DM, Hoban TM (1988). Winter depression and the phase-shift hypothesis for bright light's therapeutic effects: history, theory, and experimental evidence. *J Biol Rhythms* 3: 121-134.
[84] Lewy AJ, Rough JN, Songer JB, Mishra N, Yuhas K, Emens JS (2007). The phase shift hypothesis for the circadian component of winter depression. *Dialogues Clin Neurosci* 9: 291-300.
[85] Khalsa SB, Jewett ME, Cajochen C, Czeisler CA. (2003) A phase response curve to single bright light pulses in human subjects. *J Physiol* 549: 945-952.
[86] Minors DS, Waterhouse JM, Wirz-Justice A (1991). A human phase-response curve to light. *Neurosci Lett* 133: 36-40.
[87] Lewy AJ, Sack RL (1989). The dim light melatonin onset as a marker for circadian phase position. *Chronobiol Int* 6: 93-102.
[88] Murray G, Michalak EE, Levitt AJ, Levitan RD, Enns MW, More house R, Lam RW (2006). O sweet spot where art thou? Light treatment of Seasonal Affective Disorder and the circadian time of sleep. *J Affect Disord* 90: 227-31.
[89] Terman JS, Terman M, Lo ES, Cooper TB (2001). Circadian time of morning light administration and therapeutic response in winter depression. *Arch Gen Psychiatry* 58: 69-75.
[90] Terman M, Terman JS (2010). Light Therapy. In: Kryger MH, Roth T, Dement WC editors. *Principles and Practice of Sleep Medicine, 5th ed.* St. Louis: Elsevier/Saunders, pp 1682-1695.
[91] Riemann D, König A, Hohagen F, Kiemen A, Voderholzer U, Backhaus J, Bunz J, Wesiack B, Hermle L, Berger M (1999). How to preserve the antidepressive effect of sleep deprivation: A comparison of sleep phase advance and sleep phase delay. *Eur Arch Psychiatry Clin Neurosci* 249: 231-237.
[92] Levitan RD (2007). The chronobiology and neurobiology of winter seasonal affective disorder. *Dialogues Clin Neurosci* 9:315-324.
[93] Lee TM, Blashko CA, Janzen HL, Paterson JG, Chan CC (1997). Pathophysiological mechanism of seasonal affective disorder. *J Affect Disord* 46: 25-38.
[94] Rosenthal NE (1998). *Winter blues,* New York: The Guilford Press.
[95] Lam RW (1998). *Seasonal Affective Disorder and Beyond. Light treatment for SAD and Non-SAD conditions,* Washington, DC: American Psychiatric Press.
[96] Partonen T, Magnusson A (2001). *Seasonal Affective Disorder. Practice and Research*, Oxford: Oxford University Press.
[97] Mellerup ET, Errebo I, Molin J, Plenge P, Dam H (1993). Platelet paroxetine binding and light therapy in winter depression. *J Affect Disord* 29: 11-15.
[98] Dam H, Jakobsen K, Mellerup E (1998). Prevalence of winter depression in Denmark. *Acta Psychiatr Scand* 97: 1-4.
[99] Wirz-Justice A (2006): Biological rhythm disturbances in mood disorders. *Int Clin Psychopharmacol* 21 Suppl 1: 11-15.
[100] Thieden E, Philipsen PA, Wulf HC (2006). Ultraviolet radiation exposure pattern in winter compared with summer based on time-stamped personal dosimeter readings. *Br J Dermatol* 154: 133-138.
[101] Graw P, Gisin B, Wirz-Justice A (1997). Follow-up study of seasonal affective disorder in Switzerland. *Psychopathology* 30: 208-214.
[102] Lavoie MP, Lam RW, Bouchard G, Sasseville A, Charron MC, Gagné AM, Tremblay P, Filteau MJ, Hébert M (2009). Evidence of a biological effect of light therapy on the retina of patients with seasonal affective disorder. *Biol Psychiatry* 66: 253-258.

[103] Hannibal J, Fahrenkrug J (2002). Melanopsin: a novel photopigment involved in the photoentrainment of the brain's biological clock? *Ann Med* 34: 401-407.
[104] Møller M, Lund-Andersen C, Rovsing L, Sparre T, Bache N, Roepstorff P, Vorum H (2010). Proteomics of the photoneuroendocrine circadian system of the brain. *Mass Spectrom Rev* 29: 313-325.
[105] Kowalska E, Brown SA (2007): Peripheral clocks: keeping up with the the master clock. *Cold Spring Harb Symp Quant Biol* 72: 301-305.
[106] Dijk DJ, Duffy JF, Silva EJ, Shanahan TL, Boivin DB, Czeisler CA (2012). Amplitude reduction and phase shifts of melatonin, cortisol and other circadian rhythms after a gradual advance of sleep and light exposure in humans. *PLoS One* 7(2): e30037.
[107] Schmoll C, Lascaratos G, Dhillon B, Skene D, Riha RL (2011). The role of retinal regulation of sleep in health and disease. *Sleep Med Rev* 15: 107-113.
[108] Blouin AG, Blouin JH, Iversen H, Carter J, Goldstein C, Goldfield G, Perez E (1996). Light therapy in bulimia nervosa: a double-blind, placebo-controlled study. *Psychiatry Res* 60: 1-9.
[109] Dunai A, Novak M, Chung SA, Kayumov L, Keszei A, Levitan R, Shapiro CM (2007). Moderate exercise and bright light treatment in overweight and obese individuals. *Obesity (Silver Spring)* 15: 1749-1757.
[110] Gooley JJ (2008): Treatment of circadian rhythm sleep disorders with light. *Ann Acad Med Singapore* 37: 669-676.
[111] Crowley SK, Youngstedt SD (2012). Efficacy of light therapy for perinatal depression: a review. *J Physiol Anthropol* 6: 31:15.
[112] Wirz-Justice A, Bader A, Frisch U, Stieglitz RD, Alder J, Bitzer J, Hösli I, Jazbec S, Benedetti F, Terman M, Wisner KL, Riecher-Rössler A (2011). A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. *J Clin Psychiatry* 72: 986-993.
[113] Rahman SA, Shapiro CM, Wang F, Ainlay H, Kazmi S, Brown TJ, Casper RF (2013). Effects of filtering visual short wavelengths during nocturnal shiftwork on sleep and performance. *Chronobiol Int* ; 30: 951-962.
[114] Casten RJ, Rovner BW (2013): Update on depression and age-related macular degeneration. *Curr Opin Ophthalmol* 24: 239-43.
[115] Samel A, Gander P (1995): Bright light as a chronobiological countermeasure for shiftwork in space. *Acta Astronaut* 36: 669-683.
[116] Cajochen C, Frey S, Anders D, Späti J, Bues M, Pross A, Mager R, Wirz-Justice A, Stefani O (1985). Evening exposure to a light-emitting diodes (LED)-backlit computer screen affects circadian physiology and cognitive performance. *J Appl Physiol* 110: 1432-1438.
[117] Reiter RJ, Tan DX, Korkmaz A, Rosales-Corral SA (2013): Melatonin and stable circadian rhythms optimize maternal, placental and fetal physiology. *Hum Reprod Update[Epub ahead of print]* PMID: 24132226.
[118]Munch M., Bromundt V (2012). Light and chronobiology: implications for health and disease. *Dialogues Clin Neurosci* 14: 448–453.
[119] Westrin A, Lam RW (2007): Seasonal affective disorder: a clinical update. *Ann Clin Psychiatry* 19: 239-246.
[120] Even C, Schröder CM, Friedman S, Rouillon F (2008). Efficacy of light therapy in nonseasonal depression: a systematic review. *J Affect Disord* 108: 11-23.
[121] Oldham MA, Ciraulo DA (2014). Bright light therapy for depression: a review of its effects on chronobiology and the autonomic nervous system. *Chronobiol Int* 31: 305-319.
[122] Martiny K, Lunde M, Simonsen C, Clemmensen L, Poulsen DL, Solstad K, Bech P (2004).Relapse prevention with citalopram in SAD patients responding to one week of bright light treatment. *Acta Psychiatr Scand* 109: 230-234.
[123] Martiny K (2004): Adjunctive bright light in non-seasonal major depression. *Acta Psychiatr Scand* Suppl 425: 7-28.
[124] Kripke DF, Risch SC, Janowsky D (1983). Bright white light alleviates depression. *Psychiatry Res* 10: 105-112.
[125] Lee HJ, Rex KM, Nievergelt CM, Kelsoe JR, Kripke DF (2011). Delayed sleep phase syndrome is related to seasonal affective disorder. *J Affect Disord* 133:573-579.
[126] Wood J, Birmaher B, Axelson D, Ehmann M, Kalas C, Monk K, Turkin S, Kupfer DJ, Brent D, Monk TH, Nimgainkar VL (2009). Replicable differences in preferred circadian phase between bipolar disorder patients and control individuals. *Psychiatry Res* 166: 201-209.
[127] Kasper S, Wehr TA, Bartko JJ, Gaist PA, Rosenthal NE (1989). Epidemiological findings of seasonal changes in mood and behaviour: a telephone survey of Montgomery County, Maryland. *Arch Gen Psychiatry* 46: 823-833.
[128] Azorin JM, Adida M, Belzeaux R (2015). Frequency and characteristics of individuals with seasonal pattern among depressive patients attending primary care in France. *Gen Hosp Psychiatry* 37: 76-80.
[129] Lam R, Beattie C, Buchanan A, Mador J (1992). Electroretinography in seasonal affective disorder. *Psychiatry Res* 43: 55–63.
[130] Roecklein KA, Wong PM, Miller MA, Donofry SD, Kamarck ML, Brainard GC (2013). Melanopsin, photosensitive ganglion cells, and seasonal affective disorder. *Neurosci Biobehav Rev* 37: 229-239.
[131] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini International Neuropsychiatric Interview (M.I.N.I.) (1998). The development and validation of a structured diagnostic psychiatric interview. *J Clin Psychiatry* 59 Suppl 20: 22–33; quiz 34–57.
[132] Williams JB, Link MJ, Rosenthal NE, Terman M (1988). Structured interview guide for the Hamilton depression rating scale, seasonal affective disorders version (SIGH-SAD). New York: New York Psychiatric Institute.
[133] Pruessner JC, Wolf OT, Hellhammer DH, Buske-Kirschbaum A, Von Auer K, Jobst S, Kaspers F, Kirschbaum C (1997). Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. *Life Sci* 61: 2539–2549.
[134] Martiny K, Lunde M, Undén M, Dam H, Bech P (2006). The lack of sustained effect of bright light, after discontinuation, in non-seasonal major depression. *Psychol Med* 36: 1247-1252.
[135] Pruessner JC, Wolf OT, Hellhammer DH, Buske-Kirschbaum A, Von Auer K, Jobst S, Kaspers F, Kirschbaum C (1997). Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. *Life Sci* 61: 2539–2549.
[136] Martiny K, Lunde M, Undén M, Dam H, Bech P (2009). High cortisol awakening response is associated with an impairment of the effect of bright light therapy. *Acta Psychiatr Scand* 120: 196-202.
[137] Martiny K, Lunde M, Unden M, Dam H, Bech P (2008). Cortisol as predictor in major depression. Poster presented at 16th AEP congress Nice. *European Psychiatry* 23 Supplement 2: S175.
[138] Paykel ES (2008). Partial remission, residual symptoms, and relapse in depression. *Dialogues Clin Neurosci* 10: 431-437.

[139] Martiny K, Refsgaard E, Lund V, Lunde M, Thougaard B, Lindberg L, Bech P (2015). Maintained superiority of chronotherapeutics vs. exercise in a 20-week randomized follow-up trial in major depression. *Acta Psychiatr Scand* 131: 446-457.

[140] Dauphinais DR, Rosenthal JZ, Terman M, DiFebo HM, Tuggle C, Rosenthal NE (2012). Controlled trial of safety and efficacy of bright light therapy vs. negative air ions in patients with bipolar depression. *Psychiatry Res* 196: 57-61.

[141] Benedetti F, Colombo C, Pontiggia A, Bernasconi A, Florita M, Smeraldi E (2003). Morning light treatment hastens the antidepressant effect of citalopram: a placebo-controlled trial. *J Clin Psychiatry* 64: 648-653.

[142] Søndergaard MP, Jarden JO, Martiny K, Andersen G, Bech P (2006). Dose response to adjunctive light therapy in citalopram-treated patients with post-stroke depression. A randomised, double-blind pilot study. *Psychother Psychosom* 75: 244-248.

[143] Lieverse R, Van Someren EJ, Nielen MM, Uitdehaag BM, Smit JH, Hoogendijk WJ (2011). Bright light treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-controlled trial. *Arch Gen Psychiatry* 68: 61-70.

[144] Martiny K, Lunde M, Bech P, Plenge P (2012). A short-term double-blind randomized controlled pilot trial with active or placebo pindolol in patients treated with venlafaxine for major depression. *Nord J Psychiatry* 66: 147-154.

[145] Artigas F, Perez V, Alvarez E (1994). Pindolol induces a rapid improvement of depressed patients treated with serotonin reuptake inhibitors. *Arch Gen Psychiatry* 51: 248–251.

[146] Celada P, Bortolozzi A, Artigas F (2013). Serotonin 5-HT1A receptors as targets for agents to treat psychiatric disorders: rationale and current status of research. *CNS Drugs* 27: 703-716.

[147] Segrave R, Nathan PJ (2005). Pindolol augmentation of selective serotonin reuptake inhibitors: accounting for the variability of results of placebo-controlled double-blind studies in patients with major depression. *Hum Psychopharmacol* 20: 163-174.

[148] Ballesteros J, Callado LF (2004). Effectiveness of pindolol plus serotonin uptake inhibitors in depression: a meta-analysis of early and late outcomes from randomised controlled trials. *J Affect Disord* 79: 137-147.

[149] Portella MJ, de Diego-Adeliño J, Ballesteros J, Puigdemont D, Oller S, Santos B, Álvarez E, Artigas F, Pérez V (2011). Can we really accelerate and enhance the selective serotonin reuptake inhibitor antidepressant effect? A randomized clinical trial and a meta-analysis of pindolol in nonresistant depression. *J Clin Psychiatry* 72: 962-969.

[150] Plenge P, Mellerup ET (2003). Pindolol and the acceleration of the antidepressant response. *J Affect Disord* 75: 285-289.

[151] Personal communication by Plenge P (22.09.2013). Unpublished data from Laboratory of Neuropsychiatry, University of Copenhagen.

[152] Debonnel G, Saint-André E, Hébert C, de Montigny C, Lavoie N, Blier P (2007). Differential physiological effects of a low dose and high doses of venlafaxine in major depression. *Int J Neuropsychopharmacol* 10: 51-61.

[153] Béïque JC, Blier P, de Montigny C, Debonnel G (2000). Potentiation by (-)Pindolol of the activation of postsynaptic 5-HT(1A) receptors induced by venlafaxine. *Neuropsychopharmacology* 23: 294-306.

[154] Aellig WH, Narjes HH, Nüesch E, Oertle RJ, Devos JE, Pacha W (1981). A pharmacodynamic and pharmacokinetic comparison of pindolol 20 mg extended release and a conventional tablet. *Eur J Clin Pharmacol* 20: 179-83.

[155] Aellig WH, Nüesch E, Pacha W (1982). Pharmacokinetic comparison of pindolol 30 mg extended release and 15 mg normal tablets. *Eur J Clin Pharmacol* 21: 451-455.

[156] Bel N, Artigas F (1993). Chronic treatment with fluvoxamine increases extracellular serotonin in frontal cortex but not in raphe nuclei. *Synapse* 15:243-5.

[157] Perry EB, Berman RM, Sanacora G, Anand A, Lynch-Colonese K, Charney DS (2004). Pindolol augmentation in depressed patients resistant to selective serotonin reuptake inhibitors: a double-blind, randomized, controlled trial. *J Clin Psychiatry* 65: 238-243.

[158] Bech P, Kastrup M, Rafaelsen OJ (1986). Mini-compendium of rating scales for states of anxiety depression mania schizophrenia with corresponding DSM-III syndromes. *Acta Psychiatr Scand* 326: 1–37.

[159] O' Sullivan RL, Fava M, Agustin C, Baer L, Rosenbaum JF (1997). Sensitivity of the six-item Hamilton Depression Rating Scale. *Acta Psychiatr Scand* 95: 379–384.

[160] Bech P. The Bech– Rafaelsen Melancholia Scale (MES) in clinical trials of therapies in depressive disorders: A 20-year review of its use as outcome measure (2002). *Acta Psychiatr Scand* 106: 252–264.

[161] Gex-Fabry M, Balant-Gorgia AE, Balant LP, Rudaz S, Veuthey J, Bertschy G (2004). Time course of clinical response to venlafaxine: Relevance of plasma level and chirality. *Eur J Clin Pharmacol* 59: 883–891.

[162] Rabiner EA, Bhagwagar Z, Gunn RN, Cowen PJ, Grasby PM (2004). Preferential 5-HT1A autoreceptor occupancy by pindolol is attenuated in depressed patients: effect of treatment or an endophenotype of depression? *Neuropsychopharmacology* 29: 1688-1698.

[163] Zanardi R, Serretti A, Rossini D, Franchini L, Cusin C, Lattuada E, Dotoli D, Smeraldi E (2001). Factors affecting fluvoxamine antidepressant activity: influence of pindolol and 5-HTTLPR in delusional and nondelusional depression. *Biol Psychiatry* 50: 323-330.

[164] Tome MB, Isaac MT, Harte R, Holland C (1997). Paroxetine and pindolol: a randomized trial of serotonergic autoreceptor blockade in the reduction of antidepressant latency. *Int Clin Psychopharmacol* 12: 81-89.

[165] Geretsegger C, Bitterlich W, Stelzig R, Stuppaeck C, Bondy B, Aichhorn W (2008). Paroxetine with pindolol augmentation: a double-blind, randomized, placebo-controlled study in depressed in-patients. *Eur Neuropsychopharmacol* 18: 141-146.

[166] Martiny K, Lunde M, Bech P (2010). Transcranial low voltage pulsed electromagnetic fields in patients with treatment-resistant depression. *Biol Psychiatry* 68: 163-169.

[167] Colacicco G, Pilla AA (1984). Electromagnetic modulation of biological processes: influence of culture media and significance of methodology in the Ca-uptake by embryonal chick tibia in vitro. *Calcif Tissue Int* 36: 167-174.

[168] Bilalis DJ, Katsenios N, Efthimiadou A, Karkanis A, Efthimiadis P (2012). Investigation of pulsed electromagnetic field as a novel organic pre-sowing method on germination and initial growth stages of cotton. *Electromagn Biol Med* 31: 143-150.

[169] Rikk J, Finn KJ, Liziczai I, Radák Z, Bori Z, Ihász F (2013). Influence of pulsing electromagnetic field therapy on resting blood pressure in aging adults. *Electromagn Biol Med* 32: 165-172.

[170] Jensen A, Watkins ML (1967). *Franz Anton Mesmer – Physician Extraordinaire*, New York: Garrett Publication/Helix press.

[171] Rahbek UL, Tritsaris K, Dissing S (2005). Interactions of low frequency pulsed electromagnetic fields with living tissue: biochemical responses and clinical results. *Oral Biosci Med* 2: 29-40.

[172] Kennedy SH, Milev R, Giacobbe P, Ramasubbu R, Lam RW, Parikh SV, Patten SB,
Ravindran AV (2009). Canadian Network for Mood and Anxiety Treatments (CANMAT). Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. *J Affect Disord* 117 Suppl 1:S44-53.

[173] Carrubba S, Marino AA. (2008). The effects of low-frequency environmental-strength electromagnetic fields on brain electrical activity: a critical review of the literature. *Electromagn Biol Med* 27: 83-101.

[174]Munro U, Munro JA, Phillips JB, Wiltschko R, Wiltschko W (1997). Evidence for a magnetite-based navigational 'map' in birds. *Naturwissenschaften* 84: 26–28.

[175] Montgomery JC, Bodznick D (1999). Signals and noise in the elasmobranch electrosensory system. *J Exp Biol 202:* 1349-1355.

[176] Kolomytkin OV, Dunn S, Hart FX, Frilot C 2nd, Kolomytkin D, Marino AA (2007). Glycoproteins bound to ion channels mediate detection of electric fields: a proposed mechanism and supporting evidence. *Bioelectromagnetics* 28: 379-385.

[177] Dissing S, Tritsaris K, Hansen AJ (2012). Pulsed electrical fields cause activation of tyrosin kinase related cellular signalling in endothelial cells leading to transcription processes and angiogenesis. *FASEB J* 26: 1129.2

[178] Thamsborg G, Floresco A, Oturai P, Fallentin E, Tritsaris F, Dissing S (2005). Treatment of knee osteoarthritis with pulsed electromagnetic fields: a randomized, double-blind, placebo-controlled study. *OsteoArthritis and Cartilage* 13: 575-581.

[179] Trock DH, Alfred Jay Bollet AJ Markoll R (1994). The Effect of Pulsed Electromagnetic Fields in the Treatment of Osteoarthritis of the Knee and Cervical Spine. Report of Randomized, Double Blind, Placebo Controlled Trials. *The journal of Rheumatology* 21: 1903-1911.

[180] Smith TL, Wong-Gibbons D, Maultsby J (2004). Microcirculatory effects of pulsed electromagnetic fields. *Orthopaedic Research* 22: 80-84.

[181] Macias MY, Battocletti JH, Sutton CH, Pintar FA, Maiman DJ (2000). Directed and enhanced neurite growth with pulsed magnetic field stimulation. *Bioelectromagnetics* 21: 272-286.

[182] Website for clinicaltrials.gov, assessed 2014 April 26: http://clinicaltrials.gov/ct2/results?term=PEMF&Search=Search

[183] Sackheim HA (2001). The definition and meaning of treatment-resistant depression. *J Clin Psychiatry* 62 Suppl 16: 10-7.

[184] Remedium ApS, Venlighedsvej 6, 2970 Hørsholm, Denmark.

[185] Bech P, Gefke M, Lunde M, Lauritzen L, Martiny K (2011). The Pharmacopsychometric Triangle to Illustrate the Effectiveness of T-PEMF Concomitant with Antidepressants in Treatment Resistant Patients: A Double-Blind, Randomised, Sham-Controlled Trial Revisited with Focus on the Patient-Reported Outcomes. *Depress Res Treat* 2011: 806298.

[186] Straasø B, Lauritzen L, Lunde M, Vinberg M, Lindberg L, Larsen ER, Dissing S, Bech P (2014). Dose-remission of pulsating electromagnetic fields as augmentation in therapy-resistant depression: a randomized, double-blind controlled study. *Acta Neuropsychiatr* 26: 272-279.

[187] Leuchter AF, Hunter AM, Krantz DE, Cook IA (2015). Rhythms and blues: modulation of oscillatory synchrony and the mechanism of action of antidepressant treatments. *Ann N Y Acad Sci* page 1-14.

[188] Karabanov AN, Siebner HR (2014). Expanding the electrotherapeutic toolkit: a perspective on transcranial pulsating electromagnetic fields (T-PEMF). *Acta Neuropsychiatr* 26: 261-263.

[189] Jin Y, Phillips B (2014). A pilot study of the use of EEG-based synchronized Transcranial Magnetic Stimulation (sTMS) for treatment of Major Depression. *BMC Psychiatry* 18;14:13.

[190] Brandon S, Cowley P, McDonald C, Neville P, Palmer R, Wellstood-Eason S (1984). Electroconvulsive therapy: results in depressive illness from the Leicestershire trial*. Br Med J* 288: 22-25.

[191] Klein E, Kreinin I, Chistyakov A, Koren D, Mecz L, Marmur S, Ben-Shachar D, Feinsod M (1999). Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. *Arch Gen Psychiatry* 56: 315-320.

[192] Loo CK, Sachdev P, Martin D, Pigot M, Alonzo A, Malhi GS, Lagopoulos J, Mitchell P (2010). A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. *Int J Neuropsychopharmacol* 13: 61-69.

[193] Kayser S, Bewernick BH, Grubert C, Hadrysiewicz BL, Axmacher N, Schlaepfer TE (2011). Antidepressant effects, of magnetic seizure therapy and electroconvulsive therapy, in treatment-resistant depression. *J Psychiatr Res* 45: 569-576.

[194] Aaronson ST, Carpenter LL, Conway CR, Reimherr FW, Lisanby SH, Schwartz TL,Moreno FA, Dunner DL, Lesem MD, Thompson PM, Husain M, Vine CJ, Banov MD, Bernstein LP, Lehman RB, Brannon GE, Keepers GA, O'Reardon JP, Rudolph RL, Bunker M (2013). Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: acute and chronic effects. *Brain Stimul* 6: 631-640.

[195] Department of Clinical Neurosciences, Scientific Institute Ospedale San Raffaele and University Vita-Salute, Milano, Italy.

[196] Dallaspezia S, Benedetti F (2011). Chronobiological therapy for mood disorders. *Expert Rev Neurother* 11: 961-970.

[197] Website for Committee on Chronotherapeutics, assessed 2015 April 26:
https://www.isad.org.uk/committees/chrono_therapy.asp

[198] Steinberg H, Hegerl U (2014). Johann Christian August Heinroth on sleep deprivation as a therapeutic option for depressive disorders. Sleep Med 15: 1159-1164.

[199] Schulte W: Kombinierte Psycho- und Pharmakotherapie bei Melancholikern. In Kranz HN, Petrilowitsch (eds.): Probleme der pharmakopsychiatrischen Kombinations- und Langzeitbehandlung. Rothenburger Gespräch, Basel, Karger 1966, pp150-169.

[200] Pflug. Depression und Schlafentzug. Neue therapeutische und theoretische Aspekte. Habilitationsschrift aus der Universitäts-Nervenklinik Tübingen, 1973.

[201] Pflug B, Tölle R (1971). Disturbance of the 24-hour rhythm in endogenous depression and the treatment of endogenous depression by sleep deprivation. *Int Pharmacopsychiatry* 6: 187-196.

[202] Kuhs H, Tölle R (1991). Sleep deprivation therapy. *Biol Psychiatry* 29: 1129-1148.

[203] Wu JC, Bunney WE (1990). The biological basis of an antidepressant response to sleep deprivation and relapse: Review and hypothesis. *Am J Psychiatry* 147: 14-21.

[204] Wu JC, Kelsoe JR, Schachat C, Bunney BG, DeModena A, Golshan S, Gillin JC, Potkin SG, Bunney WE (2009). Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. *Biol Psychiatry* 66: 298-301.

[205] Wirz-Justice A, Van den Hoofdakker RH (1999): Sleep deprivation in depression: what do we know, where do we go? Biol Psychiatry *46: 445-453.*

[206] Giedke H, Schwärzler F (2002). Therapeutic use of sleep deprivation in depression. *Sleep Med Rev* 6: 361-377.

[207] Voderholzer U, Valerius G, Schaerer L, Riemann D, Giedke H, Schwärzler F, Berger M, Wiegand M (2003). Is the antidepressive

effect of sleep deprivation stabilized by a three day phase advance of the sleep period? A pilot study. *Eur Arch Psychiatry Clin Neurosci* 253: 68-72.
[208] Wirz-Justice A, Benedetti F, Berger M, Lam RW, Martiny K, Terman M, Wu J (2005). Chronotherapeutics (light and wake therapy) in affective disorders. *Psychol Med* 35: 939-944.
[209] Holsboer-Trachsler E, Hemmeter U, Hatzinger M, Seifritz E, Gerhard U, Hobi V (1994). Sleep deprivation and bright light as potential augmenters of antidepressant drug treatment--neurobiological and psychometric assessment of course. *J Psychiatr Res* 28: 381-399.
[210] Kuhs H, Färber D, Borgstädt S, Mrosek S, Tölle R (1996). Amitriptyline in combination with repeated late sleep deprivation versus amitriptyline alone in major depression. A randomised study. *J Affect Disord* 37: 31-41.
[211] Giedke H, Klingberg S, Schwärzler F, Schweinsberg M (2003). Direct comparison of total sleep deprivation and late partial sleep deprivation in the treatment of major depression. *J Affect Disord* 76: 85-93.
[212] Giedke H, Geilenkirchen R, Hauser M (1992). The timing of partial sleep deprivation in depression. *J Affect Disord* 25: 117-128.
[213] Barbini B, Colombo C, Benedetti F, Campori E, Bellodi L, Smeraldi E (1998). The unipolar-bipolar dichotomy and the response to sleep deprivation. *Psychiatry Res* 79: 43-50.
[214] Colombo C, Benedetti F, Barbini B, Campori E, Smeraldi E (1999). Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. *Psychiatry Res* 86: 267-270.
[215] Reinink E, Bouhuys N, Wirz-Justice A, van den Hoofdakker R (1990). Prediction of the antidepressant response to total sleep deprivation by diurnal variation of mood. *Psychiatry Res* 32: 113-124.
[216] Riemann D, Wiegand M, Lauer CJ, Berger M (1993). Naps after total sleep deprivation in depressed patients: are they depressiogenic? *Psychiatry Res* 49: 109-120.
[217] Sahlem GL, Kalivas B, Fox JB, Lamb K, Roper A, Williams EN, Williams NR, Korte JE, Zuschlag ZD, El Sabbagh S, Guille C, Barth KS, Uhde TW, George MS, Short EB (2014). Adjunctive triple chronotherapy (combined total sleep deprivation, sleep phase advance, and bright light therapy) rapidly improves mood and suicidality in suicidal depressed inpatients: an open label pilot study. *J Psychiatr Res* 59: 101-107.
[218] Benedetti F, Riccaboni R, Locatelli C, Poletti S, Dallaspezia S, Colombo C (2014). Rapid treatment response of suicidal symptoms to lithium, sleep deprivation, and light therapy (chronotherapeutics) in drug-resistant bipolar depression. *J Clin Psychiatry* 75: 133-140.
[219] Gottlieb JF, Terman M (2012). Outpatient triple chronotherapy for bipolar depression: case report. *J Psychiatr Pract* 18: 373-380.
[220] Loving RT, Kripke DF, Shuchter SR (2002). Bright light augments antidepressant effects of medication and wake therapy. *Depress Anxiety* 16:1-3.
[221] Wirz-Justice A, Terman M (2012). Chronotherapeutics (light and wake therapy) as a class of interventions for affective disorders. In: Vinken PJ, Bruyn GW, editors. *Handb Clin Neurol* 106: 697-713.
[222] Ravindran AV, Lam RW, Filteau MJ, Lespérance F, Kennedy SH, Parikh SV, Patten SB (2009). Canadian Network for Mood and Anxiety Treatments (CANMAT). Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. V. Complementary and alternative medicine treatments. *J Affect Disord* 117 Suppl 1: S54-64.
[223] Benedetti F, Terman M (2013). Much ado about…a moody clock. *Biol Psychiatry* 74: 236-237.
[224] Li JZ, Bunney BG, Meng F, Hagenauer MH, Walsh DM, Vawter MP, Evans SJ, Choudary PV, Cartagena P, Barchas JD, Schatzberg AF, Jones EG, Myers RM, Watson SJ Jr, Akil H, Bunney WE (2013). Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. *Proc Natl Acad Sci U S A* 11;110: 9950-9955.
[225] Jacobs BL, Azmitia EC (1992). Structure and function of the brain serotonin system. *Physiol Rev* 72: 165-229.
[226] Gardner JP, Fornal CA, Jacobs BL (1997). Effects of sleep deprivation on serotonergic neuronal activity in the dorsal raphe nucleus of the freely moving cat. *Neuropsychopharmacology* 17: 72-81.
[227] Prévot E, Maudhuit C, Le Poul E, Hamon M, Adrien J (1996). Sleep deprivation reduces the citalopram-induced inhibition of serotoninergic neuronal firing in the nucleus raphe dorsalis of the rat. *J Sleep Res* 5: 238-245.
[228] Landsness EC, Goldstein MR, Peterson MJ, Tononi G, Benca RM (2011). Antidepressant effects of selective slow wave sleep deprivation in major depression: a high-density EEG investigation. *J Psychiatr Res* 45: 1019-1026.
[229] Vogel GW, Thurmond A, Gibbons P, Sloan K, Walker M (1975). REM sleep reduction effects on depression syndromes. *Arch Gen Psychiatry* 32: 765-777.
[230] Wiegand M, Riemann D, Schreiber W, Lauer CJ, Berger M (1993). Effect of morning and afternoon naps on mood after total sleep deprivation in patients with major depression. *Biol Psychiatry* 33: 467-476.
[231] Smeraldi E, Benedetti F, Barbini B, Campori E, Colombo C (1999). Sustained antidepressant effect of sleep deprivation combined with pindolol in bipolar depression. A placebo-controlled trial. *Neuropsychopharmacology* 20: 380-385.
[232] Neumeister A, Goessler R, Lucht M, Kapitany T, Bamas C, Kasper S (1996). Bright light therapy stabilizes the antidepressant effect of partial sleep deprivation. *Biol Psychiatry* 39: 16-21.
[233] Colombo C, Lucca A, Benedetti F, Barbini B, Campori E, Smeraldi E (2000). Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. *Psychiatry Res* 95: 43-53.
[234] Voderholzer U (2003). Sleep deprivation and antidepressant treatment. *Dialogues Clin Neurosci* 5: 366-369.
[235] Benedetti F, Colombo C, Serretti A, Lorenzi C, Pontiggia A, Barbini B, Smeraldi E (2003). Antidepressant effects of light therapy combined with sleep deprivation are influenced by a functional polymorphism within the promoter of the serotonin transporter gene. *Biol Psychiatry* 54: 687-692.
[236] Neumeister A, Praschak-Rieder N, Hesselmann B, Vitouch O, Rauh M, Barocka A, Tauscher J, Kasper S (1998). Effects of tryptophan depletion in drug-free depressed patients who responded to total sleep deprivation. *Arch Gen Psychiatry* 55: 167-172.
[237] Benedetti F, Barbini B, Bernasconi A, Fulgosi MC, Dallaspezia S, Gavinelli C, Locatelli C, Lorenzi C, Pirovano A, Radaelli D, Smeraldi E, Colombo C (2010). Acute antidepressant response to sleep deprivation combined with light therapy is influenced by the catechol-O-methyltransferase Val(108/158)Met polymorphism. *J Affect Disord* 121: 68-72.
[238] Ebert D, Feistel H, Kaschka W, Barocka A, Pirner A (1994). Single photon emission computerized tomography assessment of

cerebral dopamine D2 receptor blockade in depression before and after sleep deprivation--preliminary results. *Biol Psychiatry* 35: 880-885.
[239] Gessa GL, Pani L, Fadda P, Fratta W (1995). Sleep deprivation in the rat: an animal model of mania. Eur Neuropsychopharmacol. 5 Suppl: 89-93.
[240] Benedetti F, Smeraldi E (2009). Neuroimaging and genetics of antidepressant response to sleep deprivation: implications for drug development. *Curr Pharm Des* 15: 2637-2649.
[241] Wehr TA, Wirz-Justice A (1981). Internal coincidence model for sleep deprivation and depression. In: Koella WP, editor. *Sleep 1980.* Basel: Karger, pp 26–33.
[242] Bunney BG, Bunney WE (2013). Mechanisms of rapid antidepressant effects of sleep deprivation therapy: clock genes and circadian rhythms. *Biol Psychiatry* 73: 1164-1171.
[243] Wehr TA, Wirz-Justice A, Goodwin FK, Duncan W, Gillin JC (1979). Phase advance of the circadian sleep-wake cycle as an antidepressant. *Science* 206: 710-713.
[244] Daan S, Beersma DG, Borbély AA (1984). Timing of human sleep: recovery process gated by a circadian pacemaker. *Am J Physiol* 246(2 Pt 2): R161-83.
[245] Borbély AA, Baumann F, Brandeis D, Strauch I, Lehmann D (1981). Sleep deprivation: effect on sleep stages and EEG power density in man. *Electroencephalogr Clin Neurophysiol* 51: 483-495.
[246] Borbély AA, Wirz-Justice A (1982). Sleep, sleep deprivation and depression. A hypothesis derived from a model of sleep regulation. *Hum Neurobiol* 1: 205-210.
[247] Bunney BG, Bunney WE (2013). Mechanisms of rapid antidepressant effects of sleep
deprivation therapy: clock genes and circadian rhythms. *Biol Psychiatry* 73: 1164-1171.
[248] Mongrain V, La Spada F, Curie T, Franken P (2011). Sleep loss reduces the DNA-binding of BMAL1, CLOCK, and NPAS2 to specific clock genes in the mouse cerebral cortex. *PloS One* 6:e26622.
[249] Szuba MP, Baxter LR Jr, Fairbanks LA, Guze BH, Schwartz JM (1991). Effects of partial sleep deprivation on the diurnal variation of mood and motor activity in major depression. *Biol Psychiatry* 30: 817-829.
[250] Bosch OG, Rihm JS, Scheidegger M, Landolt HP, Stämpfli P, Brakowski J, Esposito F, Rasch B, Seifritz E (2013). Sleep deprivation increases dorsal nexus connectivity to the dorsolateral prefrontal cortex in humans. *Proc Natl Acad Sci U S A* 110:19597-19602.
[251] Clark CP, Brown GG, Archibald SL, Fennema-Notestine C, Braun DR, Thomas LS,
Sutherland AN, Gillin JC (2006). Does amygdalar perfusion correlate with antidepressant
response to partial sleep deprivation in major depression? *Psychiatry Res* 146: 43-51.
[252] Wu J, Buchsbaum MS, Gillin JC, Tang C, Cadwell S, Wiegand M, Najafi A, Klein E, Hazen K, Bunney WE Jr, Fallon JH, Keator D (1999). Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulated and medial prefrontal cortex. *Am J Psychiatry* 156: 1149-1158.
[253] Wu JC, Gillin JC, Buchsbaum MS, Schachat C, Darnall LA, Keator DB, Fallon JH, Bunney WE (2008). Sleep deprivation PET correlations of Hamilton symptom improvement ratings with changes in relative glucose metabolism in patients with depression. *J Affect Disord* 107: 181-186.
[254] Gujar N, Yoo SS, Hu P, Walker MP (2011). Sleep deprivation amplifies reactivity of brain reward networks, biasing the appraisal of positive emotional experiences. *J Neurosc* 31: 4466-4474.
[255] Ebert D, Berger M (1998). Neurobiological similarities in antidepressant sleep deprivation and psychostimulant use: a psychostimulant theory of antidepressant sleep deprivation. *Psychopharmacology (Berl)* 140: 1-10.
[256] Zanardi R, Barbini B, Rossini D, Bernasconi A, Fregni F, Padberg F, Rossi S, Wirz-Justice A, Terman M, Martiny K, Bersani G, Hariri AR, Pezawas L, Roiser JP, Bertolino A, Calabrese G, Magri L, Benedetti F, Pontiggia A, Malaguti A, Smeraldi E, Colombo C (2008). New perspectives on techniques for the clinical psychiatrist: Brain stimulation, chronobiology and psychiatric brain imaging. *Psychiatry Clin Neurosci* 62: 627-637.
[257] Benedetti F, Calabrese G, Bernasconi A, Cadioli M, Colombo C, Dallaspezia S, Falini A, Radaelli D, Scotti G, Smeraldi E (2009): Spectroscopic correlates of antidepressant response to sleep deprivation and light therapy: a 3.0 Tesla study of bipolar depression. *Psychiatry Res* 173: 238-242.
[258] Benedetti F, Bernasconi A, Blasi V, Cadioli M, Colombo C, Falini A, Lorenzi C, Radaelli D, Scotti G, Smeraldi E (2007). Neural and genetic correlates of antidepressant response to sleep deprivation: a functional magnetic resonance imaging study of moral valence decision in bipolar depression. *Arch Gen Psychiatry* 64: 179-187.
[259] Hines DJ, Schmitt LI, Hines RM, Moss SJ, Haydon PG (2013): Antidepressant effects of sleep deprivation require astrocyte-dependent adenosine mediated signaling. *Transl Psychiatry* 3: e212.
[260] Longordo F, Kopp C, Lüthi A (2009). Consequences of sleep deprivation on neurotransmitter receptor expression and function. *Eur J Neurosci* 29: 1810-1819.
[261] Voderholzer U, Fiebich BL, Dersch R, Feige B, Piosczyk H, Kopasz M, Riemann D, Lieb K (2012). Effects of sleep deprivation on nocturnal cytokine concentrations in depressed patients and healthy control subjects. *J Neuropsychiatry Clin Neurosci* 24: 354-366.
[262] Voderholzer U, Hohagen F, Klein T, Jungnickel J, Kirschbaum C, Berger M, Riemann D (2004). Impact of sleep deprivation and subsequent recovery sleep on cortisol in unmedicated depressed patients. *Am J Psychiatry* 161: 1404-1410.
[263] Baumgartner A, Riemann D, Berger M (1990). Neuroendocrinological investigations during sleep deprivation in depression. II. Longitudinal measurement of thyrotropin, TH, cortisol, prolactin, GH, and LH during sleep and sleep deprivation. *Biol Psychiatry* 28: 569-587.
[264] Davies SK, Ang JE, Revell VL, Holmes B, Mann A, Robertson FP, Cui N, Middleton B, Ackermann K, Kayser M, Thumser AE, Raynaud FI, Skene DJ (2014). Effect of sleep deprivation on the human metabolome. *Proc Natl Acad Sci U S A* 111:10761-10766.
[265] Terman M, Terman JS (2013). Chronotherapeutics: light therapy, wake therapy, and melatonin. In: Mann JJ, McGrath PJ, Roose SP, editors. *Clinical Handbook for the Management of Mood Disorders*: Cambridge University Press, pp 332-345.
[266] van Bemmel AL, van den Hoofdakker RH (1981). Maintenance of therapeutic effects of total sleep deprivation by limitation of subsequent sleep. A pilot study. *Acta Psychiatr Scand* 63: 453-462.
[267] MacLean AW, Fekken GC, Saskin P, Knowles JB (1992). Psychometric evaluation of the Stanford Sleepiness Scale. *J Sleep Res* 1: 35-39.
[268] Benedetti F, Zanardi R, Colombo C, Smeraldi E (1999). Worsening of delusional depression after sleep deprivation: case reports. *J Psychiatr Res* 33: 69-72.

[269] Kräuchi K, Cajochen C, Wirz-Justice A (2004). Waking up properly: is there a role of thermoregulation in sleep inertia? *J Sleep Res* 13: 121-127.

[270] Martiny K, Refsgaard E, Lund V, Lunde M, Sørensen L, Thougaard B, Lindberg L, Bech P (2012). Nine weeks randomised trial comparing a chronotherapeutic intervention (wake and light therapy) to exercise in major depression. *J Clin Psychiatry* 73: 1234-1243

[271] Bech P, Olsen LR, Kjoller M, Rasmussen NK (2003). Measuring well-being rather than
the absence of distress symptoms: a comparison of the SF-36 Mental Health subscale and the WHO-Five Well-Being Scale. *Int J Methods Psychiatr Res* 12: 85-91.

[272] Bech P (2004). Measuring the dimensions of psychological general well-being by the WHO-5. *QoL Newsletter* 32: 15-16.

[273] Martiny K, Larsen ER , Licht RW , Nielsen CT, Damkier P , Refsgaard E, Lunde M, Straasø B, Christensen EM, Lolk A, Holmskov J Sørensen CH, Brødsgaard I, Eftekhari SZ, Bendsen BB, Klysner R, Terp IM, Larsen JK, Vestergaard P ,Buchholtz PE, Gram LF, Bech P and Danish University Antidepressant Group (DUAG*) (2015). Relapse prevention in major depressive disorder: A four-arm randomised 6-month double-blind comparison of three fixed dosages of escitalopram and a fixed dose of nortriptyline in patients successfully treated with acute electroconvulsive treatment (DUAG-7). Pharmacopsychiatry 48:274-278.

[274] Bech, P. Clinicial Psychometrics. Oxford: Wiley-Blackwell, 2012.

[275] NIMH homepage assessed 15 March 2015: http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml

[276] Vinberg M, Miskowiak K, Kessing LV (2014). Serotonin transporter genotype, salivary cortisol, neuroticism and life events: impact on subsequent psychopathology in healthy twins at high and low risk for affective disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 48: 193-198.

[277] Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 301: 386-389.

[278] Patient Expectations and Experiences from a Clinical Study in Psychiatric Care Using a Self-Monitoring System. Lise Lauritsen, Louise Andersen, Emilia Clara Olsson, Stine Rauff, Erik Frøkjær, Lasse Benn Nørregaard, Philip Kaare Løventoft, Klaus Martiny. Poster presented at Nordic CHI14 conference 2014. ResearchGate homepage assessed 13 April 2015 on: https://www.researchgate.net/publication/267148454_Patient_Expectaions_and_Experiences_from_a_Clinical_Study_in_Psychiatric_Care_Using_a_Self-Monitoring_System

[279] Krstić J, Buzadžić I, Milanović SD, Ilić NV, Pajić S, Ilić TV (2014). Low-frequency repetitive transcranial magnetic stimulation in the right prefrontal cortex combined with partial sleep deprivation in treatment-resistant depression: a randomized sham-controlled trial. *J ECT* 30: 325-331.