CHAPTER 7. General Discussion and Conclusions

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General discussion & Conclusions
IN THIS CHAPTER THE MAJOR findings of the present thesis will be presented as well as its relevance from a theoretical and clinical standpoint. Further, the most important limitations and strengths of the design will be discussed. Finally, recommendations for the positioning of BLT in mental health care as well as future research are formulated.

INTRODUCTION
Major depressive disorder (MDD) in elderly patients is a highly prevalent and debilitating disorder, resulting in high morbidity and mortality. MDD in elderly patients is frequently accompanied by symptoms suggestive of circadian dysfunction, such as altered sleep-wake patterns, diurnal mood variation, energy level, and often, endocrine dysfunction. A deteriorating suprachiasmatic nucleus (SCN) may contribute to some of these changes. Activation of the SCN has been hypothesized as one of the mechanisms of bright environmental light (bright light treatment [BLT]) on mood, sleep, circadian rhythms, and hypothalamic-pituitary axis [HPA] activity. Light induces specialized lightsensitive retinal ganglion cells to release glutamate in the SCN through a monosynaptic pathway called the retinohypothalamic tract.

However, there is no conclusive direct evidence that SCN activation is responsible for antidepressant effects of BLT or that this would be the only pathway or mechanism of action. At present, SCN stimulation is mostly a model to explain effects of BLT in ([non] seasonal) depression. There is indirect support that SCN activation is involved. Zhou et al showed evidence that in the SCN in postmortem brains of patients with depression AVP metabolism is altered. Hofman and Swaab showed that AVP in the SCN is reduced in aging. Lucassen et al further showed, in rats, that light counteracts the age-related loss of AVP, which is a sign of reactivation. BLT also targets depression-associated neurotransmitter systems (serotonin, noradrenalin, and dopamine), and target the same brain structures as antidepressant drug treatments. In primates, subcortical projections of retinal neurons do not only involve the SCN, but also the serotonergic raphe nucleus.

HPA axis hyperactivity in MDD is of clinical relevance since it may decrease treatment outcome and increase relapse rates. Stimulation of the SCN, using bright light therapy (BLT) normalizes mood in seasonal affective disorder. BLT even is considered treatment of first choice in seasonal depression subtypes. In a previous report it was shown that bright whole-day light also normalizes mood in dementia, which is another condition with disrupted SCN functioning. Also in the
elderly, circadian rhythmicity is disrupted. Remarkably, bright light treatment in nonseasonal MDD in elderly patients has never been tested in a double-blind, placebo-controlled randomized clinical trials of sufficient sample size.

The dominant question of this thesis is whether elderly patients with a MDD benefit from bright light therapy. We, therefore, performed two types of study designs. First we performed a randomized double-blind, placebo-controlled trial designed to study the effects of bright light therapy in a group of MDD patients. Second, we performed case-control studies comparing chronobiological measures in elderly MDD patients with elderly healthy controls. The chronobiological measures we focused on in the present study were subjective sleep quality, objective sleep parameters, actigraphically measured diurnal motor activity, and social rhythm stability.

**RESULTS FROM THE TRIAL**

We conclude from our RCT that active bright light produced more antidepressant benefits than placebo light directly after 3 weeks of BLT and a continuing improvement 3 weeks after withdrawal. The fact that improvement continued after withdrawal is interesting, since it suggests that our BLT protocol induced a recovery process that lasted beyond discontinuation of treatment. Moreover, we showed that BLT also normalized circadian activity rhythms, hormonal rhythms and sleep. Interestingly, effects on depression, 24-hour urinary free cortisol (UFC) diurnal cortisol and get-up time persisted, improved or became significant only after withdrawal, whereas the other sleep measures and melatonin levels changed during BLT but returned to baseline after withdrawal. The finding suggests rather acute effects on melatonin and sleep, while effects on clinical improvement in depression symptoms and cortisol hyperactivity are initiated by the treatment but take longer to develop fully.

**ON CORTISOL DATA**

We are well aware of the pulsatile aspects of hormone secretion, but also that diurnal changes in interpulse interval, pulse width or pulse peak usually result in a well-measurable diurnal rhythm. Indeed, in our study the skewed cosine model on average showed a goodness of fit = 0.79, meaning that the model explained 79% of the variance. Pulsatility together with residual errors thus accounted for only 21% of the variance.

Be that as it may, we were aware that our saliva samples were limited to 4 sequential morning samples and 4
sequential evening samples, and that we shouldn’t be drawing conclusions about midday or midnight levels. Nevertheless the skewed cosine model is a suitable and parsimonious way to prevent occurrences that may confound plain morning and evening averages for the following reason. A sequence of morning samples may in some cases contain only samples on the downward slope, but in other cases it may also contain samples prior to the morning peak level. A plain average does not account for this, although the skewed cosine curve does; we demonstrated a good fit. We have deleted all analyses on afternoon AUC, and only included the morning and evening analyses.

Analyzing the saliva data with diurnal values shows results to be completely consistent with the skewed cosine method: no statistically significant changes in the morning curves, but a selective change in the evening level between T0 and T2: At baseline there was no statistically significant group difference in the mean morning saliva cortisol (mean 10.77 [95% CI, 7.66-13.68]). Between T0 and T1, morning saliva cortisol decreased in the BLT group from 13.1 [95% CI, 6.4-19.8] to 7.8 [95% CI, 6.0-9.6], but the morning saliva cortisol in the placebo group increased from 10.3 [95% CI, 6.6-13.9] to 24.0 [95% CI, 1.9-46.1]. At T2 relative to T0, morning cortisol in BLT group (T2: 7.6 [95% CI, 5.6-9.5]) and in the placebo group (T2: 11.2 [95% CI, 6.9-15.6]) did not differ significantly from baseline ($P=0.40$). The mean of evening saliva cortisol did not differ between the BLT and placebo groups (mean 3.5 [95% CI, 2.2-4.8]). Between T0 and T1 evening cortisol decreased in the BLT group from 3.0 [95% CI, 1.5-4.6]) to 2.3 [95% CI, 1.8-2.9], but the evening cortisol in the placebo group was unchanged at 3.6 [95% CI, 2.0-5.3] and 3.6 [95% CI, 2.8-5.2]. At T2 relative to T0, evening cortisol in the BLT group (T2: 2.2 [95% CI, 1.5-2.9]) was lower when compared with the placebo group (T2: 4.6 [95% CI, 2.1-7.2]), the difference being 2.5 [95% CI, 0.4-5.3] ($P=0.049$). In conclusion, we considered the skewed cosine model more suitable.

A hyperactive hypothalamic–pituitary–adrenal (HPA) axis has frequently been found in MDD. Antidepressants are thought to influence HPA axis activity through changes to the glucocorticoid (GRs) and mineralocorticoid receptors (MRs) and these changes are thought to be partially responsible for treatment efficacy. Short term use of SSRIs and tricyclic antidepressants (TCAs) have been found to activate the HPA axis. However, long-term use of TCAs is associated with increased cortisol suppression in the dexamethasone suppression test, and increased suppression is associated with treatment response. Also, long term use of SSRIs is associated with decreases in cortisol and normalization.
of cortisol suppression,\(^\text{17}\) although not in all studies.\(^\text{18, 19}\) Only one study reported on the association of non-TCA/non-SSRI antidepressant medication.\(^\text{20}\) Our report was the first study in MDD showing that BLT was also associated with a lowering of HPA axis hyperactivity. We consider the HPA axis normalization, as evidenced by a normalization of mean total 24-hour urinary free cortisol excretion as well as a lowering of the cortisol saliva rhythm after morning hours, as indirect biological support that BLT stimulates the SCN and thereby modifies HPA axis activity. However, it remains unclear whether the antidepressant success is mediated by the HPA axis. In the NESDA study elevated cortisol was found in both current and remitted patients with depression, suggesting that altered HPA activity reflects a biological vulnerability independent of treatment response.\(^\text{21}\) Additional randomized intervention studies are needed in order to investigate the relationship between the different cortisol indicators and treatment response.\(^\text{16, 21}\)

ON MELATONIN DATA

Individual melatonin profiles vary enormously, therefore many researchers have given up using thresholds for melatonin onsets dependent on peak values, or using fixed threshold values such as 3 or 4 pg/ml as proposed by Lewy’s work in the 1990s. 4 pg/ml is not necessarily the correct method, particularly in older patients. The precision of the Bühlmann RIA assay with a functional sensitivity of 0.6 pg/ml and a great reproducibility even in the 1-2 pg/ml range allows one to use the first point clearly above the baseline as the onset point (with the condition that the next point is even higher than this first point above baseline). In many patients (particularly low secretors) onsets around 1.5 pg/ml can be clearly established (whereas for others even 3-4 pg/ml threshold is not reliable). Therefore we did determine DLMO as the first point above baseline, with the further requirement that the next point is even higher, we had to exclude 20 incomplete series. Out of 171 complete series a DLMO could only be detected in 63 (37%). In the majority (108) of the complete series (63%) the DLMO could not be determined. Below we describe treatment effects if evaluated in this limited data-set.

At baseline there were no statistically significant group differences in DLMO (mean 8:42 PM [95% CI, 8:13-9:11]). No effect of time or time by treatment was found. Thus, between T0 and T1 DLMO did not change in the BLT group (T0: 8:41 PM [95% CI, 7:43-9:39] and T1: 8:13 PM [95% CI, 7:34-8:52], or in the placebo group (T0: 20:43 PM [95% CI, 8:13-9:11] and T1: 20:45 PM [95% CI, 8:15-9:32], repeated measures.
ANOVA ($F_{1,9} = 2.661; P=0.137$). At T2 relative to T0, DLMO in the BLT group (T2: 8:50 PM [95% CI, 8:15-9:25]) and in the placebo group (T2: 8:46 PM [95% CI, 8:15-9:17]) did not differ either.

A steepness measure of melatonin we performed, for which we previously showed the biological relevance and pointed out its potential use in a methodological paper.\textsuperscript{22} We chose to estimate the steepness of the increase because the melatonin levels we found in our samples were so low that commonly applied methods were not applicable. Mean evening saliva melatonin levels were 1.0 (95% CI, 0.7-1.3) pg/ml at T0, 2.2 (95% CI, 0.5-3.8) pg/ml at T1, and 1.4 (95% CI 0.6-2.2) pg/ml at T2.

The results obtained by the DLMO method on a limited data-set do not differ from our mixed effects linear regression model estimating the intercept as a proxy measure associated with the timing of the melatonin rise. Neither method suggests a phase advance by BLT. We prefer the mixed effect model, because it uses all available data, whereas the DLMO method excludes incomplete series and did not work in 63% of the complete series.

Attenuated day-night differences in melatonin level have been associated with both depression and aging, which may have been involved in the lower than expected levels we encountered in our study in depressed elderly people. Many,\textsuperscript{23-26} but not all,\textsuperscript{27} studies report reductions of melatonin secretion in depression compared with healthy controls, as well as in aging.\textsuperscript{28} It is expected that in elderly patients with depression melatonin levels are even lower, although the literature on melatonin in elderly depression is very sparse, even more so in studies limited to saliva melatonin. In older patients with depression, Kripke et al\textsuperscript{29} found no significant relationship with melatonin excretion or to aMT6s acrophase timing, onset, offset or duration. Loving et al\textsuperscript{30} found a phase delay in the melatonin onset in the saliva of elderly patients with depression when compared with healthy controls, which lost significance after correction for age. Lewy\textsuperscript{31} concluded in his review that many, if not all, mood disturbances have a circadian misalignment component of the phase-delay type, operationally defined as a delay in the dim light melatonin onset relative to the sleep/wake cycle.

We found it interesting that we did not find the phase advance that tends to be found with morning light. It might well be that with the low levels encountered only a full 24-hour cycle of samples is needed to demonstrate a phase advance. On the other hand, lack of an advance may be a true finding because the method was sensitive enough to detect an increase in the slope of the rise. Moreover, we did not find a phase advance...
in the saliva cortisol either.

We concluded that because melatonin levels were so low that commonly applied methods were not applicable, we could only obtain a measure of the steepness of the evening rise, which has been proposed as a biological relevant parameter of use before.22

A related question concerns whether our aged patients with depression were relatively phase advanced compared to historical / published controls. For the limited data-set the DLMO at baseline was, on average at 8:42 PM [95% CI, 8:13-9:11], comparable to historical published control values. In healthy adults, Lewy, Ahmed, Jackson & Sack32 reported an average DLMO at 9:00 PM (range 6:53 PM to 12:00 PM, close to what Burgess and Fogg33 reported (8:50 PM (1:12). Previous studies on DLMO in MDD gave conflicting results (normal melatonin peak, normal or phase-delay, rather than phase-advanced peak) which may be related to methodological differences (size of samples, disease duration, duration of drug wash-out, selection of patients and comparison of patients with not strictly matched controls).26, 34, 35 Gordijn et al36 and Buckley37 could not demonstrate any difference between MDD and healthy controls. Although we did not compare our MDD with controls, we did not find arguments for a phase advance, as comparing our findings to historical published data suggested.

ON AMBIENT LIGHTING
We collected and analyzed luxometry. 46 patients (26 BLT, 21 placebo) were treated during winter (from the end of October to the end of March) and 43 patients (14 BLT, 23 placebo) were treated in the summer ($\chi^2$=2.54 (1), $P=0.11). Patients treated with BLT or with placebo did not differ significantly in mean GSS-scores at baseline whether they were included and treated in winter or in summer. Analyses of covariance showed that wintertime did not influence outcome ($F_{1,81}=0.41, P=0.84$), nor did global seasonality score (GSS) ($F_{1,71}=0.85, P=0.43$).

At instruction, the ambient light conditions were measured by an electronic lux meter. Light intensity during morning hours was measured in the horizontal plane at the eye level, in gaze direction, of every participant who sat at the exact position on the table where they should take their light therapy hours (mean 223 (s.d., 317), range 10-1570). Patients who were randomized in the BLT group had mean (s.d.) ambient light levels of 240 (247) lux and patients who were randomized in the placebo group had mean (s.d.) light levels of 206 (378) lux, which did not differ significantly from each other ($P=0.746$). Furthermore, long-
term ambient light exposure could be estimated by a light sensor built in the actigraphs that was worn on the wrist. During daytime hours (from 10:00 AM to 3:00 PM) during the intervention weeks the mean wrist-measured light intensity was 315 (s.d., 650) lux and BLT and placebo ambient lighting conditions did not differ in a statistically significant way ($P=0.06$).

ON TREATMENT ADHERENCE

We took treatment adherence into account by several methods. First, we applied four interventions to promote compliance: (1) Patients chose a fixed starting time within 1 hour after their habitual wake-up time, (2) devices were automatically switched on and off, by clock-power supplies, (3) patients were asked to note their compliance in their trial-diaries, which were discussed during and after the trial, and (4) patients were made aware of compliance-assessments using the light sensors, which were built in the wrist-worn actimeters they wore during the entire protocol. So far the precautions.

As for the actual assessment of treatment adherence three observations suggest that compliance was high: First, visual examination of actigraphy data suggested a high degree of compliance because, during treatment-hours, motor activity was consistently low. Second, the trial diaries were almost entirely and consistently completed, with daily logs of treatment starting times and duration fitting the original instructions. Third, in order to assess adherence more precisely we estimated light exposure by a light sensor built in the actigraphs worn on the wrist. Results of these analyses are as follows. Light exposure estimated from a light sensor built in the actigraphs that was worn on the wrist showed that mean maximum light intensity during the planned exposure period was higher during (mean = 247 [s.d., 284] lux) than before BLT-weeks (mean = 73 [s.d., 102] lux; $P<0.001$), or after BLT weeks (mean = 139 [s.d., 210] lux; $P=0.001$) in the active condition. In the placebo-treated group there was no difference between luxometry during placebo (mean max lux = 176 [s.d., 238] and before (mean 180 [283] lux; $P=0.920$) or after (mean 176 [251] lux); $P=0.993$).

In conclusion, compliance is supported by the fact that only BLT-assigned patients showed elevated light exposure and exclusively during treatment-hours.

ON THE SOCIAL RESULTS

We found that lower social rhythm regularity in elderly patients with MDD contributes to the prediction of treatment response to BLT, but not to placebo. Lower social rhythm regularity seems a factor...
indicative of treatment success to BLT in elderly nonseasonal major depression. We did not find other predictors for BLT effectiveness. Especially, we did not find the atypical balance to predict response with hypersomnia, afternoon or evening slump, reverse diurnal variation (evenings worse), carbohydrate craving, as Terman did in patients with seasonal affective disorder. Our results are in line with the findings by Terman et al that social withdrawal was a negative predictor of improvement with small-to-moderate effect size. This finding is of potential clinical relevance and support the social Zeitgeber/Zeisstörer theory, postulating that social rhythm disruptions precede circadian rhythm disruptions in vulnerable individuals. Ever since Ehler’s social zeitgeber theory was published in 1988 considerable research and programs have been developed to regularize social rhythms in patients with mood disorders. In bipolar disorder the concept gave rise to the Interpersonal and Social Rhythm Therapy (IPSRT). Prigerson et al suggested that the preservation of intact social rhythms could serve to protect individuals from bereavement-induced depression. Monk et al showed that social rhythm regularity, in healthy individuals, appears to increase over the life span and hypothesized that this represents an adaptation to age-related changes in the circadian system’s sensitivity to entraining agents. Moreover, high SRM-5 scores, reflecting high social rhythm regularity, have been found in extremely well-adjusted and healthy octogenarians.

In the present study, in elderly patients with nonseasonal depression, although inducing clinical recovery, BLT failed to increase social rhythm stability. Moreover, BLT, when compared to placebo, was associated with a decrease of social rhythm regularity without changing the volume of activity, i.e. ALI-scores. In another study it was shown that SRM-5 scores of recovered depressives appeared to be similar to that of controls, and mainly driven by another person’s involvement, in that SRM-5 scores of events done alone were lower than those with the active participation of others. Thus, depressives appeared to be “borrowing” their rhythmicity from others. As BLT is the strongest Zeitgeber, we hypothesize that patients with remitted depression tolerate lower social rhythm regularity (i.e. lower SRM-5 scores) more, with increased ‘social flexibility’ as a consequence. In other words, we hypothesize that BLT ‘overrules’ the social rhythm regularity. This explanation follows Monk and Kupfer, who suggested that in advancing age the circadian system is failing in the transduction of the endogenous circadian timing system of the hypothalamic suprachiasmatic nucleus to rhythms downstream.

Several limitations to this should be discussed. At baseline, there was a slight,
but statistically significant randomization imbalance for MMSE scores, indicating that BLT allocated patients had slightly lower MMSE scores than placebo allocated patients. In another study it was shown BLT to has beneficial effects on cognition in demented elderly residents of group care facilities. However, in the present study MMSE scores were well above cut-off scores for cognitive impairments. In our regression analyses we did not find MMSE to have influenced the results. Further, we did not measure bereavement or other life events, which would allow analysing the pathway between life events and social Zeitgeber changes. We did also not measure the involvement of others in the analysis of SRM-data, which is a known determinant in SRM-5. However, the present study involves non-institutionalized elderly patients, both living alone and living with somebody, there was no randomization imbalance with respect to partnership, and partnership was of no influence on HAM-D outcome or SRM-5 outcomes.

Taken together, the present study indicates that social rhythmicity could contribute to the screening for treatment response to BLT. Longer prospective study protocols comparing on-going BLT with discontinuation in longer follow-up periods are therefore wanted.

LIMITATION

Several limitations and choices in the RCT-design should be discussed. First, at baseline a slight randomization imbalance for outcome was seen for HAM-D, indicating that BLT-treated patients had slightly higher pre-treatment severity ratings than placebo-treated patients. This difference was not reflected in the other depression severity ratings, in severity distribution or in other depression characteristics. All analyses took this into account by including it as baseline covariate in the analyses. Significance of the covariate-corrected treatment effects indicated that the antidepressant effects of BLT could not be attributed to HAM-D pre-treatment score differences.

Second, the monitoring of depression symptoms was limited to T1 and T2. If the developmental course of improvement is the focus of interest, more frequent assessments for more detailed analyses will be required. Moreover, with the positive effect of BLT we found, more data points would have further increased the statistical significance. With respect to the number of assessments, feasibility and assessment quality were the most important considerations to plan three evaluations (T0, T1 and T2). Because of limitations on trial resources we had to choose between more frequent and less demanding self-evaluations or less
frequent and more demanding higher quality interviews. The gold standard of psychometry of depression is a face-to-face interview rating. This more demanding method outperforms self-evaluations, because patients with severe depression tend to downplay the severity of their symptoms, and patients with lighter severity tend to exaggerate their symptoms.38

Third, our trial only investigated the immediate and 3 week delayed effect of a 3 week BLT treatment duration. Prolonged effects, or effects of long term BLT, therefore remain to be investigated. A large study on long-term effects of light treatment on demented elderly without the diagnosis of MDD suggests preservation of antidepressant effects, rather than habituation.9

Fourth, only 89 patients were included from a total of 444 assessed. This could have been due to several factors: 1) including active case-finding efforts; 2) strict inclusion-criteria to fulfill the requirements for a diagnosis of MDD only; and 3) the criterion of absence of seasonal affective disorder. Although the findings of this specific study are thus to be limited only to elderly people with MDD, efficacy of light treatment in elderly with a profile of milder depression is suggested by previous work.9

ON TREATMENT DURATION
We chose 3 weeks of treatment duration with the following considerations for implementing our trial with multiple follow-up assessments and treatment duration of 3 weeks. Previous trials on the efficacy of light therapy to relieve depressive symptoms in non-elderly populations have tended to apply treatment for shorter or similar duration.55 Few trials were longer.30, 56-59 Based on the experience and evidence of these trials, the Canadian Consensus Guidelines for the treatment of SAD, edited by Raymond W. Lam60 states on page 71 that: “response to light therapy generally occurs within 2 to 4 days, and a measurable improvement often is seen in 1 week. Most of the initial studies used 1-week treatment periods because statistically significant improvement could be noted within that time. Even though many patients show a clinical response at 1 week, the response rate increases after 2 weeks of light therapy.61 The few studies with treatment for more than 2 weeks also show increases in response rate at 3 to 5 weeks.”62-64

As seasonal affective disorder differs from nonseasonal affective disorders and are differentially sensitive to light knowledge and evidence from non-SAD-studies cannot be inferred from SAD guidelines, available evidence. However, our arguments to use
results from SAD are as follows. First, like Michael Terman, we regard seasonality to be on a continuous dimension from noticeable (but not disturbing) to mildly, moderately and severely disturbing, with SAD falling into the latter category. The Eastman study showed that beneficial effects of BLT in SAD were already seen after 3 weeks. Second, in the elderly, both SAD and non-SAD share the involvement of the SCN. In elderly patients with non-SAD there is preclinical and clinical evidence for involvement of the SCN.

Moreover, we expected treatment response within 3 weeks, because evidence is accumulating that the antidepressive response by BLT in non-SAD is faster than with pharmacological treatment. Even with antidepressants the majority of antidepressant responders demonstrate a significant improvement within the first 3 weeks of treatment, and it has been suggested that nonresponse for trial evaluations should be checked at 2 weeks.

Taking into consideration the non-SAD literature, selected in the reviews by Tuunainen et al., Golden et al and Even et al., most studies used short term treatment of up to 1 week. Only few studies lasted 3 weeks or longer. Of these, Benedetti et al, in their study lasting 4 weeks, showed that improvement was already detectable at week 2. In their 5 week study Martiny et al showed that treatment effects reached significance at week 1 and onward. None of the reviewed trials fulfilled the criterion for ‘long term’ treatment (more than eight weeks). The Cochrane review on BLT in non-SAD concluded that there was a trend for studies evaluating short term effects to show a slightly more beneficial effect than studies evaluating medium term studies and concluded: ‘these studies do indicate that bright light may be effective in as little as 1 week.’

In order to accommodate the genuine concern to justify our choice of 3 weeks we defend this choice by saying that because most studies thus far used short term treatment of up to 1 week, and the Cochrane review on BLT in non-SAD concluded that studies indicate BLT may be effective in as little as 1 week.”

With these considerations in mind, and considering the importance of evaluating both immediate and perpetuating response to a likely fast-acting treatment, we chose to implement a clinically feasible 3 week treatment protocol with a relatively high dosage of 60 minutes of light exposure per day, and to evaluate not only its immediate efficacy at 3 weeks, but also its perpetuating efficacy 3 weeks after completing the treatment.
RESULTS FROM THE CASE-CONTROL STUDIES

Major depression (MDD) is frequently accompanied by symptoms which can be viewed as disruptions of circadian rhythms. Social Zeitgebers like daily activities, mealtimes, or social interactions are known to entrain circadian rhythms, and disruptions in social Zeitgebers have been hypothesized to trigger depression. It remains unknown to what extent social support protects against social rhythm disruptions. To our knowledge studies in MDD measuring social rhythmicity and social support are lacking. Using a case-control design, we examined the role social support (SS) may play on social rhythmicity in depression. 213 elderly MDD patients and 183 healthy controls (HC) completed a social rhythm metric (SRM-5) during 1 week, and questionnaires like the social support list-interactions-34 and discrepancies-34, and negative interactions as well as measures of well-being, self-efficacy and self-sufficiency.

Patients with MDD showed lower social rhythm regularity as well as lower measures of social support when compared to HCs. In HCs high social support was correlated with low social rhythm regularity, suggesting that increases in social support in combination with a healthy organization of biological circadian rhythms allows the social rhythm regularity to become less rigid. Interestingly, in elderly patients with MDD, no correlation between social support and social rhythm regularity was found, suggesting that patients, with hampered biological circadian rhythms have a blunted response to social stimuli and may, therefore, benefit from additional supportive treatment strategies. The strong social Zeitgebers of highly regular daily routine may be necessary for the successful entrainment of the aging circadian system that has lost some of its responsiveness to cues. Available literature related to social cognitive functioning in nonseasonal MDD show that patients with MDD are impaired in their ability to decode mental states from observable social information (e.g. facial expression). Recently, it has been argued that interventions in the treatment of depression should take these deficits of patients with depression into account, specifically aim to improve the understanding and interpretation of social information. In addition it might be useful to include psychosocial treatments and social skills training into standard treatment protocols.

MDD patients in the present study were less healthy as measured on all dimensions of the SF-20, had more ADL and instrumental ADL disability, showed a worse quality of sleep, and showed lower
well-being than healthy controls. Our data not only replicate and extend the findings of Szuba et al,\textsuperscript{89} as well as those of Brown et al,\textsuperscript{90} reporting significantly lower social rhythm stability in elderly major depressed patients than in elderly healthy controls.

Elderly patients with nonseasonal MDD in the present study were less healthy as measured on all dimensions of the SF-20, had more ADL and instrumental ADL disability, showed a worse quality of sleep, and showed lower well-being than HCs. Our data replicate and extent the findings of Szuba et al,\textsuperscript{17} as well as those of Brown et al,\textsuperscript{18} reporting significantly lower social rhythm regularity in elderly patients with MDD than in elderly HCs. However, our findings are in contrast with those of Stetler et al\textsuperscript{19} reporting no differences in social rhythm regularity. However, the outpatients in Stetler’s study were nonelderly patients and social rhythms were analysed from only 4 non-consecutive days over a 7-day span, with therefore a lower resolution.

The results of this study must be interpreted in the context of several limitations. First, the cross-sectional nature of the current data limits inference about causal directional relationships. Second, we did not measure bereavement or other severe life events. It is generally accepted that deficient SS elevates the risk of MDD and that SS protects against MDD onset. To assess the temporal and cascade effect relationship of zeitgebers, circadian rhythm disruptions, and symptoms, postulated by the social zeitgeber hypothesis, longitudinal studies are needed in which social rhythmicity assessment is combined with circadian and clinical measures.

Our actigraphy study is the first study on subjective sleep quality, objective actigraphic sleep parameter estimates and activity rhythm parameters, and their association in a large cohort of elderly MDD patients and matched controls.

Subjectively impaired sleep quality in elderly patients with MDD was frequently reported, but not detectable in the objective sleep measures assessed by actigraphy. The subjectively impaired sleep quality in elderly patients with MDD was not detectable in the objective sleep parameters estimated by actigraphy. We did find longer nocturnal intervals of sleep bouts (length of rest uninterrupted by movements in patients with depression than in healthy controls), but this could be explained by the use of benzodiazepines, since benzodiazepines are shown to elongate sleepbouttime.\textsuperscript{96} Moreover, when the patients who reported taking benzodiazepines were excluded from the analysis mean sleep-bout times did not differ between patients and controls, and all other results were unaltered.

It is a ‘well-known’ phenomenon
that objective sleep parameter estimates and subjective sleep quality do not necessarily correspond. The fact that subjectively impaired sleep quality in MDD patients did not go together with objective sleep parameter estimates, may explain that age-related fragmentation of sleep, is being equally present in patients with MDD and controls, but reported as more burdensome in patients with MDD. Another interpretation is that actigraphy fails to validly assess the sleep alterations in MDD that lead to subjective complaints. However, this discrepancy has been reported before, also as measured by the more sensitive polysomnography method.

We found that total 24-hour motor activity in elderly patients with MDD was lower than in HCs, which was especially significant in the M10-period, a measure of mean waking activity. These results are in line with what is known from the literature. Finazzi et al found adolescent depression to be related to lower M10. Raoux et al reported a motor activity increase in the 13:00-20:00 hour period after treatment response and Ueda et al reported lower rates of activity in patients with MDD v. controls in the 12:00-18:00 hour period, as did Iverson in more severely primary care depressed out-patients when compared to less severely depressed and nondepressed groups.

Another notable finding was that psychomotor variables, including psychomotor slowing, did not differ between subtypes, the melancholic, the atypical and typical subtype. Several researchers found that both medicated and unmedicated melancholic patients differed from nonmelancholic in the degree and nature of their psychomotor disturbances. Motor slowing has, therefore, become one of the main indicators of the melancholic subtype of depression. However, there is debate about whether psychomotor slowing is a key marker of melancholic depression, or a sign of symptom severity in depression. Moreover, in elderly patients studies are limited.

The present study has several limitations. The cross-sectional nature of the current data limits inference about causal directional relationships. Second, actigraphy is known to overestimate total sleep time and sleep efficiency, as well as to underestimate sleep-onset latency and wake after sleep onset when compared with polysomnography. These inaccuracies of actigraphy could theoretically have led to smaller differences between groups. Despite these limitations, our findings confirm motor activity disturbances in elderly patients with MDD, characterized by lower daytime activity levels, irrespective of subtype. We found no motor activity...
disturbances during night-time. Patients with MDD had lower subjective sleep quality, but no significant differences in any of the objective sleep parameter estimates, suggesting that age-related fragmentation of sleep is equally present in MDD and HCs, but is experienced as more burdensome in MDD.

Our results confirm the feasibility of actigraphy in the detection of psychomotor disturbances in patients with MDD, as well as to provide an objective sleep analysis providing different information than from subjective questionnaires. In the treatment of sleeping problems in MDD, therefore, actigraphy may be of help in the reality testing of sleeping problems, and could hence convince patients to limit the use of benzodiazepines as sleep promoting agents. Our findings warrant further studies to assess the contribution of the biological clock to the pathogenesis and symptoms of MDD.

The results on the SRM-5 scores are consistent with what is known from the literature. Previous research shows that patients with MDD have less stable social rhythms. Several studies showed that depression severity is inversely related to social rhythmicity. The SRM-5 score, which can be considered as the diary equivalent of the actigraphically derived inter-daily stability of motor activity (IS) variable, correlated with each other significantly. To the best of our knowledge we are the first to report SRM-5 and IS to be related variables. However the SRM-5 score was lower in patients than in controls, but the IS did not differ between patients and controls.

CONCLUSIONS

 Returning to the central issue of this thesis, whether BLT is an effective treatment option for elderly patients with a major depressive disorder, we can conclude the following. We designed and performed a lege artis randomized controlled clinical trial and incorporated advanced methods directing treatment adherence, and combined the use of psychiatric clinical data with biological neuroendocrine data. We performed the largest controlled clinical trial of bright light among patients with depression over age 60. Our study yielded a reasonably clear outcome: bright light produced more antidepressant benefit than placebo in patients with nonseasonal MDD. Moreover, we found indirect support for the contention that therapeutic effects may in part be mediated by enhancements of circadian system functioning. That a relatively robust effect size was obtained in 3 weeks is of interest in itself. The effect size was reasonably large as compared to what might be expected of pharmacotherapy,
and it occurred irrespective of the participants were using concomitant antidepressants or not. This is an important finding with immediate clinical relevance for a common disorder in the elderly. These results support inclusion of chronotherapeutic strategies in the treatment options for elderly patients with nonseasonal MDD. BLT may provide a viable alternative for patients who refuse, resist or do not tolerate antidepressants.

**FUTURE RESEARCH**

More, and longer, prospective research data are now needed, with longer follow-up periods, as well as projects implementing BLT in the treatment arsenals for elderly patients with nonseasonal MDD, as an alternative or adjuvant to antidepressant medication. Of course, continuing clinical trials with long term follow-up, meta-analyses and routine outcome measuring are mandatory. Moreover, studies optimizing treatment protocols are needed, including studies examining BLT combining other chronotherapeutic approaches. Further, studies and protocol adaptations are wanted for other indications, like adolescents with nonseasonal major depression.

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CHAPTER 7. General Discussion and Conclusions