Summary
THE RESEARCH IN THIS THESIS focusses on the effects of bright light treatment (BLT) in elderly patients with a major depressive disorder (MDD). This is relevant because of several reasons. We live in an aging society, MDD is a highly prevalent and debilitating disorder, resulting in high morbidity and mortality. According to the World Health Organization MDD by 2020, depression will be worldwide the leading condition in terms of disability and loss of quality of life, just after cardiac disease. The causes and mechanisms leading to MDD are largely unknown. However, several lines of evidence point at an involvement of the biological clock in the brain. 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 light treatment (BLT) on mood, sleep, circadian rhythms, and hypothalamic-pituitary axis (HPA) activity. Light induces specialized light sensitive retinal ganglion cells to release glutamate in the SCN through a monosynaptic pathway called the retinohypothalamic tract. Further, BLT targets depression-associated neurotransmitter systems (serotonin, noradrenalin, and dopamine), and target the same brain structures as antidepressant drug treatments.

Riemersma van der Lek et al showed 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 (RCT) of sufficient sample size. In addition, the beneficial effects of BLT on seasonal depression are well accepted. BLT is a potentially safe, nonexpensive and well tolerated treatment option.

The primary aim of the present thesis was to test whether BLT is an effective treatment for elderly patients with MDD. The research comprised two study designs. First, we performed a randomized double-blind, placebo-controlled trial (RCT) designed to study the effects of BLT 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.

Chapter 2, 3 and 4 cover the experimental section of the thesis.\(^\text{16-18}\) Our hypotheses were twofold. First, we expected BLT to lower depressive symptoms. Second, we expected this to be mediated by improved circadian functioning, as indirectly indicated by enhanced sleep and hormone rhythms. We designed (Chapter 2) the RCT for a total of 126 participants of 60 years and older with a diagnosis of major depressive disorder (MDD, DSM-IV/SCID-I).\(^\text{16}\) The treatment was a home-based treatment in patients to be recruited through referrals of psychiatric out-patient clinics and from case-finding in general practitioners’ offices in the Amsterdam region. After inclusion participants were randomly allocated to the active (bright blue light; approximately 7500 lux) or the placebo (dim red light; approximately 50 lux) condition. For this we used two BLT boxes type HF 3304 per subject, from which the light bulbs had been covered with bright blue- or dim red light-permitting filters. At 3 time points several endocrinological, psychophysiological, psychometrically, neuropsychological measures are performed: just before the start of light therapy, after completion of 3 weeks therapy period, and 3 weeks thereafter. The study was conducted (Chapter 3) with 89 out-patients 60 years or older who had MDD underwent assessment at baseline (T0), after 3 weeks of treatment (T1), and 3 weeks after the end of treatment (T2).\(^\text{17}\) The main outcome measure was the mean improvement in Hamilton Scale for Depression (HAM-D) scores at T1 and T2. Intention-to-treat analysis showed Hamilton Scale for Depression scores to improve with BLT more than placebo from T0 to T1 (7%; 95% confidence interval, 4%-23%; \(P=0.03\)) and from T0 to T2 (21%; 7%-31%; \(P=0.001\)). At T1 relative to T0, get-up time after final awakening in the BLT group advanced by 7\% (\(P\leq0.001\)), sleep efficiency increased by 2\% (\(P=0.01\)), and the steepness of the rise in evening melatonin levels increased by 81\% (\(P=0.03\)) compared with the placebo group. At T2 relative to T0, get-up time was still advanced by 3\% (\(P=0.001\)) and the 24-hour urinary free cortisol level was 37\% lower (\(P=0.003\)) compared with the placebo group. The evening salivary cortisol level was decreased by 34\% in the BLT group compared with an increase of 7\% in the placebo group (\(P=0.02\)). We concluded that in elderly patients with MDD, BLT improved mood, enhanced sleep efficiency, and increased the upslope melatonin level gradient.

In addition, BLT produced continuing improvement in mood and an attenuation of cortisol hyperexcretion after discontinuation of treatment.
Endogenously generated circadian rhythms are synchronized with the environment via Zeitgebers, of which daylight and social rhythms are the most important. MDD is associated with low social rhythm regularity, reflecting deteriorating daily life structure. However, it has never been studied whether low social rhythm regularity is, therefore, predictive for response to bright light treatment. Chapter 4 examined the effects of BLT on social rhythmicity and describes how social rhythm stability contributes to the prediction of treatment response. We determined Social Rhythm Metric-5 item version (SRM-5) scores before treatment, in which a lower score represents lower regularity, and correlated these with the percentages improvement on the 17 item version of the HAM-D at T1. We found that a lower SRM-5 score at baseline was associated with more clinical improvement on the HAM-D in the BLT group ($r = -0.502, P = 0.004$), but not at all in the placebo group ($r = 0.002, P = 0.992$). The mean SRM-5 score in the BLT group was lower in responders (4.61; s.d., 1.14) than in nonresponders (5.58; s.d., 0.71; $P = 0.008$). At the SRM-5 score cut-off of $\leq 5$, the relative risk (RR) of improvement on the HAM-D of $\geq 50\%$ was 6.14 (95% CI, 0.94 to 39.81). We concluded that low baseline SRM-5 scores contribute to the prediction of response on BLT in elderly patients with MDD, suggesting that low social rhythm regularity reflects the need for strong Zeitgebers to successfully entrain the circadian system.

According to the social Zeitgeber/Zeitstörer theory, psychosocial factors, such as life events, chronic stress, or lack of social support systems, may decrease circadian rhythm regularity in MDD. However, the effect of social support on rhythm regularity has never been investigated in MDD. Chapter 5 examines if and how social rhythmicity and social support are interconnected in MDD. Therefore, we performed a case-control study on the relation of social support (SS) with social rhythm regularity in 213 elderly patients with MDD and 183 elderly healthy controls (HC). Social rhythm regularity was studied by the social rhythm metric (SRM-5), in which a lower score represents less regularity. Social support was assessed with the social support list-interactions-34 (SSL-I), in which a lower score reflects lower amounts of support, and discrepancies-34 (SSL-D), in which lower scores represent less deficit in desired support, and negative interactions (SSL-N), in which a lower score reflects less negative social interactions. We found that in HCs social support was negatively correlated with social rhythm regularity (SSL-I, $r = -0.31$; SSL-N, $r = -0.43$; SSL-D, $r = -0.23$). Compared with HCs, elderly patients with MDD experienced lower social support (all $P \leq 0.001$) and lower social rhythm regularity.
In patients with MDD social support was not correlated with SRM-5 scores (all $r_s$<0.01; all $P<$0.05).

We concluded that 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.

MDD is frequently accompanied by subjective sleep complaints. It is unknown, however, how these are associated with objective indices of disturbances of sleep and the 24-hour activity rhythm. We reported the first study on subjective sleep quality, objective actigraphic sleep parameter estimates and activity rhythm parameters, and their association in a large cohort of 93 elderly MDD patients and 74 matched controls (Chapter 6). Actigraphic data quantified the sleep-wake rhythm and objective sleep parameters. The Pittsburgh Sleep Quality Inventory (PSQI) was used to assess subjective sleep quality. Depression severity was measured by the Montgomery-Åsberg Depression Rating Scale (MADRS).

We found that the activity during the 10 most active daytime hours (M10) was 21% lower in MDD patients (27.8 ± 11.2) than in HCs (35.3 ± 15.1) ($P$=0.002) and was inversely correlated with depression severity according to the MADRS ($r$=.373; $P$=0.001). MDD patients had a significantly higher mean PSQI (9.5 ± 4.1) than HCs (4.1 ± 3.0) ($P<$0.0001), reflecting significantly more poor sleepers (70%>cutoff-score of 5; PSQI mean 9.9 ± 3.8) than in HCs (17%; PSQI mean 6.2 ±1.2). None of the actigraphic sleep estimates differed between MDD patients and HCs, or were correlated with the MADRS.

We concluded that subjectively impaired sleep quality in elderly patients with MDD was frequently reported, but not detectable in the objective sleep measures assessed by actigraphy. Our results suggest that the age-related fragmentation of sleep is equally present in MDD and HCs, but is experienced as more burdensome in MDD.

We can finally conclude that we designed, performed and presented the largest RCT with BLT in nonseasonal MDD patients over age 60, and that our study yielded a reasonably clear outcome: bright light had a better antidepressant
effect than placebo. 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. Antidepressant drugs often need more time to evolve into significant effects. The effect size was reasonably large as compared to what might be expected of pharmacotherapy, and it occurred irrespective of using concomitant antidepressants or not. Additionally, we assessed social rhythms and actigraphy in elderly patients with MDD and HCs. We found that these methods may have practical applications, since SRM-5 scores contribute to the prediction of response on BLT in elderly patients with MDD, suggesting that low social rhythm regularity reflects the need for strong Zeitgebers to successfully entrain the circadian system. We further confirmed the feasibility of actigraphy in detecting psychomotor disturbances in patients with MDD and in providing objective sleep measures, which resulted in information that differed from that obtained by subjective questionnaires. Therefore, in the treatment of sleeping problems in MDD, actigraphy may be of help in a realistic assessment of sleeping problems.

Our findings warrant further studies to assess the contribution of the biological clock to the pathogenesis and symptoms of MDD. Our results might have immediate clinical relevance for a common disorder in the elderly. The results support inclusion of chronotherapeutic strategies in the treatment of elderly patients with nonseasonal MDD. BLT may provide a viable alternative for patients who refuse, resist or do not tolerate antidepressants. 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 monitoring are mandatory. Moreover, studies optimizing treatment protocols are needed, including studies examining the combination of BLT with other chronotherapeutic approaches. Further, studies and protocol adaptations are wanted for other indications, like adolescents with nonseasonal major depression. Chapter 8, therefore, elaborates on the evolving repertoire of chronotherapeutics in MDD (in Dutch).
REFERENCES


