Feasibility and Efficacy of Morning Bright Light Therapy for Depressed Adolescents in an Acute Psychiatric Care Setting

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Lethargics are to be laid in the light, and exposed to the rays of the sun

for the disease is gloom.

Aretaeus of Cappadocia (120 - 180 A.D.)
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1 Introduction

1.1 Juvenile Depression

1.1.1 General Characteristics and Prevalence

Depression is one of the most prominent health problems affecting mood as well as mental and physical conditions. Symptoms include an existing loss of interest and pleasure in almost all activities, disturbances of appetite, sleep, psychomotor functioning, and a decrease of energy. Moreover, difficulties in thinking and decision-making, loss of self-esteem, feelings of guilt as well as suicidal thoughts or attempts are dominating the disorder (American Psychiatric Association; APA, 2000a; Rush, 2007). Based on community samples, prevalence rates for depression are as high as 5 – 9% in women and 2 – 3% in men including a lifetime risk of 10 – 25% and 5 – 12%, respectively. Although a first major depressive episode can occur at any time during life, the average onset of a first episode is in the mid-20’s (Kessler et al., 2003).

It was not until the late 1970’s that the possibility of depression in children and adolescents, also referred to as juvenile depression, was reported (Essau, 2009). Before that time, investigators were of the general notion that children and adolescents were cognitively too immature to develop depression as seen in adults. Nowadays, the scientific community acknowledges juvenile depression as a frequent and debilitating condition. The mean age of onset of the first juvenile depressive episode is about 15 years (Essau, 2009; Lewinsohn, Clarke, Seeley, & Rohde, 1994), where an association is found between earlier onset and female gender (Giaconia, Reinherz, Silverman, & Pakiz, 1994). Juvenile depression and depression in adults show a similar clinical picture, though there are differences with respect to physical, emotional, cognitive, and social developmental stages (Birmaher et al., 1996; Lewinsohn, Pettit, Joiner, & Seeley, 2003; American Academy of Child and Adolescent
Psychiatry (AACAP), 2007). The clinical presentation of juvenile depression might rather include mood lability, somatic complaints, temper outbursts, irritability and low frustration tolerance as well as social withdrawal. Moreover, sleep disturbances and persistent problems with the sleep-wake rhythm have been reported (Chorney, Detweiler, Morris, & Kuhn, 2008; Ivanenko, Crabtree, Obrien, & Gozal, 2006), that are present in about 75 % of adolescents with depression (Ivanenko, 2004).

Full depression is diagnosed if the following symptoms are present every day for a period of two weeks or longer (for an overview see Table 1).

**Table 1 Diagnostic and Statistical Manual (DSM-V): Criteria for Major Depression**

1) Depressed mood (for children and adolescents also: irritability)
2) A reduced level of interest or pleasure in most or all activities
3) Significant loss or gain of weight (decreased or increased appetite)
4) Difficulty falling or staying asleep (insomnia), or sleeping more than usual (hypersomnia)
5) Behavior that is agitated or slowed down (others should be able to observe this)
6) Fatigue or diminished energy
7) Thoughts of worthlessness or extreme guilt
8) Reduced ability to think, concentrate, or make decisions
9) Frequent thoughts of death or suicide (or a suicide attempt)

At least five of the nine symptoms above for two weeks or more, for most of the time almost every day are required, representing a change from prior functioning. One of the symptoms must be either 1) depressed mood, or 2) loss of interest.

Adapted from Clarke and Harvey (2012).

Like in adults, juvenile depression is one of the most frequent disorders in adolescence. Prevalence rates are comparable to those reported for adults (Kessler et al., 2003), and the figures are increasing among younger children (Lewinsohn et al., 1994). For
children, prevalence is about 2 %, which rises to 4 – 8 % in adolescents (Birmaher et al., 1996). Approximately 5 – 10 % of children and adolescents show subsyndromal symptoms of depression. One depressive episode in adolescence increases the risk for a second one in the following five years up to 50 – 70 % (Emslie et al., 1997), possibly leading to severe consequences; in the long-term, depression might lead to physical illness, early pregnancies, poor academic and psychosocial functioning, increased rates of smoking, and to obesity (Thapar, Collishaw, Pine, & Thapar, 2012; APA, 2000a; APA, 2000b; AACAP, 2007). Besides depression itself, juvenile depression also predicts a range of other mental health problems later in life. These include anxiety disorders, substance abuse, and bipolar disorder (Thapar et al., 2012; Ferguson, Horwood, Riddler, & Beauvais, 2005; Copeland, Shanahan, Costello, & Angold, 2009; Kim-Cohen et al., 2003; Bardone et al., 1998). It constitutes a major risk factor for suicide, as it is the second-to-third leading cause of death in adolescence (Windfuhr et al., 2008).

Research observations indicate that the increase of depression among the younger children and adolescents can be considered a particular problem of current times. While there is a lack of clear explanations of that finding, one can assume that an earlier onset of puberty, changes of family structures, and the presence of negative life events play a crucial role (Lewinsohn et al., 1993). Moreover, increased chronic stressors (of educational nature) are present and might influence depressive development. Childhood poverty (Gilman, Kawachi, Fitzmaurice, & Buka, 2003), family dysfunctioning (Hill, Pickles, Rollinson, Davies, & Byatt, 2004) as well as parental psychopathology (Jaffe et al., 2002) are also contributing to juvenile onset of depression. Particularly for females, additional risk factors have been proposed including low birth weight (Costello, Worthman, Erkanli, & Angold, 2007), early pubertal timing, an increase in pubertal hormones (Angold, Worthman, Costello, & Hayward, 2003; Shanahan, Copeland, Costello, & Angold, 2011), as well as increased reported stress levels (Silberg et al., 1999; Nelson, Leibenluft, McClure, & Pine, 2005). Inherited factors
also play a big role in early-onset depression. To late adolescence heritability increases from zero (childhood) to around 30 – 50 % (Thapar & Rice, 2006). Although consistent evidence is still scarce, it is presumed that juvenile depression, like other early-onset forms of illness, might represent a strong genetic sub-form of depression (Todd, Neuman, Geller, Fox, & Hickok, 1993).

1.1.2 Treatment Approaches and their Limitations

Due to certain similarities of clinical features and neural activities, juvenile depression might be viewed as an early-onset sub-form of depression in adults; however, a clear distinction has to be made for treatments and treatment responses (Thapar et al., 2012). There is a range of opinions about best treatment practices from differently accepted practices and clinical guidelines across countries (Thapar, Collishaw, Potter, & Thapar, 2010). Especially, the use of antidepressant drugs in children and adolescents younger than 18 years of age are based on consensus rather than on evidence (Thapar et al., 2012), which raises ethical concerns. There is only scarce evidence concerning long-term effects of antidepressant medication, since intervention studies are predominantly focusing on short-time effects without taking into account maturational factors. Although cognitive behavioural therapy (CBT) might be the treatment of choice for milder depression, in more severe cases CBT alone might not be sufficient. Two meta-analyses investigating the use of CBT in depressive children and adolescents revealed that CBT is an effective treatment option. However, effect sizes were rather small (0.3), indicating moderate efficacy (Weisz, McCarty, & Valeri, 2006; Klein, Jacobs, & Reinecke, 2007).

Tricyclic antidepressants that can be used for treating depression in adults are not a treatment option for juvenile depression, as they do not seem to be effective (Hazell,
O’Conell, Heathcote, Robertson, & Henry, 1995). If medication is necessary, the primary choice of antidepressant drug treatment is the use of selective serotonin reuptake inhibitors (SSRI’s; Birmaher & Brent, 2007). Fluoxetine is such an antidepressant, which is most frequently used in adolescents. It blocks serotonin reuptake and increases serotonin stimulation of somatodendritic 5-HT\textsubscript{1A} and terminal autoreceptors (Gardier, Malagïè, Trillat, Jacquot, Artigas, 1996). Thus, adaptive changes in the neuronal function lead to improved mood and decreased anxiety via enhanced serotonergic neurotransmission. Fluoxetine is the only medication approved by the U.S. Food and Drug Administration for the use in children and adolescents with depression. It has shown the best medication effect - placebo ratio compared to other SSRI’s. However, SSRI’s do not seem more than moderately effective in adolescents with depression. Although good response rates are found (between 40 – 70 %), considerable placebo responses are also observed (between 30 – 60 %) (Birmaher & Brent, 2007; Kennard et al., 2009). One of the reasons for a possible ineffectiveness of medication might be the maturational stages of the serotonergic and noradrenergic systems (Bylund & Reed, 2007). Further disadvantages of the use of antidepressants are the side effects: dry mouth, nausea, and dizziness, amongst others (Ferguson, 2001). Several studies reported increased suicidal thoughts after antidepressant drug treatment, which induced a debate on drug administration within this sensitive population. The meta-analysis of Bridge et al. (2007) supported these findings and was able to show that a small but significantly increased relative risk can be found for spontaneous reported suicidality during treatment. However, considering the data gathered since the use of SSRI’s for adolescent depression has started, an overall dramatic decline of adolescent suicide was found (Olfson, Shaffer, Marcus, & Greenberg, 2003). Nowadays, investigators and clinicians share the opinion that the benefits of drug administration outweigh the risks of it if the patients are carefully monitored for suicidal thoughts and actions.
Another treatment option, especially in case of more severe forms of depression, is the usage of a combination of treatments. When considering combination treatments (CBT plus antidepressant medication), a general assumption is that these might elicit more beneficial effects on depression than each treatment alone. Study outcomes, however, indicate better results of combination treatments including fluoxetine and CBT mainly for adolescents with mild to moderate depression (Curry et al., 2006). Results of the largest, highly-controlled clinical trial including participants with juvenile depression (March et al., 2004) reflect on maximal efficacy for treatment with fluoxetine plus CBT with a 3-month remission rate of about 37% (Kennard et al., 2006) with response rates of maximum 71% (March et al., 2004).

Whereas mild and moderate depressive symptoms seem to benefit from CBT, medication or a combination of both, adolescents with a more severe form of depression are in need of alternative treatment approaches. Especially in case of co-morbid sleep disturbances, treatment efficacy might be limited. In the TADS study (March et al., 2004), insomnia was the most common residual symptom among depressed adolescents who had not yet progressed to full remission (Kennard et al., 2006; Clarke & Harvey, 2012). In depressed adults, it was shown that polysomnogram profiles (PSG) indicative of sleep disorder did not respond to “depression CBT” than patients with normal sleep (Thase, Simons, & Reynolds, 1996). Moreover, in depressed youth a decreased sleep efficiency and delayed sleep onset predicted depression recurrence after treatment (Emslie et al., 2001). Two large, double-blind randomized-controlled trials (RCT) indicated a negative impact of sleep disturbances on treatment response (Emslie et al., 2012). Adolescents were less likely to respond to fluoxetine when additionally suffering from sleep disturbances. Considering the high rates of co-morbidity of depression and sleep difficulties, treatments are needed that positively influence depressive symptoms and sleep difficulties by acting, for example, on the circadian level.
1.1.3 The Link between Affective and Circadian Functioning

The circadian rhythm is the natural rhythm of night (darkness) and day (light) regulating our life (Boyce & Barriball, 2010). It is regulated by interactions between a homeostatic and a circadian process, timing the occurrence as well as the architecture of sleep (Borbély & Achermann 1999). The circadian process, the so-called internal “human clock”, is located in the Suprachiasmatic Nucleus (SCN) in the anterior hypothalamus. It regulates circadian changes of cortisol, melatonin, thyroid hormone, and core body temperature. In addition, circadian “clock” - genes manage these processes via feedback loops. The homeostatic process, on the other hand, is wake-dependent and regulates our drive to sleep. When sleep was too short, a “sleep debt” is present that increases the homeostatic drive, which results in an increased need for deep sleep (Luca, Luca, & Calandra, 2013).

It is not surprising, that a disrupted circadian rhythm can have severe consequences on emotional functioning and health in general. When the sleep-wake cycle is interrupted, unstable, or shifted (e.g., due to shift working), dysphoria, an increased susceptibility to mood swings, poor functioning as well as an increased health risk can be found (Moore-Ede, 1993; Brown et al., 2009; Moser, Schaumberger, Schernhammer, & Stevens, 2006; Wirz-Justice, Bromundt, & Cajochen, 2009). Sleep phase delays, the preference to sleep at later hours, are common in healthy adolescents (Caskardon, Wolfson, & Seifer, 1998). Being an “evening-type” with a circadian preference towards eveningness, hence with the time preference of being mentally and physically active later during the day and the evening, has been linked to affective and behavioural problems (Gau et al., 2007). Suicidality, hyperactivity as well as substance use are identified as possible long-term consequences of being an “evening-type” (Goldstein, Hahn, Hasher, Wiprczycka & Zelazo, 2007; Lange & Randler, 2011; Van der Heijden, Sonneville & Swaab, 2013). “Morning-types”, on the other hand, show less daytime impairments and fewer behavioural and emotional problems (Schlarb, Sopp, Ambiel & Grünwald, 2013). With regards to sleep disturbances, research findings assume a strong link
between sleep disturbances and behavioural problems in adolescents (Dahl & Lewin, 2002; Fallone, Owens & Deane, 2002; Meijer, Reitz, Dekovic, van den Wittenboer & Stoel, 2010). Sleep quality and subjective feelings of one’s own sleep seem to affect daytime functioning and affect regulation (Neitzert Semler & Harvey, 2005; Van Dongen, Maislin, Mullington & Dinges, 2003). Poor sleep quality undermines emotional regulation during the following day by increasing emotional reactivity (Fallone et al., 2002). At the neuronal system, it was shown that circuits involved in emotion regulation and circuits involved in sleep regulation show a bi-directional interaction (Saper, Cano, & Scammell, 2005).

Regarding disturbances of circadian functioning in mood disorders, three distinct groups have to be differentiated: Shifts of circadian phase (phase advances/ phase delays), diminution of circadian amplitude, and day-to-day variability to circadian entrainment. In depression, disruptions of the circadian rhythm and, consequently, of sleep are frequently found as a co-morbidity. Specifically, findings indicate increased variability in day-to-day rhythms, low circadian amplitude, and abnormal circadian timing (either too late or too early; Germain & Kupfer, 2008). In depressed adolescents, co-morbid sleep problems are present in about 75 % (Ivanenko & Johnson, 2008). Thereby, both circadian rhythms and the homeostatic process of sleep have shown alterations (Borbèly & Achermann, 1999). With regards to sleep, depression has been linked to problems with sleep onset, sleep maintenance, waking-up early and daytime sleepiness (Dahl & Lewin, 2002; Chellappa, Schröder, & Cajochen 2009). Due to delayed sleep onset, depressive adolescents often have reduced sleeping time, a delayed sleep onset, and shortened latency of rapid-eye-movement sleep (REM-sleep; Brand & Kirov, 2011). The presence of co-morbid sleep disturbances seems to be associated with a more severe form of juvenile depression, including a longer duration of depressive episodes, and stronger impairment in psychosocial domains (Sunderajan et al., 2010; O’Brien et al., 2011). Underlying biological mechanisms of this co-morbidity, however, remain unexplained. It is assumed that brain regions involved in depression are also
influencing the regulation of the sleep-wake cycle (Salgado-Delgado, Tapia Osorio, Saderi, & Escobar, 2011).

Besides depression, in many other psychiatric illnesses severe circadian rhythm disturbances and sleep problems play a leading role (e.g. in attention-deficit hyperactivity disorder (ADHD), posttraumatic disorder and eating disorders; Brand & Kirov, 2011; Wirz-Justice, Bromundt & Cajochen, 2009; Ivanenko & Johnson, 2008). Until now, there is not much knowledge about causal links in the circadian-sleep/ psychopathology axis, but it is assumed to go in both directions, independent of specific diagnoses (Table 2).

Table 2 The circadian-sleep/ psychopathology axis

| 1) Most psychiatric illnesses are accompanied by sleep disturbance |
| 2) Some disorders have sleep disturbance as a diagnostic criterion (e.g. depression) |
| 3) Sleep disturbance may precede the illness episode |
| 4) Circadian sleep-wake cycle disorders have high psychiatric co-morbidity |

Adapted from Wirz-Justice, Benedetti, & Terman, 2009.
1.2 Morning Bright Light Therapy (BLT)

1.2.1 Mechanisms of Action – Direct and Indirect Effects of BLT

Morning bright light therapy (BLT) is the systematic use of light as a therapeutic agent for treating circadian irregularities, and improving mood (Pail et al., 2011). The mechanism of action is twofold, where an indirect and a direct effect of BLT are assumed: With the "indirect" circadian pathway, light, as a so called zeitgeber, falls onto the retina and is transduced to the SCN via a rethino-hypothalamic tract. This is achieved by retinal ganglion cells containing melanopsin, a photopigment which is sensitive to light (Hattar et al., 2003). As a result, the sleep hormone melatonin is inhibited in the SCN. By this mechanism, wakefulness is promoted. Also, phase shifts of the circadian rhythm, an increase in amplitude of the circadian signal (leading to to higher day-to-day stability), or both effects appear as a consequence (Wirz-Justice et al., 2009; Gooley, 2008; Wirz-Justice, 2006). Terman, Terman, Lo, and Cooper (2001) could show that the magnitude of the therapeutic effect of BLT was correlated to the advancement of magnitude of circadian phase, supporting efficacy of the circadian pathway (see Figure 1). In addition, there are “direct” effects of light on mood. Aan het Rot et al. (2008) could show that, in line with the tryptophan depletion paradigm, using BLT was able to prevent tryptophan depletion-mediated depression. Especially for non-seasonal depression, one might assume that the action of BLT is associated with an augmentation of serotonergic as well as noradrenergic transmission systems with more light eliciting higher levels of serotonin (Stephenson, Schroder, Bertschy, & Bourgin, 2012; Stastny et al., 2003).
Figure 1 The mechanism of action of BLT: Light falls onto the retina and travels to the SCN via the retino-hypothalamic tract. Consequently, melatonin production is inhibited and wakefulness is promoted, possibly leading to increased circadian amplitudes and shifted circadian phases.

1.2.2 Effects of BLT on Depression in Adults

Back in the early 1980’s, it was the observation that light is able to shift circadian phases by suppressing melatonin in animals that resulted in using light as a therapeutic modality for seasonal depression, which is called seasonal affective disorder (SAD; Rosenthal et al., 1984; Lewy, Sack, Singer, White, & Hoban, 1988). When the additional depressogenic effects of melatonin were postulated, BLT received considerable attention within the scientific community. More than seventy studies and two meta-analyses were conducted recommending BLT as first-line treatment for SAD. Therapeutic effects in SAD were shown to be mediated by the influence of the circadian rhythm, which resulted in circadian phase shifts (Terman et al., 2001).

Soon, due to co-morbid sleep disturbances, positive effects of BLT also on non-seasonal depression were assumed and led to first clinical trials. Comparing seasonal and non-
seasonal depression, a significant higher efficacy of BLT in seasonal than in non-seasonal depression can be found, in terms of improving severity of depression and in terms of percentage of responders (Even et al., 2008). Nevertheless, for adults, meta-analytic evidence has proven that BLT can be considered a potent alternative to antidepressant drug treatment in both seasonal and non-seasonal depression (Golden et al. 2005; Al-Karawi & Jubair, 2016) with a faster onset of action and fewer side effects than alternative treatments (Lam et al., 2006).

In depression, 60% of adult patients treated with BLT improved their depression scores by more than 50% (Goel et al., 2005), and about one week of treatment was necessary to elicit antidepressant effects with remission rates of up to 80% (Terman et al., 2001). Comparing one week of BLT to a placebo condition, it was shown that efficacy was similar to 4-16 weeks of treatment with antidepressant drugs (Kripke, 1998). The largest BLT study in non-seasonal depression (N= 102) with a long duration (five weeks) showed that BLT can be considered as efficient as adjuvant treatment with the SSRI sertraline (Martiny et al., 2005). Especially with adjuvant antidepressant treatment, BLT was more efficacious in reducing depressive symptoms than the placebo light condition (Loving, Kripke, & Shuchter, 2002; Prasko et al., 2002; Martiny, Lunde, Unden, Dam, & Bech, 2005) with a more rapid and more profound improvement when combined with an SSRI (Benedetti et al., 2003; Martiny, 2004).

Whereas some studies treating non-seasonal depression with BLT as monotherapy yielded inconsistent results due to a considerable heterogeneity of study designs (Epperson et al., 2004; Yamada, Martin-Iverson, Daimon, Tsujimoto, & Takahashi, 1995; Loving, Kripke, Elliott, Knickerbocker, & Grandner, 2005; Goel et al., 2005), the most recent meta-analysis showed a very clear picture (Al-Karawi & Jubair, 2016). Al-Karawi and Jubair (2016) included a total of 419 patients and revealed that the exposure to BLT as monotherapy with a
medium-term exposure of 2 – 5 weeks (without concomitant antidepressants) was most efficacious on depression of non-seasonal type.

Because of the circadian mechanisms of action, BLT has shown to be effective for other symptoms besides depression as well. It may induce a stabilization of circadian functioning, and for example, consequently improve sleep disturbances such as difficulties with sleep onset and difficulties sleeping through the night (Gooley, 2008). In 2005, due to its convincing efficacy, a work group of the American Psychiatric Association suggested the use of BLT as a first-line treatment for both seasonal and non-seasonal depression (Golden et al., 2005). Even et al. (2008) as well as Al-Karawi and Jubair (2016) indicated that, at least subgroups of non-seasonally depressed patients might considerably benefit from the use of BLT due to its effects on the serotonergic system. Presumably, for patients with a disrupted circadian rhythm and/ or sleep disturbances, efficacy can be assumed and treatment might be superior to other treatment approaches.

1.2.3 Effects of BLT on Depression in Children and Adolescents

Thanks to its simplicity and rare side effects, BLT can be used to treat depression and sleep disorders throughout the entire life span (Wirz-Justice et al., 2009). In spite of the positive results for adults, in adolescents, trials investigating feasibility and efficacy of BLT for non-seasonal depression are scarce. First BLT trials were conducted in the 1990’s and showed promising results for treating SAD and sleep disturbances with light (Sonis et al, 1987; Mghir & Vincent, 1991). Swedo et al. (1997) enrolled 28 children and adolescents (7 - 17 years) with a paediatric form of SAD. After one week of treatment with one hour of BLT depression scores were significantly decreased in parent ratings. Self-ratings showed a similar trend, however, they did not reach significance. Unfortunately, it remained unclear whether
the observed effect was a result of BLT or of the control condition with dawn simulation, or the combination of both methods.

In non-seasonal depression, a randomized cross-over trial with mildly depressed adolescents between 14 and 17 years of age showed that add-on BLT was superior to a dim-light placebo condition. Unfortunately, the sample size in this study was small (N= 28), and an appropriate control condition was absent due to the cross-over design (Niederhofer & von Klitzing, 2012). Since almost all studies involving children and adolescents differed in type of depression, total duration, and light intensities which were used, these results have to be considered preliminary and be interpreted with caution.

When treating children and adolescents with light, certain aspects should be taken into account. First, children and adolescents might differ in the needed dose of BLT because of maturational differences. For example, younger patients until the age of forty transmit much more light to the retina than those of older people, thus, absorb higher light doses. Moreover, an intriguing finding indicated that dysregulated circadian rhythm patterns in children are comparable, independent of whether they were diagnosed with seasonal or non-seasonal depression (Glod, Teicher, Polcari, McGreenery, & Ito, 1997). This finding might imply that efficacy of BLT treatment in children and adolescents with non-seasonal depression might differ and even be better than in adults with non-seasonal depression, where inconsistent results were reported. Moreover, when treating children and adolescents with light, one particular problem may arise: Non-compliance. One has to keep in mind that the chronotype, hence the circadian preference, changes with age (Roenneberg et al., 2004). In adolescence, circadian preferences are naturally shifted towards eveningness. There is a strong peer pressure to socialize late into night which might make it difficult to explain an adolescent participant the benefit of advancing the circadian rhythm, possibly complicating the implementation of BLT treatments.
1.2.4 A Novel Field of BLT Application: Affective and Behavioural Dysregulation

During the last few years, researchers have increasingly acknowledged the potential of BLT. It has become more accepted that BLT can be used as co-treatment for any psychiatric disorder in which circadian irregularities or sleep disturbances are present. This led to initiating studies investigating novel applications of BLT including antepartum depression, premenstrual dysphoric disorder, Bulimia nervosa, dementia, Parkinson’s disease amongst others with promising results (Wirz-Justice et al., 2009).

When considering the intimate relationship between emotion regulation, circadian functioning and sleep disturbances, one might take into account spreading BLT to a mood disorder condition among children and adolescents that has been discussed in recent literature: affective and behavioural dysregulation. Affective and behavioural dysregulation is a condition characterized by abnormal baseline mood (including irritability, anger and sadness, “affective storms”), hyperarousal and temper outbursts (Leibenluft 2011; Holtmann et al., 2007). Like in depression, dysregulation of affect and behaviour has consistently been found to be associated with sleep disturbances and disruptions of circadian functioning (Ayer et al., 2009; Holtmann, Goth, Wöckel, Poustka & Bölte, 2008; Legenbauer, Heiler, Holtmann, Fricke-Oerkermann & Lehmkuhl, 2012; Mehl et al., 2006). Specifically, circadian dysfunctions including reduced need for sleep, disturbances of sleep continuity at sleep onset and through the night, lower sleep efficiency, reduced REM sleep, and impaired daytime behaviour have consistently been reported (Mehl et al., 2006; Harvey, 2009). Legenbauer et al. (2012) evaluated whether sleep disturbances and symptoms of affective and behavioural dysregulation in school children were related. They found that restless legs, level of sleep onset/ maintenance problems, nocturnal events, and impaired daytime behaviour were significantly more present in children with symptoms of affective and behavioural
dysregulation, compared to healthy children and children with a sub-clinical form of symptoms.

Treatment approaches for affective and behavioural dysregulation include mood stabilizers and stimulants and have shown some positive effects (Waxmonsky et al., 2008; Dickstein et al., 2009). Also, CBT indicated improvements of depressive symptoms, mood lability and global functioning (Waxmonsky et al., 2012). Like in depression, achieving full remission of the symptomatology of affectively and behaviourally dysregulated adolescents is difficult, and significant impairments seem to remain even after successful treatment with CBT and medication (Waxmonsky et al., 2008). In a “phenotype-similar” disorder, ADHD, BLT has been shown to directly elicit symptom reductions after three weeks of treatment (Ryback, McNeely, Mackenzie, Jain, & Levitan, 2006). Both, decreases in subjective and objective measures of core ADHD pathology as well as improved mood were found. A circadian phase advance seemed to be the strongest predictor for improved core ADHD pathology. It is logical to assume that, like in depression and ADHD, one influencing factor on treatment outcome might be the presence of circadian disturbances. Considering the preliminary results of light application for ADHD with positive influences on affective and behavioural regulation and on circadian functioning, BLT might constitute a reasonable co-treatment for symptoms of affective and behavioural dysregulation itself.

1.3 Summary and Unresolved Issues

Circadian irregularities and sleep disturbances (problems with sleep onset and/ or sleep maintenance, poor sleep quality) often co-occur in juvenile depression, which is one of the most frequent disorder in adolescence (Kessler et al., 2003). They contribute to depression onset and -maintenance (Ivanenko & Johnson, 2008; Sunderajan et al., 2010; O’Brien et al., 2011). In addition, co-morbid sleep disturbances have shown to be the most common residual
symptom when depression is incompletely remitted (Nierenberg et al., 2010; Carney et al., 2007; Clarke & Harvey, 2012). For mild to moderate depression treatments including CBT, SSRI’s or combinations of both are possible approaches. Efficacy, however, has been found to be limited since SSRI’s, for example, do not seem more than moderately effective, especially in more severe cases of depression, and when co-morbid sleep disturbances are present (Birmaher & Brent, 2007; Kennard et al., 2009).

An alternative treatment influencing depression, circadian functioning, and, thereby, sleep disturbances is by conducting morning BLT. It is an effective, rapid, safe, and inexpensive method which is well tolerated (Michalak & Lam, 2002). In adults, though some studies were of poor quality or showed heterogeneous trial protocols, considerable effects on depressive symptoms, and on circadian functioning have been observed for depression (Golden et al. 2005; Even et al., 2008; Al-Karawi & Jubair, 2016). Because of its favorable risk-to-benefit ratio (Terman & Terman, 1999), the use of BLT in children and adolescents seems a reasonable choice. However, there are still substantial gaps of knowledge when considering applying morning BLT in this sensitive population, especially regarding a feasible treatment protocol for adolescent inpatients in an acute psychiatric setting. It can be assumed that, like in adults, by using add-on morning BLT depressive symptoms, problems with the circadian rhythm, and sleep can be treated mutually, possibly going beyond effects of sole depression treatment. Compliance, however, might be worse than in adults due to social peer pressure to socialize late into the night, which is common in adolescence. One aim of this work, therefore, was to set up a detailed protocol for BLT in depressed children and adolescents being in an intensive psychiatric care setting (Chapter 2.1).

In adolescents, the effects of BLT on depression, circadian functioning, and sleep are preliminary but promising (Swedo et al., 1997; Niederhofer & von Klitzing, 2012). Up till now, there is currently no randomized - controlled study investigating the effects of add-on BLT on non-seasonal juvenile depression in unmedicated inpatients in an intensive
psychiatric care setting. Although it seems likely, there is no clear knowledge whether two weeks of 45 minutes of daily morning BLT can be effective for improving depressive symptoms, shifting and stabilizing circadian rhythms, and/or improving sleep parameters in moderately to severely depressed adolescents (Chapter 2.2).

Since recent literature suggested that BLT is an effective co-treatment for any psychiatric disorder in which circadian irregularities and sleep disturbances are present (Wirz-Justice et al., 2009), one might consider using BLT in another adolescent mood disorder as well: affective and behavioural dysregulation. This mood disorder comprises a disabling phenotype with symptoms of affective and behavioural dysregulation including “affective storms”, irritability, and hyperarousal. Like in juvenile depression, in affective and behavioural dysregulation co-morbid circadian irregularities and sleep disturbances have been observed (Mehl et al., 2006; Legeinbauer et al., 2012), that possibly influence emotional regulation and daily functioning in a negative way, worsening overall functioning and mood, respectively. Thus, the recovery of correct internal-external circadian synchronization should be considered a possible treatment strategy not only for juvenile depression but also for affective and behavioural dysregulation (Chapter 2.3). For a potential clinical implementation of BLT as a treatment approach for symptoms of affective and behavioural dysregulation, explorative studies investigating effects on mood, sleep, and circadian functioning are needed (Chapter 2.4).
This thesis aims to reply to the following major questions:

1. **What can be a feasible and easy-to-apply trial protocol for moderately to severely depressive adolescent inpatients in an acute psychiatric care setting?**

   This question will be addressed in the trial protocol outlined in chapter 2.1.

2. **Will a 2-week morning BLT intervention result in improved depression scores, subjective sleep parameters and a shift of circadian preference?**

   This question is main part of the second manuscript, a randomized-controlled trial, outlined in chapter 2.2.

3. **What is the rationale for expanding morning BLT to another mood disorder that is frequently seen in adolescents, affective and behavioural dysregulation?**

   This question will be addressed in a hypothetical review, indicating positive effects of BLT that go beyond depression treatment, illustrated in chapter 2.3.

4. **Is morning BLT an efficacious add-on treatment for depressive adolescents with additional symptoms of affective and behavioural dysregulation?**

   The fourth study consists of a sub-sample of the randomized-controlled study (Chapter 2.2) with a focus on direct effects of morning BLT on symptoms of affective and behavioural dysregulation, sleep parameters and circadian preference, outlined in chapter 2.4.
2 Publications and Contributions

This chapter is comprised of the following articles that were either published or accepted for publication up to submission of the thesis. My own contribution to the publications include: Conceiving the research project, designing the study and tailoring the study protocol, conducting the intervention, and analyzing the data. All authors contributed to the writing of the manuscript with me, Sarah Bogen, as the lead author, respectively. Publication Nr. 2 was written with a shared first authorship.


Further publications can be found at the end of this thesis.
2.1 Morning light therapy for juvenile depression and severe mood dysregulation: study protocol for a randomized controlled trial

This manuscript is the first of its kind to address the complexity of a feasible intervention protocol for conducting morning BLT as add-on treatment in an intensive psychiatric care setting with depressed adolescents. Specifically, it explains the trial design, rationale, and setup as a randomized and placebo-controlled treatment approach for medication naïve moderately to severely depressed adolescents who partly show symptoms of severe mood dysregulation. A total of 60 inpatients between 12 and 18 years are planned to be included. They will be randomly allocated to either the active light condition (10,000 lux) or to the inactive placebo light condition (approximately 100 lux). To control for possible expectation bias participants will be instructed that aim of the study will be an evaluation of two different kinds of bright light therapy. The rationale for using bright light therapy for a total of two weeks, 45 minutes each morning in a group setting is explained. A comprehensive test battery evaluating depression severity, circadian preference, sleep, symptoms of affective and behavioural dysregulation, among others, will be assessed pre- versus post-treatment and during a 3-week follow-up, respectively. Furthermore, the rationale for assessing the dim-light melatonin onset to monitor changes of the circadian rhythm on a physiological level will be explained. Data analyses will be based on the intention-to-treat population.
Morning light therapy for juvenile depression and severe mood dysregulation: study protocol for a randomized controlled trial

Sarah Bogen1*, Tanja Legenbauer1, Thorsten Bogen1, Stephanie Gest1, Thomas Jensch1, Silvia Schneider2 and Martin Holtmann1

Abstract

Background: The prevalence of depression in young people is increasing. The predominant co-morbidities of juvenile depression include sleep disturbances and persistent problems with the sleep-wake rhythm, which have shown to influence treatment outcomes negatively. Severe mood dysregulation is another condition that includes depressive symptoms and problems with the sleep-wake rhythm. Patients with severe mood dysregulation show symptoms of depression, reduced need for sleep, and disturbances in circadian functioning which negatively affect both disorder-specific symptoms and daytime functioning. One approach to treating both depression and problems with the sleep-wake rhythm is the use of light therapy. Light therapy is now a standard therapy for ameliorating symptoms of seasonal affective disorder and depression in adults, but has not yet been investigated in children and adolescents. In this trial, the effects of 2 weeks of morning bright-light therapy on juvenile depression and severe mood dysregulation will be evaluated.

Methods/design: A total of 60 patients with depression, aged between 12 and 18 years, in some cases presenting additional symptoms of affective dysregulation, will be included in this trial. Morning bright-light therapy will be implemented for 2 weeks (10 sessions of 45 minutes each), either with ‘active’ light (10,000 lux) or ‘inactive’ light (100 lux). A comprehensive test battery will be conducted before and after treatment and at follow-up 3 weeks later, to assess depression severity, sleep, and attention parameters. Melatonin levels will be measured by assessing the Dim Light Melatonin Onset.

Discussion: In this pilot study, the use of morning bright-light therapy for juvenile depression and severe mood dysregulation shall be evaluated and discussed.

Trials registration: Current Controlled Trials ISRCTN89305231

Keywords: Bright-light therapy, Depression, Adolescents, Sleep disturbances, Severe mood dysregulation
symptoms can lead to serious negative psychosocial consequences, including impaired academic and occupational functioning, high-risk sexual activity, and social difficulties [8]. Moreover, the predominant symptoms of juvenile depression implicate sleep disturbances and persistent problems with the sleep-wake rhythm [9,10], which are present in about 75% of adolescents with depression [11].

Second, treating juvenile depression is difficult. The available treatments have substantial shortcomings, and remission rates of moderate to severe depression are low [12,13]. Although cognitive behavioral therapy (CBT) is the treatment of choice for mild depression, CBT alone might not be sufficient in more severe cases. Several randomized controlled trials (RCTs) have indicated no or only small differences between pharmacotherapy with a selective serotonin reuptake inhibitor (SSRI), psychotherapy, and placebo (for an overview, see the American Academy of Child and Adolescent Psychiatry website [14]). Combination trials of both SSRIs and psychotherapy, a treatment that is commonly implemented in clinical practice, have not shown superiority to treatment with either therapy alone, and remission rates have been reported to be less than 40% [14,15]. Another important point is that treatment research has primarily focused on acute treatment, whereas early-onset depression is often chronic and recurrent. One influencing factor might be the presence of co-occurring sleep disturbances, which often remain as a residual symptom even after successful acute treatment [13]. These problems with the sleep-wake rhythm have been suggested to be a robust risk factor for the development of both the first depressive episode and recurrent episodes [1]. Sleep disturbances and insomnia presenting in juvenile depression are associated with higher depression severity, greater fatigue, and higher rates of suicidal behavior [16]. Emslie et al. noted in two large, double-blind RCTs [17] that sleep disturbances may negatively affect treatment response, as adolescents receiving treatment with the SSRI fluoxetine were less likely to respond to the treatment if they also had sleep disturbances. Based on these results, it is essential that sleep disturbances are adequately assessed and co-treated consistently along with the depression. However, there is as yet no evidence-based treatment for insomnia in adolescents with depression [17].

One possible non-pharmacological treatment approach for ameliorating depressive symptoms and co-occurring sleep disturbances is morning bright-light therapy, which has been used successfully for adults [18,19]. Light therapy has primarily been studied in patients with seasonal affective disorder (SAD) and has been shown to have good efficacy in ameliorating depressive symptoms in this subgroup. In adults with SAD, Lam et al. [20] reported that light therapy was as efficient as antidepressant treatment with fluoxetine, but had a faster onset of action and fewer side effects. The effects of light therapy are apparent after about 1 week of treatment [21], and remission rates of up to 80% have been reported for SAD [22]. In addition, Even and colleagues [19] carried out a systematic review based on 15 studies, and reported efficacy of light therapy as an adjuvant treatment to antidepressants in non-seasonal depression as well. However, they concluded that the evidence for the effects of light therapy alone (without antidepressant) was still inconsistent [19].

Light therapy has also been shown to be effective for other symptoms besides depression. For example, it may induce stabilization of the circadian rhythm (the biological rhythm controlling the sleep-wake cycle) and thereby, improve difficulties with sleep onset and difficulties sleeping through the night [23]. This is of particular interest because an intimate relationship between sleep and emotion regulation has been reported [24], with the consequences of disturbed sleep including symptoms such as heightened impulsivity and aggressive behavior. Preliminary evidence indicates that light therapy has a positive influence on behavior, irritability and attention parameters [25-27]. Furthermore, it has been suggested that, independent of specific diagnoses, the severity of psychiatric symptoms increases and long-term outcomes worsen when circadian disturbances are present [28], reinforcing the crucial relationship between sleep and regulation of emotions. Therefore, it is reasonable to assume that light therapy might be a useful method of stabilizing circadian functioning and thereby inducing more general improvements on emotional regulation. Despite these positive results in adults, there have only been very few studies investigating light therapy for adolescents. One RCT of children and adolescents with SAD showed that 1 week of light therapy significantly decreased parent-rated depressive symptoms [29]. A more recent 1-week trial of light therapy as an adjunctive treatment for young people with mild depression showed significant improvements in depression scores on the Beck Depression Inventory (BDI) from baseline to the end of therapy in the active treatment group [30]; however, participants received concomitant CBT and pharmacotherapy during the trial, which may have led to additional positive effects.

One phenotype that has a high prevalence rate in clinical populations and that elicits considerable problems with emotional regulation, depression, and circadian disturbances is severe mood dysregulation (SMD). Children and adolescents with SMD show severe affective and behavioral dysregulation, including irritable mood, hyperarousal, and increased reactivity to negative emotional stimuli [31,32]. Characteristics of SMD include not only depressive symptoms that might develop into MDD later on [33], but also
circadian dysfunctions such as reduced need for sleep, disturbances in sleep continuity at sleep onset and through the night, lower sleep efficiency, reduced rapid eye-movement (REM) sleep and impaired daytime behavior, which have consistently been reported [34-36]. The initial treatment approaches, similar to those for pediatric bipolar disorder and attention deficit hyperactivity disorder (ADHD), include mood stabilizers and stimulants, and have shown some positive effects [37,38]. A novel psychosocial treatment with CBT indicated improvements in depressive symptoms, mood lability, and global functioning [39]. Although these initial treatment approaches were reported to have some positive effects on SMD symptoms, children and adolescents with SMD and additional ADHD were more likely to remain significantly impaired than those with only ADHD after a 3-week combination trial with stimulants and behavior modification therapy [37]. Therefore, a wider range of treatment approaches for SMD is needed, as those that have been evaluated to date have shown only limited improvements. It is possible that, as in juvenile depression, circadian disturbances might be an influencing factor on treatment outcome in SMD. Considering that preliminary results of light application besides SAD and MDD have shown positive influences on affective and behavioral regulation and on circadian functioning, light therapy might constitute a reasonable co-treatment for SMD symptoms as well [40].

The proposed study is an RCT of bright-light therapy in juvenile depression. We plan to enroll 60 adolescents with depression. We hypothesize that 2 weeks of morning bright-light therapy will improve depressive symptoms and additional sleep disturbances in these adolescents. On an exploratory basis, the study will additionally evaluate the outcomes of morning light therapy on SMD symptoms.

### Methods/design

#### Participants and recruitment

Participants of this study will be recruited from the inpatient unit of the LWL (University Hospital Hamm, Ruhr University Bochum, Germany), a tertiary-care hospital for child and adolescent psychiatry. The hospital provides child psychiatric care for a population of 1.6 million inhabitants, covering both urban and rural areas, and is the sole provider of inpatient care serving the study area.

All patients between 12 and 18 years who are referred to the hospital will be screened consecutively for participation. Patients with moderate or severe depression (according to the International Classification of Diseases, version 10; ICD-10), based on parent and child interviews and assessed using the second edition of the BDI (BDI-II [41]), will be included in the trial. Diagnoses will be confirmed using the Diagnostic Checklist for Depressive Disorders [42] conducted by a clinical psychologist or child psychiatrist. Presence of co-morbid disorders will be allowed, excluding bipolar 1 disorder and schizophrenia. The specific eligibility criteria of the study are listed in Table 1.

#### Ethics and written consent

The study has been approved by the medical ethics committee of the Ruhr-University Bochum, Germany (registration number 3996–11), and will be conducted in accordance with the Helsinki Declaration. Before entering the study patients will be informed about the study objectives, study design, and potential risks by one of the main investigators and will also receive this information in writing. Patients will be informed about their right to withdraw from the study at any time. Written consent will be obtained from the persons in charge with primary custody. After informed consent is obtained, the

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**Table 1 Eligibility criteria**

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<th>Inclusion criteria</th>
<th>Moderate to severe depression (ICD-10/BDI-II)</th>
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<td>Being 12 to 18 years of age</td>
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<td>Ability to understand character and individual consequences of the trial</td>
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<td>Written informed consent of the person with primary custody must be available before enrolment in the trial</td>
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<tr>
<th>Exclusion criteria</th>
<th>Acute suicidal tendencies</th>
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<td>Treatment with antidepressants</td>
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<td>Treatment with beta-blockers</td>
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<td></td>
<td>Treatment with high-potency neuroleptic drugs</td>
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<td></td>
<td>Diagnosis of bipolar 1 disorder or schizophrenia</td>
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<td></td>
<td>Diseases of the eye with involvement of the retina</td>
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<td>Pregnancy or lactation</td>
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therapist in charge will be informed by mail about the patient entering the study.

Randomization and blinding
After screening, patients will be randomized and allocated to either the active light intervention (experimental group; 10,000 lux) or to the inactive light intervention (control group; 100 lux). Randomization will be carried out by randomly drawing group allocations by hand from a randomizer box in which the number of possible group allocations is equal. For practical reasons, the primary investigator of the study who is performing the randomization and delivering the treatments (but is not involved in outcome ratings) will be aware of the participants’ allocation, but all therapists on the patients’ units will be blinded to the allocation groups.

Interventions
Interventions will be conducted following the protocols described by Wirz-Justice et al. [43]). Based on empirical evidence indicating good results for light therapy with a duration of 7 to 14 days for non-seasonal depression [18,19], two parallel interventions will be created, each lasting 2 weeks, and will be conducted in the mornings, in addition to usual treatment in the respective treatment units.

Experimental group
Patients randomly allocated to the experimental group will receive 2 weeks of active morning light therapy with 10,000 lux at eye level in gaze direction (LD 110; DAVITA Medizinische Produkte GmbH & Co. KG, Kleve, Germany), with each session lasting for 45 minutes. The therapy will start about 7.5 hours after the estimated individual dim light melatonin onset (DLMO), estimated by the Morningness-Eveningness-Questionnaire (MEQ) [44]), as it has been shown that by administering light at that time point, the efficacy of light therapy is increased [22].

Control group
A valid placebo group will be created by randomly assigning half of the patients to the control group to receive 2 weeks of inactive light therapy not exceeding 100 lux at eye level in gaze direction (Luxor LED light alarm clock, lowest level; DAVITA Medizinische Produkte GmbH & Co. KG, Kleve, Germany), with each session lasting for 45 minutes. Each session will commence about 7.5 h after the estimated DLMO to parallel the experimental group.

Finding an appropriate control group for light therapy to minimize placebo effects is difficult, because these effects are expected to be relatively high [19,45,46]. To design conditions that the patients will not consider a control group, we have chosen professional light-therapy devices for both groups, adjusting the lux levels respectively. To control for possible expectation bias, both groups will be instructed that the aim of the study is to compare two different types of light therapy. Moreover, to minimize bias, the therapists on the respective units will be informed that the light therapy for both groups is active.

To ensure that an appropriate and constant number of lux is administered in each group, intensities will be quantified using a lux meter (PCE-172; PCE Instruments, Meschede, Germany). The light intensity that will be used in this study lies within the range of normal daylight exposure. Its long-term ocular safety has been shown in patients with SAD who received bright-light therapy at an illuminance level of 10,000 lux [47].

During the interventions, patients will be allowed to have breakfast or read magazines and books with neutral content (for example, magazines containing plain information without emotionally arousing material). To ensure that every participant has received the same amount of light therapy at the end of the treatment period, treatment can be prolonged for up to 1 day if a patient misses a light-therapy session for some reason (for example, somatic illness). If a patient misses more than two sessions, he/she will be excluded from the study. In total, about three patients can be treated in parallel within each group (see Figure 1 for a flow chart of the study).

Primary and secondary endpoints
The primary endpoint of the study is the change in depression symptoms (BDI-II total score) during the trial. Secondary endpoints include changes in general psychopathology, sleep, circadian functioning (including melatonin assessment), affective dysregulation, behavior, and attention parameters. All questionnaires will be presented in German, and will be completed within the hospital.

Assessments
BDI-II BDI-II is a measure of the severity of depressive symptoms and has been used widely in treatment studies for juvenile depression [41]. It can be used to directly compare effect sizes between different kinds of interventions. The German version has shown good psychometric properties, with good test-retest-reliability ($r \geq 0.75$) in a non-clinical population, and good internal consistency ($\alpha$ coefficient = 0.92) for adolescent inpatients with depression [48,49].

Clinical global impression scale Assessment of general psychopathology will be performed using the Clinical Global Impression Scale (CGI) for estimating symptom severity (CGI-S) and improvement (CGI-I) [50,51]. The
CGI is a 7-point scale that requires a rating of illness severity at the time of assessment. Because severity estimation in the CGI is performed in relation to other patients, it is a subjective assessment tool. In the proposed study, rating will be performed by clinicians blinded to group allocation.

Sleep questionnaire B - revised Sleep and sleep difficulties will be assessed by using the Sleep Questionnaire (Schlaffragebogen) B - Revised (SF B/R) described by Görtelmeyer et al. [52]. This questionnaire contains 31 questions, assessing the 2 weeks prior to assessment. Completion takes about 5 to 10 minutes, and 11 sleep indices can be created including: difficulties in sleep onset and in sleeping through the night, premature awakening, general sleep characteristics, total sleep duration, and sleep factors consisting of sleep quality, feeling of recovery after sleeping, mental balance before going to sleep, feeling of mental exhaustion before going to sleep, and psychosomatic symptoms during sleep phase. Internal consistency is moderate to excellent (α coefficient = 0.68 to 0.92) for clinical populations. Test-retest reliability indicates that relatively stable sleep-related behavior and experiences can be assessed (r = 0.53 to r = 0.91).

DLMO Melatonin production by the pineal gland is under the influence of the suprachiasmatic nucleus of the hypothalamus (SCN), which receives information from the retina about daily patterns of light and darkness [53]. Production of melatonin is inhibited by light and induced by darkness. Hence, when dim lighting is provided, the human body starts producing melatonin about 2 hours before bedtime, and this physiological process is called DLMO. Assessment of the DLMO can be considered the gold standard for measuring melatonin levels and circadian rhythms. In the present study, at the assessments T1, T2, and T5, four sequential melatonin saliva samples will be collected at hourly intervals, respectively. Collection starts from 4 hours before predicted bedtime (19.00 to 22.00 hours) under conditions of dim light. Light therapy has been shown to be most effective when it is applied about 7.5 to 9.5 hours after the individual DLMO [22].

Saliva will be sampled using sterile collection devices (Salivettes; Sarstedt AG & Co, Nümbrecht, Germany). On the day of sampling, patients will be instructed to avoid caffeinated beverages, orange juice, eggs, chocolate, and bananas, because all these have been shown to have a possible influence on melatonin level. During the evening, electronic devices such as video games, TV, and cell phones will not be allowed because the light produced by such devices may have a melatonin-suppressing effect [54]. Patients will be instructed to refrain from food or drinks for 30 minutes before sampling, and directly before sampling they will be instructed to rinse their mouth with water. Samples will
be stored at −26°C until analysis, and all samples will be analyzed simultaneously. This will be performed in a specified laboratory in which melatonin concentrations will be determined, and the individual DLMO will be calculated.

Morningness-eveningness questionnaire For estimating circadian preferences independent of physiological parameters, the German version of the Morningness-Eveningness Questionnaire (MEQ) will be used [44,55]. With this questionnaire, the individual chronotype can be estimated based upon 19 questions that are summed to give a total score and the individual DLMO is then estimated, as it has been shown to have a good correlation with the MEQ [56]. Using this procedure, the optimal time point for light exposure can be estimated directly (about 7.5 h after the individual DLMO) without the requirement for physiological data.

Child behavior checklist The Child Behavior Checklist (CBCL) is one of the best-studied, empirically derived parent checklists for measuring general child and adolescent psychopathology [57]. It assesses the child’s behavior over the past 6 months using a total of 118 items (plus two optional questions), and is rated by the parents or primary caregivers. The questionnaire includes a total problem score, two higher level scales (externalizing problems and internalizing problems), and eight syndrome scales (withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, and aggressive behavior). The reliability, factorial validity and discriminant validity of the German adaptation of the CBCL have been confirmed by previous studies [58,59]. Recently, a specific ‘dysregulation profile’ has been identified in the CBCL, capturing severe affective dysregulation (CBCL-DP) [60]. This profile is characterized by simultaneous high values on the syndrome scales ‘anxious/depressed,’ ‘attention problems,’ and aggressive ‘behavior.’ The CBCL-DP has been consistently found to be associated with disruptive behavior disorders, suicidal behavior, and reduced need for sleep [61-64], and it will be calculated to assess the phenotype of affective dysregulation.

Strengths and difficulties questionnaire In addition to the CBCL, the Strengths and Difficulties Questionnaire (SDQ) will be used in order to assess short-term changes and to evaluate parent and patient ratings. The SDQ is a brief behavioral screening questionnaire assessing 25 attributes, some positive and others negative, which can be allocated to five scales (emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and pro-social behavior) [65]. These scales can be summed to calculate a total difficulties score and, like in the CBCL, a dysregulation profile can be calculated that corresponds to the CBCL-DP, with the advantage of being able to assess short-term changes [66]. In this study, patient and parent rating versions of the SDQ will be used. The sensitivity to change of the SDQ allows estimation of treatment efficacy (α = 0.73; retest stability = 0.62) [67], thereby allowing monitoring of symptom changes of affective dysregulation and behavior during the trial.

Tests of attentional performance With the Tests of Attentional Performance (TAP), a large spectrum of specific attentional performances can be assessed in a computerized form [68]. The following four subtests will be administered to evaluate highly relevant attention-related parameters.

1) Covert shift of attention. This assesses the ability to shift the attentional focus, measuring reaction times for valid and invalid cues in a visual reaction time task.
2) Go/nogo. Assesses the ability to suppress a response in the presence of irrelevant stimuli.
3) Alertness. Assesses the general level of arousal (tonic arousal), its stability over a longer period (intrinsic arousal) and the magnitude of elevation of arousal, induced by a warning signal (phasic arousal).
4) Divided Attention. Assesses the ability to divide attention to auditory and visually presented target stimuli.

Internal consistency for all these subtests lies between 0.60 and 0.83 [68].

Seasonal pattern assessment questionnaire The Seasonal Pattern Assessment Questionnaire (SPAQ) is a questionnaire for retrospectively assessing change in mood and vegetative functions with the seasons [69]. It is a frequently used screening instrument for assessing symptoms of SAD, with a high internal consistency [70] and has recently been used in young adults [71]. In the present study it will be administered to calculate a total seasonality score, with seasonality being the degree to which seasonal changes affect criteria such as mood, energy, sleep length, appetite, food preference, or the wish to socialize with other people [69], and thus will be used to control for seasonal effects.

Therapy expectancy Therapy expectancy will be assessed by using a modification of the Credibility/ Expectancy Questionnaire, which is a quick and easily administered scale for measuring treatment expectancy and rationale credibility for use in clinical outcome studies [72]. High internal consistency has been reported,
lying between 0.84 and 0.85 for the whole scale. Inter-item correlations between studies ranged from 0.53 to 0.85 for the items on the expectancy factor, and between 0.62 and 0.78 for items on the credibility factor. Test-retest reliability over a 1-week period was also found to be good, at 0.82 for expectancy and 0.75 for credibility [72]. In the proposed study, the questionnaire will be used to control for placebo effects, which are expected to be relatively high for light-therapy studies.

**Culture fair intelligence test 20 – revised** The Culture Fair Intelligence Test 20 – Revised (CFT20-R) is an economic, computerized general intelligence screening test assessing ‘general fluid ability’ [73], that is, the ability to solve formal logic tasks with varying complexity within a specific time frame. The CFT20-R uses language-free tasks and is therefore also appropriate for people with language deficiencies. It is standardized for children and adults (8.5 years of age and above) and has high test-retest coefficients ($r = 0.80$ to 0.83, uncorrected) and high internal consistency ($\alpha = 0.95$).

**Adverse events** At each assessment, the participants will be asked to report any adverse events (AEs). Reported AEs of light therapy side effects include jumpiness, jitteriness, headache, or nausea (for an overview, see Terman et al. [22]). AEs will be assessed by using open questions, asking about general AEs and their severity during the study period.

**Time points of assessments** The assessment time points are as follows.

- **T1**: The initial assessment for eligible patients will be carried out after about 1 week of care in the unit. At this point, patients will have become used to being in the hospital, and will probably have a more regular day and night rhythm.
- **T2**: After 2 weeks of morning light-therapy intervention, there will be a comprehensive post-therapy assessment.
- **T3**: One week later, depression severity will be assessed to monitor changes.
- **T4**: Another week later, there will be another assessment of depression severity.
- **T5**: Three weeks after the light-therapy interventions have ended, another comprehensive assessment will be carried out.

An overview of the timeline of the study is shown in Figure 2.

**Data analysis**

**Sample-size calculation**

Estimates of a clinically relevant effect size were derived from a meta-analysis that evaluated effects of bright-light therapy for seasonal and non-seasonal depression in adult outpatients [74]. A similar study for adolescent inpatients is not available. Therefore, effect-size calculation will be based on evidence from adult outpatients. Although research is generally scarce, it is assumed that the active light therapy intervention for SAD will have an effect size (pre-post) of about 0.78 [75], which can be considered a conservative estimate because effect sizes might be considerably higher [74]. Golden et al. [74] divided the studies used in their meta-analysis into four categories, and derived effect sizes for them. In the category ‘non-seasonal depression,’ an effect size of 0.53 was reported for bright-light treatment, with a 95% confidence interval of 0.18 to 0.89. Conservative calculations indicate that the expected outcome for our study will require a total sample size of 54 subjects ($\alpha = 0.05$, two-sided test) to achieve a power of 80%.

**Statistical analyses**

Data will be assessed using SPSS software (version 20; SPSS Inc., Chicago, IL, USA). Correctness of the data will be assured by double-entry of the data. Data will be analyzed according to both intention-to-treat (ITT) and per-protocol (PP; efficacy population) principles. ITT will assess all randomized patients, while PP analyses will assess patients who receive 2 weeks of morning light therapy with no violation of the study protocol.

All planned comparisons will compare T2 to T5 relative to T1. The primary endpoint of the study is change in depressive symptoms (BDI-II total score) during the trial. Baseline depression level (that is, BDI-II total score at T1) will be controlled for in the two-factor repeated-measures ANCOVA. This model accounts for differences between groups at baseline. Furthermore, the study will evaluate whether the effects of morning light therapy on mood might partly be mediated by its effect on the circadian rhythm, and will be assessed by questionnaires and saliva samples. For missing values, the multiple imputations (MI) technique will be used, because a recent meta-analysis for RCTs in obesity found this to have modest superiority to fitting mixed linear models or using last observation carried forward (LOCF) methods [76]. With the MI technique, plausible values for the missing data are imputed. Each of the datasets is then analyzed separately using the desired model (in this case, the two-factor repeated-measures ANCOVA). With this parameter, estimates are made for each of the datasets, and these are then combined using standard rules for MI analyses [77,78]. These combined parameter estimates can then be used for hypothesis testing and for
Morning light therapy for juvenile depression and affective dysregulation – a randomized controlled pilot study

**Diagnosis: depression**
- Informed consent
- Check inclusion criteria

**Screening**

**Pre-tests (T1)**
- BDI-II
- CFT 20-R
- MEQ
- SPAQ
- SF B/R
- SDQ parent/ self
- TAP
- CGI-S
- Assessment of expectations
- **Saliva tests:** melatonin (DLMO)

**Intervention phase**

**“active” light therapy**
- 2 weeks morning light therapy
- 10,000 lux
- 45 minutes

**“inactive” light therapy**
- 2 weeks morning light therapy
- 100 lux
- 45 minutes

**Post-tests (T2)**
- BDI-II
- Adverse events
- SF B/R
- SDQ parent/ self – follow-up
- TAP
- CGI-I
- **Saliva tests:** melatonin (DLMO)

**Post-test (T3)**
- BDI-II

**Post-test (T4)**
- BDI-II

**Follow-up tests (T5)**
- BDI-II
- Adverse events
- MEQ
- SF B/R
- SDQ parent/ self follow-up
- TAP
- CGI-I
- **Saliva tests:** melatonin (DLMO)

**Number of week**
- 0
- 1
- +
- 2
- 3
- 4
- 5

*Figure 2* (See legend on next page.)
making inferences. In this RCT, two-factor repeated-measures ANCOVA will be used with group as between-subject factor and time as within-subject factor (T1 to T5). In cases of significant correlations with the primary endpoint, covariates will include baseline BDI-II score, gender, intelligence, seasonality, and circadian preference. The 95% confidence intervals and pre-post effect sizes will be derived for each analysis. All tests of statistical significance will be interpreted with a criterion of $P < 0.05$, two-sided.

**Discussion**

We have presented a design and protocol for an RCT of light therapy for juvenile depression and severe affective and behavioral dysregulation in a naturalistic tertiary-care inpatient setting. This initial pilot study will evaluate the feasibility and acceptance of this chronobiological intervention for depressive adolescents by implementing a 2-week period of bright-light therapy. Because it will be implemented in an inpatient setting, there are several limitations, such as the short duration of bright-light therapy, interruption by weekend breaks, and lack of daily mood self-assessments that would allow a detailed picture of response to this chronobiological intervention. An additional challenge is the issue of blinding. In their systematic review, Even et al. [19] discussed the possibility that some patients in a control group exposed to a device that only delivers 100 lux may correctly guess that they have been allocated to the placebo group. To control for possible expectation bias, both groups in this study will be instructed that the aim of the study is to compare two different types of light therapy. In accordance with this, it is important to bear in mind that even 100 lux in the morning might have some subtle effect on the circadian system. However, the answers to the questions of whether morning light therapy will have a beneficial effect on non-seasonal depressive symptoms in young people, and whether 2 weeks of morning light will be sufficient to elicit more general positive effects on the sleep-wake rhythm and on affective dysregulation, should be answered. Moreover, we expect insight into possible changes on a physiological level, such as shifts in DLMO.

After this pilot study has been conducted and specific effects of bright-light therapy have been observed, a combination of various chronotherapeutic interventions, such as light therapy, wake therapy, and additional sleep-phase advance could be conducted to investigate effects in young people more thoroughly.

**Trial status**

Ongoing trial.

**Competing interests**

MH has served in an advisory or consultancy role for: Lilly, Novartis, and Bristol-Myers Squibb, and has received conference attendance support or was paid for public speaking by AstraZeneca, Janissem-Cilag, Lilly, Neurocon, Novartis, Medice, and Shire. The present work is unrelated to the above grants and relationships. The other authors have no conflicts of interest.

**Authors’ contributions**

SH conceived the research project; SH, TL, SSC, and MH designed the study; and SH, TL, SSC, and MH designed and tailored the study protocol. All authors contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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2.2 Lighting the mood of depressed youth: Feasibility and efficacy of a 2 week - placebo controlled bright light treatment for juvenile inpatients

This BLT study is the first randomized-controlled ITT study investigating feasibility and efficacy of add-on morning BLT in moderately to severely depressed, medication-naive adolescent inpatients. We ask whether conducting morning BLT in an acute psychiatric care setting will be a feasible treatment approach for adolescents with depression. Furthermore, we hypothesize that two weeks of BLT will improve depression, sleep and stabilize circadian functioning in patients of the “active” BLT condition compared to a dim-light “placebo” condition (CON). As was described in the study protocol (see 2.1), morning BLT is conducted for 45 minutes each morning for a total duration of two weeks (with 10,000 lux). In CON a different light device is used (max. with 100 lux) using the same trial protocol as in the BLT condition. Participants (N= 57) are randomly allocated to either active BLT (N= 30) or CON (N= 27). Conditions are compared to each other at three points of assessment (pre-/ post-treatment and during a 3-week follow-up). In this specific patient group morning BLT proved to be a feasible add-on treatment. Against our expectations, depression symptoms improved irrespective of BLT condition. Sleep restoration showed improvements only in the active BLT condition. Improved sleep quality and a shift of circadian preference towards morningness were found in both BLT condition, however, revealing long-term effects only in the active BLT condition. Moreover, correlation analyses revealed significant positive associations between a reduction of depressive symptoms, enhanced sleep and a circadian shift towards morningness. The results of the regression analysis indicated that increased sleep quality and a circadian shift towards morningness had a significant influence on the change of depressive symptoms at posttreatment.
Research report

Lighting the mood of depressed youth: Feasibility and efficacy of a 2 week-placebo controlled bright light treatment for juvenile inpatients

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1. Introduction

Major depression (MDD) has been shown to be one of the most frequent psychiatric disorders in adolescence. Prevalence rates for MDD in the young, also called juvenile depression are about 4–8% with a tendency to increase (Birmaher et al., 2007). Symptoms of juvenile depression are similar to symptoms of MDD in adults; however, mood lability, irritability, low frustration tolerance, somatic complaints, and social withdrawal might be more pronounced (Mehler-Wex and Kölich, 2008; Lewinsohn et al., 2003).

Treating juvenile depression constitutes a challenge since remission rates of moderate to severe depression are rather low (Kennard et al., 2009). For mild depression, cognitive behavioural therapy (CBT) might be sufficient, but for more severe cases, a combined therapy with antidepressants is often indicated. Studies show remission rates of less than 40% even in combination trials with both selective serotonin reuptake inhibitors (SSRIs) and psychotherapy (Emslie, 2012; Kennard et al., 2006). Treatment decisions are further complicated by safety concerns of antidepressant-related self-harm and suicide in youth (Holtmann et al., 2006). Another challenge is that early-onset depression is often chronic and recurrent. One of the underlying reasons for recurrences might lie in co-morbid problems, such as sleep disturbances (Ivanenko et al., 2005; Lofthouse et al., 2009). A recent study with depressive youth showed that 72.7% also reported some type of sleep disturbances (Liu et al., 2007). More specifically, sleep-onset and sleep maintenance problems, as well as insomnia, were reported by children and adolescents with a diagnosed MDD (Puig-Antich et al., 1982).

Very often, the primary reason for sleep abnormalities and several mood disorders is the disruption and desynchronisation of the circadian system. Circadian rhythms are regular, approximately 24-h cycles found in nearly every hormonal, biochemical and behavioural process. Regular circadian rhythmicity is essential for maintaining somatic and mental health.

A disruption, by contrast, might lead to instability of the rhythm, thereby possibly leading to neuropsychiatric disorders such as MDD (Salgado-Delgado et al., 2011; Bozin, 2000).

A possible treatment approach targeting both depressive symptoms and co-morbid sleep disturbances by stabilising the circadian rhythm is morning bright light therapy (BLT). In adults, meta-analytic evidence has proven that BLT is a potent alternative to antidepressant drug treatment both in seasonal (effect-size .84, 95% CI .60–1.08) and non-seasonal depression (effect-size .53, 95% CI .18–.89; Golden, 2005; for review see also Even et al. (2008)). Although the exact mechanism of action of BLT is still unknown, it is assumed that light has an effect on mood via an indirect circadian way. Light has shown to improve depressed mood and sleep as a zeitgeber by synchronising rhythms and thereby correcting shifted sleep phases as well as by enhancing circadian amplitude (Wirz-Justice, 2009; Gooley, 2008). In addition, there are “direct” effects of light, such as on regulation of different neurotransmitters, hormones, alertness, and cognitive performances (Parry and Maurer, 2003; Chellappa et al., 2011; Cajochen, 2007; LeGates et al., 2014). Regarding depression, a specific effect of BLT on serotonin levels has been reported with more light eliciting higher levels of serotonin (Stephenson et al., 2012).

Despite promising results in adults, BLT has not yet been studied sufficiently in children and adolescents (Gest et al., 2014). One RCT with children and adolescents suffering from SAD has shown a significant decrease of parent-rated depressive symptoms (Swedo et al., 1997). More recently, BLT as add-on therapy for mildly

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depressed adolescent inpatients showed significant improvements in self-rated depression scores after a one-week intervention (Niederhofer and von Klitzing, 2012). However, participants also received CBT and additional pharmacotherapy in this trial, which might have influenced outcome measures.

To sum up, BLT has been shown to be an effective and feasible treatment approach for MDD and for stabilising circadian rhythms (Even et al., 2008; Golden, 2005). First studies also show promising results for juvenile depression. To our knowledge, there is currently no randomised-controlled study investigating the effects of BLT on juvenile depression in unmedicated inpatients. Therefore, our main study goal, besides the evaluation of feasibility in this specific setting, was to show that BLT in depressed young inpatients results in greater improvements of depressive symptoms compared to a dim light control group. Additionally, we hypothesise that BLT can positively affect subjective sleep parameters and leads to a stabilisation of the circadian rhythm which will be reflected by a shift of chronotype from eveningness to morningness. Since sleep disturbances and depression share an intimate relationship (Van der Helm and Walker, 2009), we also assume that improvements of depressive symptoms are related to improvements of sleep. Finally, we aimed to evaluate whether changes in sleep quality and a late chronotype are of predictive value for treatment response.

2. Methods

2.1. Sampling

A total of 57 juvenile, medication-naive depressive inpatients between the age of 12 and 18 were recruited over a one year period from the LWL-University Hospital Hamm for Child and Adolescent Psychiatry. The hospital provides child psychiatric care for a population of 1.6 million inhabitants comprising both rural and urban areas and is the sole provider of inpatient care serving the study area.

Participants were diagnosed with a primary diagnosis of moderate to severe depression according to ICD-10 (MDD: F32.1 and F32.2; WHO, 1992). Study inclusion criteria were (i) age between 12 and 18; (ii) a clinical diagnosis of a moderate to severe depression; and (iii) a BDI-II score of 20 or higher. Exclusion criteria involved (i) the use of psychotrophic medication; (ii) treatment with beta-blocker; (iii) being diagnosed with schizophrenia or Bipolar 1 disorder; and (iv) eye diseases with involvement of the retina. Regardless of participation in this study, multimodal inpatient treatment following the German guidelines for treating unipolar depression in youth was provided (Dolle and Schulte-Körne, 2013). Multimodal inpatient treatment included individual and group psychotherapy in addition to medical, psychological, and nursing care; approaches such as schooling (within the hospital), occupational therapy, arts therapies, sports and movement therapy, family-focused interventions and treatment for comorbidity complement the inpatient treatment. Moreover, afternoon outdoor activities are part of the multimodal treatment. Durations and intensities of daylight exposure, that might have an effect on circadian functioning, were equal for all participants in this study independent of group allocation.

2.2. Materials and procedure

2.2.1. Depression severity

Depression severity was assessed by conducting the self-rating scale Beck Depression Inventory-II (BDI-II). It is a severity measure of depressive symptoms calculated as a sum score and can be used to directly compare the efficacy and effect sizes of interventions. Therefore, it has widely been used in treatment studies for depression (Beck et al., 1996). Psychometric properties for the German version show good internal consistency (alpha-coefficient = .92) for depressive adolescent inpatients and good test-retest-reliability (r = .75) in a non-clinical population (Besier et al., 2008; Kühner et al., 2007). Information on comorbid disorders was extracted from the digital medical charts.

2.2.2. Sleep

Subjective sleep characteristics and -difficulties were assessed by using the revised version of the German sleep questionnaire (SFB/R; Görtelmeyer, 2011). The SFB/R is well established and validated. It consists of 31 items with dichotomous or continuous answer possibilities. From the single items, five sleep indexes and six factor scales can be calculated. Within the present study, the two composite scales “sleep quality (SQ)” and “restorative sleep (RS)” were assessed. The factor SQ includes the indexes “difficulty to fall asleep” (e.g. item: falling asleep immediately after going to bed), “waking at night” (e.g. item: nocturnal awakening), “pre-mature awakening” (e.g. item: waking up to early), “general sleep characteristics” (e.g. item: good sleep) and the single item “being able to sleep in an unfamiliar environment”. The second factor RS consists of items concerning feelings after wake up (e.g. “need time to wake-up properly”, “feeling fresh after awakening”). The manual does not provide normative values for children and adolescents; however, in healthy emerging adults (age 16–32 years) the mean score for SQ is 3.94 (.62) and for RS 3.12 (.75). In order to evaluate clinical relevance of improvements in sleep quality and the degree of restorative sleep, we considered sleep quality/restorative sleep level markedly improved/remitted when the baseline value was exceeded by 1 standard deviation at either posttest or follow-up (e.g. baseline mean ± .68 for SQ and ± .69 for RS respectively).

Psychometric properties show that internal consistency can be considered moderate to excellent (alpha-coefficient = .68–.92) for clinical populations. Test–retest reliability indicates that relatively stable sleep related behaviour and –experiences are assessed (r = .53 to r = .91).

2.2.3. Chronotype

The German version of the Morningness–Eveningness Questionnaire (MEQ) was administered to estimate individual circadian preferences (Griefahn et al., 2001; Horne and Ostberg, 1976) and to indirectly determine the most efficient time point for light application. Nineteen questions about morningness and eveningness of experience are assessed (alpha-coefficient = .92) for depressive adolescent inpatients and good test-retest-reliability (r = .75) in a non-clinical population (Besier et al., 2008; Kühner et al., 2007).

Seasonality, IQ and therapy expectancy were assessed as possible moderators at T1.

2.2.4. Seasonal Pattern Assessment Questionnaire (SPAQ)

The SPAQ is a frequently used screening instrument that retrospectively assesses change in mood and vegetative functions with the seasons (Kasper et al., 1989) and thus serves as screening tool for seasonal affective disorder (SAD). Recently it has been employed in young adults (Steinhausen et al., 2008). In the present study a total “seasonality score” was calculated to assess the degree of seasonal influences on mood.

2.2.5. Intelligence screening

The Culture Fair Intelligence Test 20 – Revised (CFT20-R) is an economic, computerised general intelligence screener (Weiß,
It was used in this study to control for baseline IQ differences. High test-retest coefficients (r=.80–.83, uncorrected) were reported as well as high internal consistency (.95).

2.2.6. Therapy expectancy

Therapy expectancy was assessed following the credibility/expectancy questionnaire by Devilly and Borkovec (2000). This questionnaire allows assessing therapy credibility and client expectancy and thereby ensures initial equivalence among compared therapy conditions. High internal consistencies were found within each factor and for the whole scale (expectancy factor:.79–.90; credibility factor:.81–.86; whole scale:.84–.85).

2.2.7. Adverse events

Adverse events of light therapy (e.g. headaches, nausea) are rare, do not last long and occur only irregularly (Terman et al., 2001). Nevertheless, patients were instructed to pay attention to possible events and report them immediately. Adverse events were assessed using open questions after one week of light therapy and at the end of the intervention phase, respectively.

2.2.8. Light therapy devices

The active light therapy device used in the experimental condition was PhysioLight LD1100 (DAVITA medical products, Kleve, Germany) radiating white light with a power of 10,000 lx at a distance of about 65 cm (centimetres). The device for the dim light control condition (DAVITA Luxor LED; max. 2500 lx) can be used as a “light alarm clock” but can individually be set and adjusted to achieve a constant lux number. In this study, it was set to about 60% power which resulted in about 100–150 lx at a distance of 65 cm, i.e. within the range of normal daylight exposure.

Long-term oculary safety has been shown for SAD patients that received BLT with a luminance level of 10,000 lx (Gallin et al., 1995).

About one week after admission to the hospital participants were screened for eligibility; after informed consent was obtained pre-tests (T1) were conducted. Hereafter, patients were randomly allocated to either the active condition (BLT) or the dim light control condition (CON) by drawing condition allocations from a “randomiser box” in which the number of possible condition allocations was equal across conditions. In the active condition, participants received 45 min of morning BLT (10,000 lx of bright white light at eye level in gaze direction) five times a week for two weeks in total. To create equal settings in both conditions, participants assigned to the dim light condition (CON) received two weeks of 45 min inactive, dim light each morning (not exceeding 150 lx at eye level in gaze direction).

Participants in both conditions were told that efficacy of two different light therapy devices shall be evaluated. For a more detailed description of the study design and trial procedures see Bogen et al. (2013).

2.3. Statistical analyses

Repeated measure ANOVAs were calculated with condition as between-subject (bright vs dim light therapy) and time (T1, T2, T3) as within-subject factor for the following outcome variables: depression scores (BDI-II), sleep factors: “sleep quality”, “restorative sleep”, and chronotype (MEQ). In order to further explore changes depending on treatment effects and to better understand stabilisation of possible effects within the follow-up period, further post-hoc analyses with paired t-tests were applied for T1–T2 and T2–T3. To evaluate possible relations between changes of depression and changes of sleep parameters during the course of BLT Pearson correlations were calculated. Furthermore, regression analyses were performed in order to identify possible predictors for reduction in depressive symptoms. Since this randomised-controlled study design with medication-naive juvenile inpatients is novel, estimates of clinically relevant effect sizes had to be derived from a meta-analyses evaluating effects of BLT for seasonal and non-seasonal depression in adult outpatients (Golden, 2005). Taken into consideration the limitation of only restricted comparability, a pre–post effect size of about .78 was found for seasonal depression whereas an effect size of .53 was reported for non-seasonal depression (Kripke et al., 1992). This is a very conservative estimate, since effect sizes might be considerably higher (Golden, 2005). To achieve a power of 80%, conservative calculations point towards a required total sample size of 54 subjects for the expected outcome (alpha = .05; two-sided testing). All analyses were based on an intention-to-treat (ITT) sample. Missing values were replaced by using a Last-Observation-Carried-Forward (LOCF) approach. This method has shown to be a very conservative data substitution, likely to even underestimate within-group changes (Prakash et al., 2008).

2.4. Ethics

Participants and persons with primary custody were extensively informed about study objectives, study design and potential risks and about the possibility to withdraw from the study at any time. Oral and written consent was obtained. Ethical permission was approved by the local medical ethical committee. The study protocol is published (Bogen et al., 2013) and the trial has been registered: doi: 10.1186/ISRCTN89305231.

3. Results

3.1. Baseline sample characteristics

Mean age of all participants was 15.4 (1.6) years. Participants were predominantly female (73.6%). There were no significant group differences regarding: age, IQ, severity of depression, presence of co-morbidities, number of co-morbidities, seasonality, chronotype, therapy expectancy and total number of drop-outs (all p > .05). Adverse events (mostly headaches) were reported in both groups (BLT: n = 9 (30%); CON: n = 11 (40.7%); X2 (1) = .720, p = .396). Degree of depressive symptoms assessed with the BDI-II (t (55) = -.458, p = .649), sleep quality (t (41.5) = .170, p = .866) and the sum score of the MEQ (t (55) = 1.935, p = .058) were comparable between the groups; however, the reported degree of restorative sleep at baseline differed between the groups with those allocated to the active BLT reporting significantly lower levels (t (48) = 2.396, p = .021). For a detailed patient flow, please see Fig. 1. Sample characteristics are displayed in Table 1, baseline score of the dimensional assessments in Table 2.

3.2. Effects on depressive symptoms

Both light conditions revealed short-term improvements of depression (BDI-II; F (2, 110) = 39.48; p < .001, partial eta²=.418). The kind of intervention did not add significantly to the change in depressive symptoms (F (2, 110) = .768, p = .466). Post-hoc within-group comparisons revealed highly significant improvements from pre to post treatment in both groups (CON: t (26) = 5.016, p < .001; BLT: t (29) = 4.423, p < .001) with pre-post remission rates (cut-off < 10) of 20% and 11.1% for BLT and dim light, respectively. Remission rates, however, were not significantly different between light conditions (X2 (1, N = 57) = .844, p = .29); only in the active BLT condition, did a further significant decrease in depressive symptoms emerge during follow-up (BLT: t (29) = 2.566; p = .016; CON: t (26) = 1.825; p = .079 ). Remission rates at follow-up were
46.7% for BLT and 25.9% for dim light, again without a significant difference between conditions ($X^2(1, N=57) = 2.637, p = .09$). For means and standard deviations see Table 2.

### 3.3. Effects on subjective sleep

Short-term improvements of sleep quality (SQ) and restorative sleep (RS) differed between groups (SQ: $t(23) = -2.414; p = .024$; and $t(25) = -2.966; p = .007$); restorative sleep improved during BLT treatment ($t(24) = -5.100; p < .001$), and remained stable during follow-up ($t(26) = -.474; p = .640$). In CON, there was only a significant improvement in sleep quality during follow-up ($t(24) = -10.00; p = .021$; and $t(26) = -2.490; p = .020$, respectively), but no changes over time in the degree of restorative sleep ($t(24) = -0.384; p = .704$; and $t(26) = -3.83, p = .705$, respectively). For means and standard deviations see Table 2. Regarding SQ remission rates for posttests of 26.7% for BLT and 7.4% for dim light were found, showing a significant difference between light conditions ($X^2(1, N=49) = 4.388, p = .03$). Including follow-up measures remission rates of 40% for BLT and 22.2% for dim light were found ($X^2(1, N=49) = 3.562, p = .06$). For restorative sleep a total of 50% of the participants in the BLT and 14.8% for dim light were found ($X^2(1, N=26) = -5.231, p = .001$), and remained stable during follow-up ($t(23) = -2.637, p = .024$). For restorative sleep a total of 50% of the participants in the BLT and 14.8% for dim light were found ($X^2(1, N=26) = -5.231, p = .001$).

### 3.3.1. Indirect estimate of circadian phase by chronotyping

Considering the characteristics of chronotype that were assessed with the MEQ, a time x group interaction effect emerged ($F(2, 110) = 5.190, p = .007$, partial $\eta^2 = .086$). Evaluations of within-subject comparisons indicated significant shifts of chronotype towards "morningness" (from T1 to T2 as well as from T2 to T3) only in the BLT condition ($t(29) = -3.358; p = .002$; and $t(29) = -2.294; p = .029$, respectively), whereas in CON a significant change emerged only from pre to post treatment ($t(26) = -2.235; p = .034$; and $t(26) = -2.215; p = .032$, respectively). For means and standard deviations see Table 2.
3.4. Relationships between depression, sleep and chronotype

Significant correlations between difference scores of depression both at posttreatment and follow-up assessment and difference scores of “sleep quality” \((r = –.655, p < .001; r = –.483, p < .001)\) as well as “restorative sleep” \((r = –.589, p < .001)\) were found, implying that improvements of depression and improvements of “sleep quality” and “restorative sleep” were related. Moreover, difference scores of depression and changes of chronotype at posttreatment were correlated \((r = –.509, p < .001)\). This result indicated a relationship between improvements of depression and a shift toward morningness during treatment. Difference scores of chronotype (T1–T2) and difference scores of the sleep factors “sleep quality” and “restorative sleep” both at posttreatment and follow-up showed significant correlations as well \((SQ: r = .443, p = .001 and r = .357, p = .009; RSQ: r = .556, p < .001 and r = .277, p = .043)\), pointing towards a greater “sleep quality” and “restorative sleep” in combination with a shift towards morningness.

3.5. Predictive value of sleep factors and chronotype on changes in depressive symptoms

In order to ascertain the influence of sleep and chronotype on the change of depressive symptoms, we performed linear regression analyses with BDI-II difference score at posttreatment and follow-up. The regression model was significant \((F(4,443) = 12.043, p < .001)\) and explained 48.4% of variance of changes in BDI-II scores. Whereas “restorative sleep” changes and the kind of treatment did not influence the treatment outcome, enhanced “sleep quality” \((\beta = –.7962, r = 1.811, \beta = –.625, t = –4.408, p < .001)\) and a shift towards morningness \((\beta = –.375, t = –2.962, p = .005)\) had a significant influence on the change of depressive symptoms at posttreatment.

4. Discussion

To our knowledge, this is the first randomised-controlled ITT design study investigating feasibility and clinical effects of 2 weeks add-on BLT on juvenile, unmedicated inpatients with moderate to severe depression. BLT was compared to a dim light control condition and proved to be a feasible add-on treatment in this specific patient group. Compliance was good by both juvenile participants and the hospital staff that had to incorporate the trial interventions into the schedules of their inpatient units. However, several aspects need to be discussed.

4.1. Depression

In contrast to our expectations, we found highly significant improvements of depressive symptoms in both groups independently of the intervention type. Because patients took part in the study few days after admission to multimodal inpatient care, we assume that in addition to unspecific effects of the inpatient setting per se with structured schedules, this result mainly reflects the well-known and repeatedly replicated phenomenon of marked symptom improvements in depression immediately after treatment initiation. A further contribution to this effect may be a placebo response: there is evidence from antidepressant drug trials indicating placebo response rates being higher in children and adolescents \((~50\%)\) than in adults \((~38\%); \text{Weimer et al., 2013}\). This implies that more young people have to be included in trials to achieve the same degree of security of efficacy as in adults. The same may not only be true for drugs but also for complementary antidepressant treatments such as BLT. As a consequence, the present sample size may not have had sufficient power to detect differences between groups.

A further aspect that might account for the finding on depressive symptoms refers to the characteristics of BLT applied within the study. When considering BLT, four parameters have to be taken into account: intensity, timing, spectrum of the light source and duration \((\text{Stephenson et al., 2012; Wirz-Justice et al., 2005})\). We used a standard protocol regarding intensity, timing and light spectrum, but a total of 10 days of BLT in the course of two weeks might have been too short to elicit specific antidepressant effects. However, a previous study of BLT in youth reported an antidepressant effect after only one week of BLT \((\text{Niederhofer and von Klitzing, 2012})\), but in contrast to the participants of the present study, those were only mildly depressed and received additional antidepressant medication that might have elicited own beneficial effects. Irrespectively, we found a significant further decrease of depressive symptoms during follow-up in the active light condition, but not in the dim-light condition. This may be interpreted as a hint to incipient efficacy of BLT. Several studies revealed that effects of BLT need some time to develop and that efficacy of BLT increases with longer intervention duration \((\text{Goel et al., 2005; Martiny et al., 2005})\). Therefore future studies may need to prolong the duration of exposure to BLT. Since the average length of stay in a hospital may not permit more than two weeks of BLT in many inpatients, the chronotherapeutic intervention should be extended to the subsequent outpatient setting.

4.2. Sleep and chronotype

While phase-shifting effects of BLT have long been known \((\text{Rosenthal et al., 1990})\), and a direct beneficial influence of BLT on sleep has been described for adult circadian rhythm disorders \((\text{Gooley, 2008; Chesson et al., 1999})\), this study is the first to show a clinically relevant specific effect of BLT on different indices of sleep and circadian preference in youth. Sleep restoration occurred.
only during BLT and remained stable during follow-up, while dim light remained without any effect. Sleep quality improved during BLT and increased further over the follow-up period, while in CON there was only a moderate improvement during follow-up, still considerably below that of BLT. Similarly, a shift of the circadian preference towards morningness (from T1–T2 as well as from T2–T3) occurred in the BLT condition only, whereas in CON this phase-shift emerged only during treatment. This is in line with previous studies showing that appropriately-timed exposure to BLT can adjust sleep and wake times, and improve sleep quality (for review, see Gooley (2008)). Likewise the depressive symptoms the effects on sleep and circadian preference may, however, have needed a longer duration of BLT to develop completely.

4.3. Association of depression, sleep and chronotype

The interplay between depression, sleep and circadian rhythmicity is complex (Legenbauer et al., 2012). In our sample, a reduction of depressive symptoms was positively correlated with improvements of sleep and a phase advance towards morningness. In addition, the shift to morningness itself was closely related to improved sleep quality and sleep restoration. Reduction of depressive symptoms was to a large extent (almost half of the explained variance of changes in BDII scores) predicted by enhanced sleep quality and a shift towards morningness. Since sleep disturbances such as sleep-onset and sleep maintenance problems, and insomnia are very common among youth with depression (Liu et al., 2007; Puig-Antich et al., 1982) our results merit replication in a larger sample with an extended period of BLT to confirm its potential as an adjunct therapy for juvenile depression.

5. Limitations of the study

As pointed out above, the presented results have to be interpreted with care due to the naturalistic character of the study. We included consecutively admitted juvenile depressed inpatients who were willing to participate in this randomised-placebo-controlled study. However, standard multimodal treatment should not be affected and patients were discharged when necessary irrespective of the study protocol. Therefore, we chose duration of BLT of only two weeks which represents the main limitation of the present study. We also have to consider that the chosen “placebo” of 100–150 lx might have been somewhat active, thus diminishing the possible difference between BLT and a really biologically inactive dim light. Finally, there is an overlap between sleep disturbances and depression: both sleep questionnaire and depression inventory ask for sleep difficulties; however, we controlled for influence on the results by comparing the single sleep items (sleeping habits) and “tiredness/fatigue” from the BDII between the chronotherapeutic conditions and found no difference. (p > .05). Finally, all of the assessments of this study were of subjective nature.

6. Conclusion

BLT is an easy applicable add-on treatment with few side-effects and good acceptance in an inpatient psychiatric setting. Our results indicate that short duration of BLT seems to exert its effects in particular on sleep and associated features such as chronotype. The latter may indirectly impact reduction in depression symptoms. Future studies are needed to replicate the presented results in larger adolescent samples and with a longer duration of BLT that might be transferred to the outpatient setting. These should incorporate additional external ratings of symptoms, objective parameters of sleep and activity (e.g., actigraphy) and biological markers, such as the individual dim light melatonin onset. Finally, future studies may also examine the effect of BLT in non-depressed youth with sleep problems.

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2.3 Severe mood dysregulation: In the “light” of circadian functioning

This hypothetical manuscript evaluates the rationale for using morning BLT for a recently discussed phenotype which has been found among adolescent psychiatric patients: affective and behavioural dysregulation also called severe mood dysregulation (SMD). Patients with SMD show severe impairments across multiple settings including irritability, non-episodic anger, and an increased reactivity to negative emotional stimuli. Furthermore, depressive symptoms as well as disruptions of the circadian rhythm have been reported. Recent studies suggest the use of morning BLT for a range of disorders with a disrupted circadian rhythm, irrespective of specific diagnoses. In children and adolescents with “phenotype-similar” disorders such as ADHD or Bipolar Disorder a stabilization of the circadian rhythm (a sleep phase advance), improvements of overall daily functioning and a decrease of core symptoms have been reported. Also, studies are reported that investigated the effects of BLT on behavioural parameters such as aggressive thoughts and actions and found significant reductions as a consequence of BLT. Based on this, it is postulated that the use of morning BLT might stabilize circadian functioning in children and adolescents with symptoms of SMD and lead to improved core symptoms in the long-term.
Severe mood dysregulation: In the “light” of circadian functioning

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A B S T R A C T
Severe affective and behavioral dysregulation, labeled as severe mood dysregulation (SMD), is a widely spread phenomenon among adolescent psychiatric patients. This phenotype constitutes severe impairment across multiple settings, including various symptoms, such as non-episodic anger, mood instability, and hyperarousal. Moreover, SMD patients often show depression and reduced need for sleep. Despite a lifetime prevalence of 3.3%, systematic research is still scarce, and treatments that have been established do not account for the range of symptoms present in SMD. Considering the circadian dysfunctions, two hormones, melatonin and cortisol, are essential. When these hormones are dysregulated, the circadian rhythm gets out of synchrony. Since evidence is emerging showing that the worse the sleep-wake cycle is entrained, the worse the psychiatric symptoms are depicted, the importance of proper circadian functioning becomes clear.

Chronotherapy as the controlled exposure to environmental stimuli (e.g. light) acting on biological rhythms has shown therapeutic effects. In both seasonal and major depression chronotherapy has been implemented, decreasing depressive symptoms and stabilizing circadian rhythms. Preliminary evidence from SMD related disorders, namely attention-deficit/hyperactivity disorder and pediatric bipolar depression, indicates that morning light therapy elicits positive influences on other symptoms as well. Hence, light therapy might not only be effective for depressive symptoms and circadian rhythms, but might also be beneficial for symptoms including inattention and irritability.

We hypothesize that light therapy might be a helpful adjunctive treatment enhancing affective and circadian functioning, and eliciting positive influences on behavior. Physiologically, changes of both cortisol levels and melatonin production are expected.

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Clinical picture

A considerable size of youth present with a clinically challenging phenotype that can hardly be assigned to existing diagnostic categories. These “nosologic orphans” [1] show severe affective and behavioral dysregulation, including non-episodic anger, irritability, hyperarousal, and increased reactivity to negative emotional stimuli [2,3]. Disagreement regarding proper classification often occurs because of a high comorbidity to other disorders. A considerable amount of symptom overlap to attention-deficit/hyperactivity disorder (ADHD), pediatric bipolar disorder (PBD) and to oppositional defiant disorder (ODD) can be found, complicating firm diagnoses [4]. Until now, this phenotype is called severe mood dysregulation (SMD), ADHD plus affective dysregulation, or PBD-broad phenotype (PBD-BP). Considering the difficulties to find diagnostic consent for this phenotype, there is a current discussion about adding a new diagnostic entity within the mood disorders section of the forthcoming DSM-5 called disruptive mood dysregulation disorder (DMDD). For this dysregulated phenotype, which will be further referred to as SMD, a substantial lifetime prevalence of 3.3% can be found [3].

Evidence suggests that children and adolescents with SMD show severe impairment across multiple settings. A longitudinal study indicated that adults with higher dysregulation scores in childhood were at increased risk for ADHD, mood and substance use disorders, suicidality, and poorer overall functioning at age 19 [5]. The authors further suggest that “severe dysregulation represents an early risk marker of a persisting deficit of self-regulation of affect and behavior underlying different psychiatric disorders” [5] p.5/6. Importantly, associations between irritability in childhood and depression in young adulthood can be found [3]. Moreover, characteristics of SMD are a reduced need for sleep and the depressive symptomatology itself that might develop into major depressive disorder or generalized anxiety disorder in the longitudinal course [6–11]. These results highlight the importance of early interventions with combination treatments considering the range of symptoms present in this specific phenotype. Due to missing diagnostic categories, the development of specific treatment approaches and systematic research that account for the severity of the disorder has until now been complicated. Nevertheless, first clinical trials with medication and behavioral therapy were established based on the considerable overlap to ADHD and PBD.

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First treatment approaches for SMD

Regarding the similarity to PBD, a clinical trial with the mood stabilizer lithium was conducted for children with SMD which, however, did not show any superiority to placebo and was not associated with significant clinical or neurometabolic alterations [4]. Furthermore, given the high comorbidity to ADHD, stimulants have been in the focus as a possible treatment approach [12]. Following stimulant medication, significant improvements were reported, indicating a decrease of ADHD, ODD, and mood symptoms. A first combination treatment including varying intensities of behavior modification therapy (BMOD) and stimulant medication (methylphenidate, [MPH]) was established for ADHD and SMD subjects [12]. Results show that MPH and BMOD are effective and tolerable treatments for children presenting with both disorders. The authors, however, state that SMD subjects were more likely to remain significantly impaired than non-SMD subjects after an intervention period of 3 weeks. In another treatment trial, Waxmonsky et al. (2010) created a novel group-based therapy [13]. Children with ADHD and SMD were randomized to receive either psychosocial community treatment or group therapy for 11 weeks. They were held on an optimal dose of stimulant medication prior to randomization. Group therapy program consisted of concurrent 90 min sessions of parent and child groups. Following these groups, children showed a significant decline in levels of suicidal ideation whereas parents showed more positive parenting behaviors. More recently, controlled combination trials with divalproex and behavioral therapy have been initiated for a phenotype similar to SMD, showing that this treatment is superior to combination trials including stimulants, behavior therapy and placebos [14,15].

These first treatment approaches are promising but, nevertheless, they are preliminary and indicate that no treatment up to date does account for the severity and the range of symptoms that is present. One of such a possible new treatment approach might lie in the change of a specific biological rhythm, i.e. the sleep-wake cycle that is also called the circadian rhythm. The following section provides insight why this idea is worthwhile considering.

The circadian rhythm and sleep homeostasis – their role in affective functioning and psychiatric disorders

There are two different systems that regulate sleep and waking: the circadian rhythm, which is the endogenous 24 h cycle influenced by physiological and environmental (e.g. light–dark cycle) processes, and a homeostatic mechanism. The latter is a regulatory system enabling organisms to, e.g. compensate for the loss of sleep. This homeostatic process reflects sleep pressure and can be measured quantitatively in electroencephalographic (EEG) slow-wave activity [16]. The “two-process model of sleep regulation” by Borbély (1982) assumes that it is the interaction between both, the sleep-wake independent, circadian and the sleep-wake dependent, homeostatic process, which is essential for satisfactory sleep [16,17]. Interestingly, during waking, both processes may also influence neurobehavioral functions, that might have an effect on attention, memory, and learning [18].

The circadian rhythm itself is essential in daytime functioning and has been found to be disturbed in various psychiatric conditions [19]. Sleep parameters appear to be directly linked to mood, stress, and emotions [20]. Considerable evidence suggests that emotional regulation is undermined by sleep deprivation the night before [21] and that severe and adverse effects on cognitive functioning can be observed as a result [22]. Furthermore, it was shown that solely the perception of one’s own sleep affects one’s daytime functioning [23]. Interestingly, there is a bidirectionality of affect and sleep regulation [24], indicating multiple consequences of disturbed sleep including impulsivity, difficulties with attention, and cognitive disruptions [25]. Longitudinal studies indicate that sleep quality and time in bed has a substantial impact on adolescent problem behavior. Poor sleep quality seems to be related to internalizing problem behavior, such as depression, and anxiety [for a review, see [26,27]], but has also been related to externalizing problems, such as aggressive behavior. These results indicate a complex interaction between sleep problems, psychosocial factors, and behavioral dysregulation [28], emphasizing the importance of a well-functioning circadian rhythm.

Two hormones, melatonin and cortisol, can be described as the “hands” of the circadian clock modulating the sleep-wake cycle [29]. These are regulated by the suprachiasmatic nucleus (SCN) across the 24 h day, which receives input from the environmental light/dark cycle [30]. When melatonin and/or cortisol are dysregulated, the circadian rhythm gets out of synchrony. This desynchronization plays an essential role in many psychiatric conditions [19].

With regards to sleep homeostasis in psychiatric disorders, it has been suggested that slow wave sleep is typically reduced in e.g. depressed patients [31], and that sleep regulation has been found to be deficient [32]. It can also be assumed that both circadian dysfunctions and homeostatic abnormalities play a role in PBD [20,33,34]. For example, a significant delay in circadian phase, thus a delay of sleep onset and late waking, has been hypothesized to be a core symptom of PBD [35]. Furthermore, a hallmark of PBD and SMD is a reduced need for sleep [7.9–11,20,36]. Objective sleep measures in PBD in adolescents showed that this group exhibits lower sleep efficiency, longer slow-wave sleep and reduced rapid eye-movement sleep (REM sleep) compared to healthy controls. REM sleep has been associated with affects aversive functioning ([for a review, see [20]], and disruptions in REM sleep seem to be associated with psychiatric conditions. Moreover, these sleep disturbances contribute to relapse, negative effects on mood, motivation, and deficits in cognitive functioning. Harvey (2008) suggests that sleep disturbance is commonly co-morbid with PBD, indicative for the quality of life and important for affective dysregulation, since better sleep positively influences affect regulation [29]. Disturbed sleep characteristics, such as disturbances in sleep-continuity at sleep onset and throughout the night can also be observed for children with SMD [37]. It is noteworthy, that children with so-called PBD have significantly higher rates of sleep difficulties than children with ADHD [38,39].

However, in ADHD, circadian phase delays can be observed as well. Approximately 40% of adults with ADHD have a delayed circadian phase. This delay is correlated with subjective problems of impulsivity, and results in problems adapting to daily schedules and demands [40]. Moreover, by a delayed endogenous circadian pacemaker influences on a physiological level can be seen. The dim light melatonin onset (DLMO) is delayed and a greater phase angle between DLMO and wake-up time is visible [41]. Subjectively, in about 25–50% of all subjects with ADHD sleep problems such as night awakenings, alterations in REM sleep [42], restless sleep or difficulties falling asleep can be found [43]. In a recent meta-analysis, Cortese et al. (2009) could show that children with ADHD show significantly higher parent-reported impairment in some objective sleep parameters, revealing fragmented sleep, poor sleep efficiency, and more excessive daytime sleepiness than healthy controls [42]. It is indicated that these disturbances are likely to contribute to executive dysfunction [44].

Summing it up, circadian dysfunctions and sleep problems are characteristics of ADHD, SMD and affective disorders, and might contribute to, and even worsen symptoms during the course of the disorders. Therefore, sleep improvements might significantly contribute to improvements in behavioral and emotional functioning. One way to achieve circadian rhythm improvements is by applying chronotherapy.

What is chronotherapy?

Chronotherapy is the controlled exposure to environmental stimuli (e.g., light) acting on biological rhythms for achieving therapeutic effects in the treatment of psychiatric conditions [45,46]. Chronotherapy comprises sleep deprivation (SD) as well as light therapy (LT) in order to accomplish antidepressant and mood stabilizing responses [45]. LT has evolved as a promising, non-invasive antidepressant primary agent for the treatment of seasonal affective disorder (SAD) and more recently for major depressive disorder as well [47–49]. Moreover, improvements in the level of anxiety were observed as a result of a chronobiological intervention [50].

Although only few randomized-controlled trials have been conducted up till now, LT might be the treatment of choice when dealing with psychiatric disorders in which the circadian rhythm is clearly disrupted. LT is safe, cost-effective and high patient compliant because of only 30–60 min of daily administration necessary [45]. Physiologically, when administered in the early morning, LT has been shown to have an effect by suppressing melatonin production and thereby advancing circadian rhythms [48,51]. Moreover, morning exposure to bright light decreases cortisol levels that usually peak after waking-up [52]. Hence, with morning light administration, phases (timing of sleep) can be shifted, and circadian rhythms can be stabilized [45,53].

Recent literature suggests using LT not only for SAD for which it actually was designed. Any psychiatric disorder in which circadian rhythm disturbances are present might be eligible for adjunctive co-treatment with light: “Evidence is emerging that the worse entrainments of the sleep-wake cycle, the worse the psychiatric symptoms, independent of diagnosis” [53, p.2]. Thus, co-treatment with LT is likely to have substantial effects on psychiatric symptoms and may be considered to be applied on a regular basis in order to positively influence circadian and affective functioning.

Chronotherapy in bipolar depression and ADHD

Evidence indicates the efficacy of chronotherapy in SAD and major depressive disorder [46,50,53]. In other disorders with circadian dysfunction, such as SMD, ADHD, and bipolar depression (BD), the evidence has to be considered more preliminary. In BD, for example, antidepressant response was observed as a result of a combination of SD and morning LT. Additionally, improved daytime activity as well as sleep phase advance, i.e. the advance of sleep onset, were shown [54].

In ADHD, chronotherapy has been studied in first treatment trials. In an early single case intervention study including a girl with attention deficit disorder, bedtime was delayed by 3 h a night for 7 consecutive nights [55], improving her irritability, alertness, and oppositional behavior considerably. Due to the nature of the study, however, results have to be interpreted with caution. Another case study of a girl with symptoms of ADHD, SAD and delayed sleep phase syndrome showed improvement in energy level, concentration, and sleep phase advance as a result of morning LT [56].

Ryback et al. [2006] applied LT in a more systematic manner [40]. After 3 weeks of LT, improvement of ADHD symptoms in adults from impaired to normative was noted on measures of attention and impulsivity, on signal detectability and on a measure of visual perceptual ability. Thus, morning bright LT was associated with a significant reduction in both subjective and objective measures of core ADHD pathology, improved mood symptoms, and a significant phase advance in circadian preference, with the strongest predictor of improvement being the circadian phase advance. These results highlight the clinical benefits of LT that go beyond the treatment of SAD.

Approaching SMD with light: evaluation of a hypothesis

Even though first interventions have shown improvements of specific symptoms that are present in SMD, they have failed to find a treatment accounting for the whole range of symptoms, highlighting the importance of finding an adequate approach. This paper introduces such a novel therapeutic treatment for SMD. LT has shown positive effects on circadian functioning beyond depression, indicating more general benefits. Based on the overlap to disorders such as ADHD, children and adolescents with SMD are very likely to show disturbed circadian functioning, as first results support this notion by showing a reduced need for sleep [9].

Since a decrease of symptoms, a stabilization of circadian rhythms, sleep phase advance, and improvement in overall daily functioning can be observed as a result of LT in ADHD and BD, we hypothesize a similar positive influence as a consequence of applying chronotherapy, specifically LT, in SMD. Stabilizing circadian rhythmicity in SAD has shown positive influences on behavior, irritability and core ADHD pathology, an improvement that might be observed in SMD as well. Importantly, a study with substance-abusing adolescents indicated that improved sleep time resulted in a significant reduction in aggressive thoughts and actions [57]. In demented patients, a significant reduction of aggression was observed following 10 weeks of LT [58]. Thus, we hypothesize that corrected sleep and LT treatment might not only contribute to enhancements in emotional functioning, but also to beneficial influences on behavior, a desirable outcome for youth with SMD. On a physiological level, positive effects on cortisol levels and melatonin production are expected.

Secondly, since SMD is a mood disorder with depression being a core symptom, and since children with SMD are likely to develop a major depression later in life [6], we hypothesize LT to be an essential preventative treatment. It is expected to induce similar chronobiological effects in SMD as in other psychiatric disorders (e.g. in SAD), thereby leading to positive, direct influences on mood dysregulation, and to alleviation of depressive symptoms.

In conclusion, by means of LT, circadian functioning, sleep, externalizing behavior, depressive symptoms, and general daytime functioning in adolescents with SMD might benefit.

Conflict of interest statement

Prof. Holtmann served in an advisory or consultancy role for Lilly, Novartis, and Bristol-Myers Squibb, and received conference attendance support or was paid for public speaking by AstraZeneca, Janssen-Cilag, Lilly, Neuroconn, Novartis, Medice and Shire. The present work is unrelated to the above grants and relationships. The other authors have no conflicts of interest.

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2.4 Morning bright light therapy: a helpful tool for reducing co-morbid symptoms of affective and behavioural dysregulation in juvenile depressed inpatients? A pilot trial

In this pilot trial with a sub-sample (EG: N= 16 vs. CG: N= 11) of the main study (see 2.2) it is investigated whether depressed inpatients with co-morbid symptoms of affective and behavioural dysregulation benefit from using morning BLT, and whether BLT elicits direct effects on the symptom level of affective and behavioural dysregulation (assessed with the Strengths and Difficulties Questionnaire-Dysregulation Profile; SDQ-DP). Since we assume an intimate relationship between sleep, circadian preference, affect regulation, and emotional and behavioural functioning we hypothesize that changes in sleep quality and sleep restoration, shifts of circadian preference and improvements of symptoms of affective and behavioural dysregulation are correlated with each other. Improvements of sleep and a circadian phase advance as a result of BLT, moreover, are assumed to be of predictive value for a reduction of affective and behavioural problems. As described in the main study (see 2.2), participants are randomly allocated to active BLT (10’000 lux) or control BLT (approx. 100 lux), and receive 45 minutes of BLT for a duration of two weeks. SDQ-DP scores, sleep parameters and circadian preference are assessed at baseline, after the intervention and three weeks later. As expected, after two weeks of add-on morning BLT a circadian phase advance was found in participants of the active BLT condition. Sleep quality and restorative sleep showed improvements independent of group allocation. Contrary to our hypothesis, the results did not indicate an additional direct effect on the symptom level of affective and behavioural dysregulation as assessed with the SDQ-DP. However, the correlation and regression analyses indicate that improved sleep parameters and a circadian phase advance seemed to be associated with a reduction of SDQ-DP scores. Therefore, one might assume that improved sleep and an advanced circadian phase might have positively influenced SDQ-DP scores as secondary effect by an indirect, circadian mechanism.
Morning bright light therapy: a helpful tool for reducing comorbid symptoms of affective and behavioral dysregulation in juvenile depressed inpatients? A pilot trial

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Summary: Objective: In recent years, bright light therapy (BLT) has been used to treat depression and to stabilize circadian rhythms. In this study we evaluated whether it is also helpful for comorbid symptoms of affective and behavioral dysregulation in depressive inpatients. Method: This article reports a secondary analysis comparing two subgroups of depressive participants with comorbid affective and behavioral dysregulation, captured with the dysregulation-profile of the Strengths and Difficulties Questionnaire (SDQ-DP; n = 16 vs. n = 11). Participants were randomly allocated to active BLT (10,000 lux) or control BLT (approx. 100 lux), and received 45 minutes of BLT for 2 weeks. SDQ-DP scores, sleep parameters, and circadian preference were assessed at baseline, after the intervention, and 3 weeks later. Results: No direct effects on SDQ-DP scores were observed. Sleep improved in both conditions. Only in the active BLT condition was a circadian phase advance found. Correlation and regression analyses indicated an indirect, circadian effect for improved SDQ-DP scores. Conclusions: The data of this pilot trial should be considered preliminary and merely descriptive. Further research is warranted.

Keywords: Bright light therapy, adolescent inpatients, SDQ-dysregulation profile, sleep, circadian preference

Introduction

A mixed psychiatric condition conceptualized as severe affective and behavioral dysregulation in children and adolescents has gained interest in recent years and can be captured by specific dysregulation subscales derived from existing items on either the Child Behavior Checklist (CB-CL-Dysregulation profile [CBCL-DP]; Althoff, Verhulst, Retew, Hudziak & van der Ende, 2010; Holtmann et al., 2007; Hudziak, Althoff, Derks, Faraone & Boomsma, 2005) or the Strengths and Difficulties Questionnaire (SDQ-Dysregulation profile [SDQ-DP]; Holtmann, Becker, Banaschewski, Rothenberger & Roessner, 2011; Woerner, Becker & Rothenberger, 2004). Predominant symptoms of
children and adolescents with severe affective and behavioral dysregulation include irritability, aggression, “affective storms,” hyperarousal, mood instability, and suicidal behavior (Holtmann et al., 2007). Moreover, severe dysregulation of affect and behavior has consistently been found to be associated with difficulties falling sleep and sleeping through the night as well as a reduced need for sleep (Ayer et al., 2009; Holtmann, Bölte, Goth & Poustka, 2008; Legenbauer, Heiler, Holtmann, Fricke-Oerkermann & Lehmkuhl, 2012; Mehl et al., 2006). Since a complex interaction exists between sleep and both internalizing and externalizing symptoms (Fallone, Owens & Deane, 2002; Meijer, Reitz, Dekovic, van den Wittenboer & Stoel, 2010), one gateway for the treatment of severely dysregulated youth – and for the prevention of devastating long-term consequences – may lie in the resolution of their sleep problems. Interventions targeting sleep disturbances in youth showed improvements of both behavioral and emotional functioning (Harvey, Mullin & Hinshaw, 2006).

One type of intervention influencing sleep disturbances and shifting circadian preference is morning bright light therapy (BLT; Gooley, 2008). The use of BLT as an adjuvant, innovative treatment option for affective and behavioral problems was recently proposed (Heiler, Legenbauer, Bogen, Jensch & Holtmann, 2011). Initially developed as a treatment for seasonal affective disorder, BLT was subsequently shown to improve depressive symptoms, sleep quality, and reset circadian parameters (Even, Schroeder, Friedman & Rouillon, 2008). In a primary analysis of a 2-week randomized controlled study on the feasibility and clinical effects of BLT in 57 depressed juvenile inpatients, compared to a dim light control condition BLT led to specific improvements of subjective sleep parameters as well as to a shift of circadian preference toward morningness (Bogen, Legenbauer, GEST & Holtmann, 2015). Enhanced sleep quality and the circadian phase advance largely predicted the reduction of depressive symptoms. Based on these results, this explorative secondary analysis examines whether BLT also has beneficial effects on the regulation of sleep and circadian phase in youths with comorbid severe affective and behavioral dysregulation as well as on the symptom level of affective and behavioral dysregulation (Heilozc et al., 2011). Because one may assume an intimate relationship between sleep, circadian preference, affect regulation, and emotional and behavioral functioning (Neizert Semler & Harvey, 2005; Van Dongen, Maislin, Mullington & Dinges, 2003; Gau et al., 2007; Harvey et al., 2006), we hypothesize that changes in sleep quality and sleep restoration, shifts of circadian preference and improvements in affective regulation are correlated with each other. Improvements of sleep and a circadian phase advance as a result of BLT are assumed to be of predictive value for a reduction of affective and behavioral problems.

**Methods**

**Sampling**

A group of 57 medication-naïve participants between 12 and 18 years were recruited from an inpatient psychiatric care setting. All of them had a diagnosis of moderate to severe depression according to ICD-10. Thereof, 27 participants additionally showed symptoms of affective and behavioral dysregulation as assessed with the SDQ-DP. For a detailed participant flow chart of the original sample see Bogen et al. (2015).

**Design and Procedure**

One week after admission to a tertiary care hospital for child and adolescent psychiatry, eligible participants were informed about study objectives and the study design by one of the main investigators. They randomly received 2 weeks of either active (10,000 lux) or inactive (100 lux) BLT in addition to treatment as usual on the respective units (TAU – including individual and group psychotherapy in addition to medical, psychological, and nursing care; approaches such as in-hospital schooling, occupational therapy, arts therapies, sports and movement therapy, and family-focused interventions). In order to reduce possible expectation bias, participants were informed that the aim of the study was to compare to different types of BLT. Interventions were conducted following the “Clinician’s Manual for Light and Wake Therapy” (Wirz-Justice, Benedetti & Terman, 2009), and were conducted five times a week, 45 minutes each, for a total duration of 2 weeks. Behavioral assessments were made before entering the study (T1), after 2 weeks of intervention (T2; T1-T2 → 2 weeks in between), and 3 weeks later (T3; from T2-T3 → 3 weeks in between).

This study was approved by the Medical Ethical Committee of the Ruhr University Bochum, Germany (Reg.-No. 3996-11). Written consent was given by both the participant and the person with primary custody. For a more detailed description of the study design and trial procedures see Bogen et al. (2013).

**Measures**

**Strengths and Difficulties Questionnaire (SDQ)**

The SDQ was used to identify participants with symptoms of affective and behavioral dysregulation. Normally, the SDQ is conducted as a brief behavioral screening questionnaire comprising 25 attributes assessing emotional symp-
toms, conduct problems, hyperactivity/inattention, peer-
relationship problems, and prosocial behavior (Goodman,
1997, 2001; Klasen et al., 2000). More recently, a score de-
ferred from certain existing items of the SDQ has been used
to assess symptoms of affective and behavioral dysregula-
tion (SDQ-DP; Holtmann et al., 2011a) and to monitor
short-term changes of SDQ-DP scores during the BLT trial
(Goodman, 1997). The following items were identified as
capturing this so-called SDQ-DP: Item 13 “often unhappy,
down-hearted or tearful”; item 8 “many worries, often
seems worried”; item 12 “often fights with other children or
bullies them”; item 22 “steals from home, school or else-
where”; item 2 “restless, overactive, cannot stay still for
long”. The self-report version of the SDQ was used since
self-ratings from adolescents were shown to better contribute
to the diagnostic process in the clinical setting than rat-
ings by parents (Arman, Amel & Maracy, 2013; Van der
Meer, Dixon & Rose, 2008). Psychometric properties of the
SDQ-DP were robustly tested and validated (Holtmann et
al., 2011a; Woerner et al., 2004). Instructions were given
that the SDQ was used to assess affective and behavioral
symptoms over the last week.

Sleep Questionnaire B – revised (SF-B/R)
The SF-B/R was used to subjectively assess sleep and sleep
difficulties (Görtelmeyer, 2011). It contains 31 questions
assessing the last 2 weeks. Sleep indices can be calculated
including “sleep quality” and “restorative sleep.” For clinical
populations, internal consistency can be considered
moderate to excellent (alpha = .68 to .92). Test-retest reli-
ability indicates that relatively stable sleep-related behav-
ior and experiences are assessed (r = .53 to r = .91).

Morningness – Eveningness Questionnaire (MEQ)
The MEQ was administered to estimate circadian prefer-
ence (Griefahn, Künemund, Bröde & Meinert, 2001; Horne & Östberg, 1976). This questionnaire assesses
circadian preference based upon 19 questions that can be
added up to a total score, with higher scores indicating
“morningness” (scores ranging from 59 to 86: moderate
to definite morningness) and lower scores implying
“eveningness” (scores ranging from 16 to 41: moderate to
definite eveningness), with a neutral circadian preference
scores with in between (scores ranging from 42 to 58:
neutral type). Full-scale internal consistency can be con-
sidered sufficient (.82; Shahid, Khairandish, Gladanac &
Shapiro, 2012); a high test-retest reliability was repeated-
ly reported with up to r = .96 (Griefahn, 2002; Kerkhof,
1984).

Statistical Analyses
Secondary analyses of the data were also conducted (for
primary data analyses, see Bogen et al., 2015). The analy-
ses were based on an intention-to-treat sample (ITT sam-
ple). Missing values were replaced by using “last-observa-
tion-carried-forward” values. This method has shown to
be a very conservative data substitution, likely to underes-
timate within-group changes (Prakash, Risser & Mallinck-
rodt, 2008). In order to investigate the course of means of
SDQ-DP scores, sleep quality, restorative sleep, and circa-
dian preference during BLT, 3 × 2 repeated measures GLM
analyses were conducted with time x light condition, with
an alpha level set at .05 to detect significant interactions.
Furthermore, bivariate Pearson’s correlations were calcu-
lated to investigate possible linear relationships between
changes in SDQ-DP scores, sleep quality, restorative sleep,
and circadian preference using difference scores (T1-T2
and T1-T3, respectively). Standard multiple regression
analyses were performed to further analyze the predictive
value of changes in sleep parameters and circadian prefer-
ence on changes in SDQ-DP scores.

Results

Sample Characteristics
Based on self-report ratings, 27 out of 57 participants
(47%) were classified as SDQ-DP positive (exceeding the
SDQ-DP cutoff of 5). Significant group differences at base-
line were found for age and MEQ total score, and were
taken into consideration in further analyses1. No signifi-
cant group differences could be found in relation to gender
or number of co-morbidities (p < .05). Details are shown in
Table 1.

Differences Between BLT Conditions
for Sleep Parameters, Circadian
Preference and SDQ-DP Scores During
the Course of BLT
Results of sleep parameters including sleep quality and re-
storative sleep indicated that participants in both BLT con-
ditions showed improvements, so that GLM measures did

1 In this subsample, no significant group differences of depression scores over time during the course of BLT were found. Therefore, depression
scores were not considered in secondary analyses (F(2, 48) = 0.335; p = .72).

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not reveal significant time × light condition interactions. If we take into account baseline group differences for circadian preference, the scores of participants in the active BLT condition shifted more toward morningness than scores of the control condition, resulting in a statistically significant time × light condition interaction effect. For test statistics please see Table 2.

Against our expectations, BLT did not have an additional direct influence on the symptom level of affective and behavioral dysregulation as measured with the SDQ-DP. Although active BLT proved to positively influence the course of SDQ-DP scores, especially in the short term, GLM repeated measures revealed no significant time × light condition interaction effect. Please see the course of SDQ-DP scores in Figure 1.

### Correlations Between Changes in SDQ-DP Scores, Sleep Parameters, and Circadian Preference

We found significant moderate to large negative correlations between difference scores of SDQ-DP with difference scores of sleep quality, restorative sleep and circadian preference. Details are shown in Table 3.
Predictive Value of Sleep Parameters and Circadian Preference for SDQ-DP Scores

In order to estimate the proportion of variance in the change of SDQ-DP scores that can be accounted for by changes of sleep quality, restorative sleep, and circadian preference, we performed standard multiple regressions. Directly after 2 weeks of BLT (T1-T2), the regression model did not explain a significant proportion of variance. Including follow-up measures (T1-T3), a total of 50% of variance of SDQ-DP difference scores were explained by the coefficients. Changes of sleep quality thereby showed to be a statistical significant predictor for changes in SDQ-DP scores. Statistical indices of the linear regression models are displayed in Table 4.

Discussion

The results of this explorative analysis indicate no additional direct effect of BLT on the symptom level of affective and behavioral dysregulation as assessed with the SDQ-DP. However, the results of the correlation and regression analyses indicated that improved sleep parameters and a circadian phase advance were associated with a reduction of SDQ-DP scores. Only improved sleep quality was of predictive value for a reduction of SDQ-DP scores in the long-term. Based on these results, one might assume that improved sleep and an advanced circadian phase might have positively influenced SDQ-DP scores as a secondary effect by an indirect, circadian mechanism, as was already assumed by Heiler et al. (2011).

Whereas a circadian phase advance was observed in the active BLT condition, neither direct light-induced nor indirect secondary influences of the circadian phase advance on sleep and SDQ-DP were found. Both the daily structures on the units and the therapeutic setting may have positively affected sleep quality and restorative sleep beyond the additional effects of 2 weeks of added BLT. Another aspect to consider is a possible placebo effect, which might have led to improved sleep in both conditions. Placebo effects are relatively high in BLT trials since it is difficult to “blind” a participant when using broad-spectrum intense white light as the active condition (Goldsen et al., 2005). Existing approaches to find a suitable placebo are the use of either dim light (< 300 lux), light of a specific wavelength (dim red light), or using low-density negative air ion exposure as placebo conditions (Goel et al., 2005). However, these approaches often led participants to guess which condition they have been allocated to, thereby influencing expectations. To minimize expectation bias elicited by either bright or dim light, in this trial all participants, irrespective of group allocation, received the same kind of neutral information regarding the use and efficacy of BLT. Since this study was conducted in an acute psychiatric setting and not in a sterile laboratory, setting effects as well as expectation bias cannot fully be excluded and might have elicited additional effects. Further research including different types of placebo conditions is warranted to clarify this issue.

It was assumed that, next to improved sleep, a circadian phase advance would also be reflected in the regression models as an essential factor for a reduction of SDQ-DP scores as was also found by Ryback et al. (2006). This, surprisingly, was not the case in this sample. It is common knowledge that circadian preference, part of normative development in adolescence, shifts toward eveningness. It is, however, unclear how much time is needed for a circadian phase advance to become clinically relevant or to indirectly influence other symptoms such as affective and behavioral dysregulation as secondary effect. Since circadian preferences show rather long-term effects on affect and behavior (Gau et al., 2007; Goldstein et al., 2007; Lange & Randler, 2011; Van der
Heijden et al., 2013), the time frame in this sample might have been too short to assess the follow-up effects of a shifted circadian rhythm.

Limitations

Several limitations have to be discussed. First of all, this article reports results of a secondary analysis including subgroups with only few participants of a larger sample, which is a main weakness. Also, BLT was added to TAU on the respective units. TAU was identical for all participants, although we did not assess, for example, the number of psychology sessions or potential other confounders such as menstrual phase, another limitation of the study. Affective and behavioral problems were assessed by using the SDQ-DP score (Woerner et al., 2004), which only constitutes a screening measurement and cannot be compared to a thorough clinical evaluation. There are no norms for the SDQ for a 2-week window as it was used in this study. However, it has proved to be a robustly tested and validated possibility of assessment (Holtmann et al., 2011a). Whereas in population-based studies prevalence rates of affective and behavioral dysregulation generally vary between 1%–3.8%, in clinical contexts the rate is considerably higher. It is important to keep in mind that prevalence of affective dysregulation may vary due to age (Juksch et al., 2011). In the present sample, however, the rate of participants with a positive SDQ-DP was considerably higher with 47% of all participants. One has to consider that the SDQ-DP partly assesses depression-related symptoms with the items “often unhappy, down-hearted or tearful” as well as “many worries, often seems worried”. Since all of the participants had a diagnosis of moderate to severe depression, one might assume that the high rate of SDQ-DP positive in this sample might rather have reflected the severity and variety of affective and behavioural difficulties instead of the specific phenotype discussed in the literature (Holtmann et al., 2011; Juksch et al., 2011).

Another limitation constitutes the short time frame in which BLT treatment was possible. Although a short duration (2 weeks) seems to be just as effective as a longer duration (5 weeks; Levitt & Levitan, 2003) for depressive symptoms, for symptoms of affective and behavioral dysregulation no empirical recommendations are yet available. This study was conducted in an intensive psychiatric care setting. Therefore, taking into account the first week in which the participants got the possibility to familiarize with the setting, daily interventions and the possibility to monitor follow-up effects were restricted. The effects of sleep and circadian preference on affect can, particularly, be seen in the long term (Gau et al., 2007; Goldstein et al., 2007; Lange & Randler, 2011; Van der Heijden et al., 2013). In future studies, it seems essential to monitor the long-term effects of BLT to follow-up on the secondary effects of a circadian shift toward morningness. It can be assumed that more time is needed for a phase advance to positively affect affective and behavioral dysregulation.

In summary, although no direct effects on the symptom level of affective and behavioral dysregulation were found, results indicated that sleep quality and a shift of circadian preference toward morningness might positively influence SDQ-DP scores by an indirect, circadian mechanism. These results seem promising, although they need further testing, since the data presented must be considered as preliminary with merely descriptive, hypothesis generating results that should be interpreted cautiously.

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3 Discussion

The discussion section of this thesis is subdivided into a brief introduction which is followed by a question-based discussion of the results. In the end, general limitations of using BLT for children and adolescents including a conclusion will be presented. Future perspectives will be outlined.

Juvenile depression is one of the most prevalent psychiatric illnesses in adolescence (1.1.1). For many years, a bi-directional association between the psychopathology of depression, disruptions of the circadian rhythm and sleep disorders has been postulated (1.1.2). Specifically, juvenile depression has been linked with problems of sleep onset, sleep maintenance, waking up early and daytime sleepiness. Prevalence of co-morbid sleep disturbances with up to 75 % in juvenile depression seems to exceed those found in adults. In addition, sleep disturbances are a common residual symptom when depression is incompletely remitted (1.1.3).

Morning BLT is a non-invasive, well tolerated and well accepted method that is able to shift circadian rhythms, improve sleep and depression (1.2.1). It has a very favorable risk-to-benefit ratio, side effects are rarely found. So far, BLT has mainly been conducted with depressed adults, of seasonal and non-seasonal type. Meta-analytic evidence has proven that BLT can be considered a potent alternative to antidepressant drug treatment in non-seasonal depression (1.2.2). In adolescents, clinical trials investigating feasibility and efficacy of BLT for non-seasonal depression are scarce and have to be considered preliminary. First BLT trials that were conducted in the 1990’s showed promising results for treating seasonal depression and sleep disturbances (1.2.3). In non-seasonal depression, a recent randomized cross-over trial with mildly depressed adolescents between 14 - 17 years showed that add-on BLT was superior to a dim-light placebo condition (Niederhofer & von Klitzing, 2012).

Literature indicates that BLT can be used as co-treatment for any psychiatric disorder in which circadian irregularities or sleep disturbances are present due to its favorable effects
on circadian and emotional functioning as a whole. One of such a psychiatric disorder among children and adolescents that has been discussed in recent literature is affective and behavioural dysregulation (1.2.4). This condition is characterized by abnormal baseline mood, including irritability, anger and sadness, “affective storms”, hyperarousal, and temper outbursts. Like in depression, dysregulation of affect and behaviour has consistently been found to be associated with sleep disturbances and disruptions of circadian functioning, which indicates that BLT might constitute a potential treatment approach for this phenotype as well.

Major aims of this thesis were to 1) design and establish a trial protocol for depressive adolescent inpatients and to investigate whether 2) an intervention like morning BLT constitutes a feasible treatment option for depressed adolescents in an intensive psychiatric care setting. It should also be explored whether 3) two weeks of morning BLT improve juvenile non-seasonal depression, and positively affect sleep parameters and the circadian rhythm. Further aims of this thesis were to 4) illustrate the rationale for using BLT for symptoms of affective and behavioural dysregulation, and to 5) investigate whether morning BLT can be an effective add-on treatment option for co-morbid symptoms of affective and behavioural dysregulation.
3.1 What could be an effective and feasible trial protocol for using BLT in depressive adolescent inpatients in an intensive psychiatric care setting?

Below, the rationale and design of the trial protocol is presented. It was published in the journal TRIALS in 2013.

BLT has been accepted in the Clinical Practice Guidelines by the US Department of Health and Human Services as well as in Treatment of Psychiatric Disorder by the American Psychiatric Association (Rosenthal, 1995). However, since there is a considerable heterogeneity of study protocols with differences regarding types of depression (seasonal vs. non-seasonal), control conditions (dim red light vs. dim white light), total durations (1 – 5 weeks), and light intensities (1,000 – 10,000 lux) that are currently used, a necessary requirement and the first aim of this thesis was to design a standard trial protocol for a feasible and effective use of BLT in an intensive psychiatric care setting for depressive adolescents.

Practical considerations that have to be made when using BLT as a therapeutic agent comprise light intensities, durations of light sessions, time point of light exposure, frequency of the applied light, and possible control conditions. Generally, BLT is conducted using a light box with fluorescent lamps, a reflector and a diffusing screen. For the achievement of a therapeutic effect light intensities of 5,000 – 10,000 lux (measured at eye level using a lux meter) with a distance of about 60 - 80 cm from the light box are considered a standard requirement (Konstantinidis & Winkler, 2004). Although the patient is required to face the screen, it is not necessary to directly gaze into the light. Peripheral retinal stimulation can be fully achieved with a downward gaze. However, eyes have to remain open throughout treatment. Light treatment is recommended to start with a dose of 30 minutes and a light intensity of 10,000 lux and can be extended in case of insufficient response (Lam & Levitt, 1999). To ensure that all participants (also those that might be late for the light session) receive a minimum of 30 minutes of BLT per day, in this trial protocol the total duration was
set to be 45 minutes each day. During the interventions, patients can be allowed to have breakfast or read magazines and books with neutral content (e.g. magazines containing plain information without emotional arousing material). Since a total duration of 7 – 14 days has shown to be effective when treating non-seasonal depression (Wirz-Justice et al., 2009; Al-Karawi & Jubair, 2016), a total duration of two weeks was proposed in the trial protocol to be effective and possible within the inpatient stay. With an average inpatient hospital stay of about 3 – 4 weeks, the first week should be used to give the patient the possibility to accustom to the new situation. The second and third weeks can then be used to conduct the light interventions. In case of one missed intervention (e.g. due to somatic illness) treatment should be prolonged for one day, respectively.

Interventions should be conducted in the mornings. Morning BLT seems to be superior to BLT applied in the evening, since melatonin secretion is thereby reduced, which leads to a beneficial circadian phase advance (Even, Schroeder, Friedmann, & Rouillon, 2008; Golden, 2005; Pail et al., 2011). Compliance of the adolescents is required and can be best achieved by giving clear instructions and information about utilization and duration of light treatment. To achieve a maximum of efficacy, the exact timing of BLT is crucial. By applying BLT about 7,5 hours after the estimated dim-light melatonin onset (DLMO), treatment efficacy can be increased (Gooley, 2008). The DLMO is the time point when melatonin secretion rises over a predefined threshold in the evening, indicating the onset of the subjective night. It can be directly measured via saliva samples or indirectly estimated by using the Morningness-Eveningness Questionnaire (MEQ) developed by Horne and Ostberg (1976). Using this method, BLT can be scheduled individually, thereby increasing efficacy (for an overview of BLT guidelines as they were proposed for this trial protocol, see Table 3).
Table 3 BLT guidelines as proposed in the trial protocol

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity of bright-light device</td>
<td>Fluorescent light box using a light intensity of 10,000 lux (measured at the level of the eyes of the patient using a lux-meter)</td>
</tr>
<tr>
<td>Wavelength of bright-light device</td>
<td>Full-spectrum visible light, fluorescent lamps should have a smooth diffusing screen that filters out ultraviolet (UV) radiation</td>
</tr>
<tr>
<td>Distance from light source</td>
<td>Patients should remain positioned at approximately 60 – 80 cm from the light source (staring into the light source is not necessary)</td>
</tr>
<tr>
<td>Time of day for application</td>
<td>Morning light therapy is more effective than evening light, preferably applied about 7, 5 hours after the individual DLMO for increasing efficacy</td>
</tr>
<tr>
<td>Dose of light</td>
<td>About 45 minutes at 10,000 lux</td>
</tr>
<tr>
<td>Onset of therapeutic effect</td>
<td>For non-seasonal depression: 7 – 14 days</td>
</tr>
<tr>
<td>Maintenance of therapeutic effect</td>
<td>Effect will vanish shortly after discontinuation of therapy</td>
</tr>
<tr>
<td>Possible side effects</td>
<td>Headache, eyestrain, nausea, and agitation; for patients susceptible for hypomanic or manic episodes, BLT might elicit episodes of hypomania or mania</td>
</tr>
</tbody>
</table>

Adapted from Wirz-Justice et al. (2009); Pail et al., (2011).

The exact spectrum of light is still a matter of debate (Kronfeld-Schor & Einat, 2012; Wirz-Justice et al., 2009). There is a considerable amount of studies proving efficacy of white light being superior to other colors. Following the discovery of a novel circadian photoreceptor containing the photopigment melanopsin and which is sensitive to blue wavelengths, blue light therapy devices were introduced to the market without proving superiority over white light. Long-term safety issues for using blue light have not been considered up until now, where blue light might contribute to certain retinopathies (Wirz-Justice, 2010). White light, by contrast, has proven long-term ocular safety (Gallin et al.,...
1995), and has therefore been chosen for this trial protocol involving adolescents. Nevertheless, before a patient can be treated with bright light, an ophthalmological evaluation might be recommended in case of a family history of eye illnesses. Other contraindications besides pre-existing medical conditions of the eyes and skin include the intake of photosensitizing drugs (neuroleptics, antirheumatic drugs, St. John’s Wort etc.) that have to be assessed when controlling for eligibility.

Developing a placebo condition for BLT is difficult and controversially discussed in the literature. In the beginning of BLT trials dim-light control conditions were commonly applied (< 300 lux), often by using different colors than in the respective experimental conditions. These studies revealed that expectations of the subjects often predicted trial outcomes. Blinding participants when white light is applied is a difficult challenge, since participants can often guess in which condition they are. Up to date, there have been numerous approaches to find a suitable placebo condition for BLT, including dim bright light, dim red light as well as using low-density negative ion generators which have been used in more recent studies (Pail et al., 2011; Burgess, Fogg, Young, & Eastman, 2004). A different approach of creating a valid placebo condition, and which was proposed in this trial protocol, might involve changing participants’ expectation by instructing them that two different (but equally effective) types of light therapy devices are compared. For this reason, we have chosen professional light devices for both light conditions, adjusting the lux levels to 100 lux and 10,000 lux, respectively. Importantly, all therapists on the patient’s units should be blinded with regards to the allocations of patients to either the active or inactive light condition.

Despite all difficult issues that have to be considered in light trials, BLT is a well-tolerated and a well-accepted treatment tool (Michalak & Lam, 2002). It has a very favorable risk-to-benefit ratio (Terman & Terman, 1999). Side effects are rare. Sometimes headache,
eyestrain, nausea, and agitation are found; these adverse events should be monitored throughout the trial, but are supposed to remit spontaneously after dose reduction (Terman & Terman, 2005; Labbate, Lafer, Thibault, & Sachs, 1994).

3.2 Is morning BLT a feasible treatment approach for depressive adolescent inpatients?

When treating depressed adolescent inpatients in a psychiatric care setting with light, several aspects of feasibility have to be considered. In this thesis, feasibility was informally defined by evaluating of whether the proposed trial protocol (2.1) can indeed be conducted and implemented in the tertiary care setting with juvenile depressed inpatients or whether there is no compliance for such a treatment at all. First of all, a necessary requirement for fulfilling study protocols is the staff’s flexibility and compliance on the respective inpatient units. Since participants were recruited based on depression severity (either moderately or severely depressed) and not divided by units, inpatients of a variety of units took part in the study at the same time, which might constitute an organizational difficulty. This challenge was overcome by repeatedly educating the unit’s staffs and by highlighting the importance of an unproblematic organizational procedure (due to the restricted time frames in which BLT application was possible to ensure a maximum of efficacy). This aspect of feasibility and the possibility of implementing the required aspects given in the study protocol (see 2.1) can be considered fulfilled.

When treating adolescents one particular problem may arise: Non-compliance. A BLT session requires the patients to sit still for about 45 minutes early in the morning (between 7.30 am - 9 am). This can be particularly difficult in comparison to the intake of a pill which needs considerably less effort. One has to keep in mind that chronotype changes with age (Roenneberg et al., 2004), and that circadian preferences are shifted towards eveningness in adolescence. There is a strong peer pressure to socialize late into the night which might make it difficult to explain the benefits of advancing the circadian rhythm by means of BLT.
Considering the drop-out rates of the participants, during the two weeks of morning BLT in the “active” condition N= 2 participants dropped out of the study. In the dim-light control condition there was a total of N= 5 drop outs. However, this difference was statistically nonsignificant. To sum it up, compliance was good by both juvenile participants and the hospital staff that had to incorporate the trial interventions into the schedules of their inpatient units.

Figure 2 illustrates the patient flow for the randomized-controlled trial.

![Figure 2: Patient flow](image)
3.3 Is BLT effective on juvenile depression? Can effects on subjective sleep parameters and circadian preference be found?

Below, the findings of the main randomized-controlled intention-to-treat (ITT) trial investigating clinical effects of two weeks of add-on BLT on juvenile, medication-naïve inpatients with moderate to severe depression are presented (see 2.2). These data were published in the Journal of Affective Disorders in 2016.

With regards to depressive symptoms (assessed with Beck’s depression inventory – II; BDI-II; Beck, Steer & Brown., 1996), the results of two weeks of morning BLT on juvenile depression revealed short-term improvements of depression in both conditions. In addition, remission rates did not differ significantly between light conditions pre-post. Including follow-up measures, after three weeks after interventions have ended, only in the active BLT condition a further statistically significant decrease in depressive symptoms was observed. Although remission rates at follow-up remained on a trend level, almost twice as much remission in the active BLT condition compared to dim-light was found (46.7 % for BLT and 25.9 % for dim-light). Overall, the results on depressive symptoms did not reveal an additional antidepressant effect of active BLT in the short-term; the results of the follow-up assessment, however, might be interpreted as an indication for incipient efficacy of BLT.

With regards to subjective sleep parameters that were assessed with the revised version of the German sleep questionnaire by Goertelmeyer (SFB/R; 2011), short-term improvements of sleep quality (SQ) and restorative sleep (RS) differed between conditions. Post-hoc evaluations of within-subject comparisons indicated that RS occurred only during active BLT and remained stable during follow-up, while the dim-light condition remained without any effect pre-post or during follow-up. Moreover, SQ improved during BLT and increased further over the follow-up period, while in the dim-light condition only a moderate improvement during follow-up was observed, still considerably below that of active BLT. In sum, one can assume light-specific effects of BLT on SQ and RS as assessed in a subjective
manner. These findings are in line with results indicating direct beneficial influences of BLT on sleep which have, for example, been reported for circadian rhythm disorders in adults (Gooley, 2008; Chesson et al., 1999).

Considering the characteristics of chronotype that were assessed with the MEQ (Horne & Ostberg, 1976), in line with our expectations, a time x group interaction effect emerged, indicating that the circadian preference of participants in the active BLT condition shifted towards morningness. Further evaluations of within-subject comparisons indicated significant shifts of circadian preference towards morningness pre-post and including follow-up only in the active BLT condition, whereas in the dim-light condition a significant change emerged only pre-post. In this sample, the results of the circadian preference indicated phase-shifting effects of BLT that have long been observed for BLT (Rosenthal et al., 1990).

To further investigate the relationships between depressive symptoms, SQ, RS, and circadian preference, additional correlations were calculated. Significant correlations between difference scores of depression both pre-post and at follow-up assessment and difference scores of SQ as well as RS were found, implying that improvements of depression and improvements of SQ and RS were related. Moreover, difference scores of depression and changes of circadian preference pre-post were significantly correlated. This result indicated a relationship between improvements of depression and a circadian phase advance during treatment. In addition, difference scores of circadian preference and difference scores of the sleep factors SQ and RS both at pre-post and follow-up showed significant correlations, indicating greater SQ and more RS in combination with a circadian phase advance. To ascertain the influence of sleep and circadian preference on the change of depressive symptoms, linear regression analyses with BDI-II difference scores pre-post and at follow-up were performed. The pre-post regression model was significant and explained 48.4 % of variance of changes in BDI-II scores. Whereas RS-changes and the light condition did not
influence treatment outcome, enhanced SQ and a circadian phase advance were significant predictors for improved depressive symptoms.

Overall, the results of this randomized-controlled trial indicated clinically relevant specific effects of BLT on sleep parameters including SQ and RS, and on circadian preference in moderately to severely depressed adolescents. Whereas, no light-specific effects on depressive symptoms were observed, an incipient efficacy might be assumed when considering follow-up measures. Further, it was shown in line with previous observations, that appropriately-timed exposure to BLT can shift circadian preferences and improve SQ (Gooley, 2008; Rosenthal et al., 1990). Terman et al. (2001) found a shift of circadian preference to be positively associated with changes in depression scores, which was also observed in our results. Since sleep disturbances such as sleep-onset and sleep maintenance problems, and insomnia are very common among adolescents with depression (Liu et al., 2007; Puig-Antich et al., 1982) replication of the presented results in a larger sample with an extended period of BLT is necessary to confirm its potential as an adjunct therapy for juvenile depression.

3.4 What is the rationale for treating affective and behavioural dysregulation with BLT?

Our hypothetical review article (see 2.3) aimed to illustrate the rationale for using BLT as a potential therapeutic tool for treating symptoms of affective and behavioural dysregulation. It was published in the journal Medical Hypotheses in 2011.

In this review it was highlighted that a considerable size of children and adolescents present with a clinically challenging phenotype with symptoms of severe affective and behavioural dysregulation, including non-episodic anger, irritability, hyperarousal, and increased reactivity to negative emotional stimuli (Leibenluft, 2011). Even though first interventions have shown improvements of specific symptoms which are present in affective and behavioural dysregulation (Waxmonsky et al, 2008; Dickstein et al., 2009), up till now,
they have failed to find a treatment accounting for the whole range of symptoms, highlighting the importance of finding an adequate approach. In this hypothetical review a novel therapeutic treatment approach was introduced. Since BLT has shown positive effects on circadian functioning beyond depression, it was proposed that children and adolescents with considerable problems of affect and behaviour are very likely to show disturbed circadian functioning, for example a reduced need for sleep (Holtmann et al., 2007). In “phenotype-similar” disorders (e.g. ADHD or Bipolar disorder), which partly display comparable psychopathologies, BLT was observed to lead to a reduction of core pathology symptoms, a stabilization of circadian rhythms, sleep phase advance, and to improvements in overall daily functioning (Dahl, Pelham, & Wierson, 1991; Benedetti et al., 2007). Specifically, stabilizing circadian rhythmicity in ADHD has shown positive influences on behaviour, irritability and core ADHD pathology (Ryback et al., 2006). Further effects on behaviour were illustrated in a study with substance-abusing adolescents indicating that improved sleep time resulted in a significant reduction in aggressive thoughts and actions (Rosenthal, 1995b). Also, in demented patients a significant reduction of aggression was observed following ten weeks of BLT (Haynes et al., 2006).

Thus, it can be hypothesized that corrected sleep by means of BLT might not only contribute to enhancements in affective and emotional functioning, but might also lead to beneficial influences on behaviour, a desirable outcome for adolescents that show symptoms of affective and behavioural dysregulation. In addition, since symptoms of affective and behavioural dysregulation is a mood disorder with depression being a core symptom, and since these symptoms are likely to develop into a major depression later in life (Stringaris, Cohen, Pine, & Leibenluft, 2009), this review also emphasizes that BLT might constitute an essential preventive treatment. It is expected to induce similar chronobiological effects as in other psychiatric disorders (e.g. in seasonal and non-seasonal depression), thereby leading to positive, direct influences on mood, and to alleviation of depressive symptoms. Overall, the
results that were presented in this hypothetical review indicate that by means of BLT, circadian functioning, sleep, externalizing behaviours, depressive symptoms, and general daytime functioning in adolescents with symptoms of affective and behavioural dysregulation might benefit.

3.5 Does BLT influence affective and behavioural dysregulation? Is there an additional influence on sleep and circadian preference?

Below, the findings of an explorative analysis of a sub-sample of the main randomized-controlled study (2.1) are presented, specifically evaluating the effects of BLT on additional symptoms of affective and behavioural dysregulation, sleep, and circadian preference. This article was accepted for publication in the “Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie” in 2016.

Based on self-report ratings, 27 out of 57 depressive participants (47 %) were classified as additionally suffering from affective and behavioural dysregulation as assessed with the Strengths and Difficulties Questionnaire – Dysregulation Profile (SDQ-DP; Holtmann, Becker, Banaschewski, Rothenberger, & Roessner, 2011a; Woerner, Becker, & Rothenberger, 2004). Against our expectations, the results indicated no additional direct effect of BLT on the symptom level of affective and behavioural dysregulation as assessed with the SDQ-DP. **Figure 3** illustrates the course of the SDQ-DP scores from baseline to follow-up, separated by BLT condition. Although active BLT showed to positively influence the course of SDQ-DP scores especially in the short term (from T1 – T2), no statistically detectable difference was found.
As expected, with regards to scores of circadian preference (MEQ) it was shown that a greater circadian phase advance was observed in the active BLT condition, resulting in a statistically significant time x light condition interaction effect. Results of the subjective sleep parameters (SFB/R) in this sub-sample, including SQ and RS indicated that participants in both BLT conditions showed improvements.

By additionally evaluating the relationship between SDQ-DP scores, SQ, RS, and circadian preference, it was indicated that improvements of sleep and a circadian phase advance were associated with a reduction of SDQ-DP scores short-term and during follow-up, respectively. Further regression analyses including the predictors SQ, RS, and shifts of circadian preference as respective difference scores showed that in the long-term (T1 – T3) the model could explain 50% of variance of changes in SDQ-DP scores. However, only improved SQ showed to be a statistical significant predictor for improvements in SDQ-DP scores, indicating that an indirect influence of improved SQ might have led to improvements.
of affective and behavioural problems as reflected in reduced SDQ-DP scores. It has previously been described that altered SQ positively influences symptomatology, severity and outcome of a condition (Dueck, Thome, & Haessler, 2012). In addition, Meijer, Reitz, Dekovic, van den Wittenboer and Stoel (2010) found that aggressive behaviours as well as internalizing problem behaviours were related to SQ, which is in line what we found in the regression model. However, we argued beforehand that next to improved sleep, a circadian phase advance would be reflected in the regression model as an essential predictor for a reduction of SDQ-DP scores as was also found by Ryback et al. (2006). This, surprisingly, was not the case in this sub-sample. Since shifts of circadian preference show rather long-term effects on affect and behaviour (Gau et al., 2007; Goldstein et al., 2007; Lange & Randler, 2011; Van der Heijden et al., 2013), it might be assumed that the restricted time frame of this study might have prevented follow-up effects of a shifted circadian rhythm to become visible. It is not clear how much time is needed for a circadian phase advance to become clinically relevant or to indirectly influence other symptoms such as affective and behavioural dysregulation as secondary effect. Since this was an explorative analysis with preliminary and mere descriptive data, further research is warranted.

3.6 General Limitations

There are several major limitations that have to be considered within the scope of this thesis: First of all, due to the naturalistic character of the study, treatment durations were short. During the first week the participants got the possibility to familiarize with the setting. Daily interventions and the possibility to assess follow-up effects were chronologically restricted. Also, standard multimodal treatment should not be affected by the add-on BLT interventions; if necessary, participants of the study were discharged irrespective of the study protocol. With regards to the results on mood, treatment duration of BLT might have been too short to have elicited specific antidepressant effects. For BLT to be efficacious four specific
parameters have to be taken into account: intensity, timing, and frequency of light, as well as the total duration of treatment (Stephenson, Schroder, Bertschy, & Bourgin, 2012; Wirz-Justice et al., 2005). We designed and conducted a trial protocol based on sufficient light intensity, -timing, and –frequency, respectively. Due to the intensive care setting the participants were in, longer durations were not possible in this sample. The most recent meta-analysis investigating the effects of BLT on non-seasonal depression in adults did reveal the greatest efficacy of light when administered for 2 – 5 weeks (Al-Karawi & Jubair, 2016). However, several studies indicated that effects of BLT might need some time to develop and that efficacy increases with a longer treatment duration (Goel et al., 2005; Martiny et al., 2005).

Another limitation is the subjectivity of assessment since solely self-report measurements were used to repeatedly assess affect and behaviour, sleep parameters and circadian preferences. One reason for that is that in adolescents between 11 – 17 years, self-reports seem to contribute better to the diagnostic process than ratings by parents in clinical settings (Arman, Amel, & Maracy, 2013; Bettge, Ravens-Sieberer, Wietzker, & Hölling, 2002; Van der Meer, Dixon, & Rose, 2008). Specifically, reliance on adolescents’ self-reports can be assumed because their subjective perceptions seem to be significant determinants of their behaviour (Meijer et al., 2010; Santor, Messervey, & Kusumakar, 2000). Furthermore, in an actigraphy study it was indicated that, for example, sleep quality can best be assessed by self-reports (Sadeh, 1996). Nevertheless, there were neither external ratings nor any objective measures explicitly restraining the interpretation of the results.

To monitor effects of BLT in the course of the interventions, depressive symptoms as well as affective and behavioural problems were assessed by using the BDI-II and the SDQ-DP, respectively (Woerner et al., 2004; Beck et al., 1996). These are only screening measurements and cannot be compared to thorough clinical evaluations. Especially with regards to the SDQ-DP of the sub-sample (2.4), one has to bear in mind that the rate of
participants with a positive SDQ-DP was considerably high with 47 % of the sample. In population-based studies prevalence rates of affective and behavioural problems are about 1 % - 3.8 %, in clinical contexts the rate might be higher and seems to vary due to age (Juksch et al., 2011). Furthermore, the SDQ-DP score partly comprises depression-related symptoms. Since all participants were moderately to severely depressed as assessed with the BDI-II, one might assume that the high rate of positive SDQ-DP might not have reflected the specific phenotype as it is discussed in the literature (Holtmann, Buchmann, Esser, Schmidt, Banaschewski, & Laucht, 2011b; Juksch et al., 2011), but might rather have reflected severity and variety of affective and behavioural difficulties in general.

Since this study was conducted in an acute psychiatric setting and not in a sterile laboratory, setting effects as well as expectation bias cannot fully be excluded. Positive expectations, positive staff contacts, spontaneous remission, and/ or the “placebo” effect may have contributed to positive responses beyond BLT and, therefore, constitute further limitations. In studies involving mildly or moderately depressed adolescents placebo responses have been reported to be very high in general (Cheung, Emslie, & Mayes, 2005). There is evidence from antidepressant drug trials indicating placebo response rates being higher in children and adolescents (~50 %) than in adults (~38 %; Weimer et al. 2013). Specifically in BLT trials placebo effects are very high since it is difficult to “blind” participants when using broad-spectrum intense white light as the active light condition (Golden et al., 2005). It only seems logical to assume that participants might have been able to correctly guess whether they were allocated to the active or inactive BLT condition (Even et al., 2008). To overcome this bias, participants in both groups were instructed that the aim of this study was to compare two different, but equally effective types of light therapy devices. Besides a possible placebo response, the chosen control condition using dim light of 100 – 150 lux might have had some subtle effect on the circadian rhythm, which could explain the
fact that, regarding depression and symptoms of affective and/or behavioural dysregulation, participants of both BLT conditions improved significantly after two weeks of BLT.

In addition, we exclusively focused on the mere severity of the disorder, not taking into account subtypes of depression, underlying mechanisms and causal explanations for depressive symptoms. By incorporating causal explanations for depressive disorders one can assume that depressions arising from psychosocial difficulties might benefit more from CBT, focusing on the correction of maladaptive thinking and negative lifestyle patterns (Boyce & Barriball, 2010). On the other side, “biologically caused depression” or depression with a seasonal aspect might benefit to a greater extent by influencing circadian functioning with light. It was, for example, shown that for non-seasonal depression modifying circadian functioning and the neurotransmitter system by administering BLT, tryptophan depletion-mediated depression can be prevented by interacting with serotonin function (aan het Rot et al., 2008).

Other minor limitations include interruption by weekend breaks, and lack of daily mood self-assessments that would allow a more detailed picture of responses to BLT. The effects of BLT soon vanish after treatment has stopped. Therefore, it is crucial to continue BLT on a maintenance basis at home. Unfortunately, due to the pilot character of the study, maintenance treatment was not an option in this sample.

3.7 Conclusion and Future Perspective

Overall, based on the results that were presented in this thesis, one might conclude that two weeks of add-on morning BLT do not directly influence depressive symptoms or symptoms of affective and behavioural dysregulation. However, sleep quality, sleep restoration and circadian preference seem to be beneficially influenced. Improved sleep and a circadian phase advance seem to be associated with or are of predictive value for improved depression and improved symptoms of affective and behavioural dysregulation. It seems
likely that some limitations in our study regarding our sample (e.g. treatment duration, sample size, concomitant CBT, severity of depression, the inpatient care setting) might have led to this negative outcome on depression and symptoms of affective and behavioural dysregulation.

Thus, regarding the high co-morbidity of depression and sleep disorders, one might consider adding other chronotherapeutical interventions such, for example, wake therapy which has shown to be a feasible treatment approach for depressive adolescent inpatients in a first clinical trial and which might strengthen the effects on depression (Gest et al., 2015). Additionally, in future studies it seems essential to monitor long-term effects of BLT to follow-up secondary effects of a circadian phase advance. It can be assumed that more time is needed for a phase advance to positively affect depressive symptoms and affective and behavioural dysregulation (Gau et al., 2007; Goldstein et al., 2007; Lange & Randler, 2011; Van der Heijden et al., 2013). Also, future studies may need to prolong the duration of exposure to BLT with larger adolescent samples to replicate the presented results. Since the average length of stay in a hospital may not permit more than two weeks of BLT in many inpatients, BLT should be extended to the subsequent outpatient setting to prevent the disappearance of the acute effects of treatment. Furthermore, to get a more complete picture of the effects of BLT on adolescents with depressive symptoms, and/ or symptoms of affective and behavioural dysregulation, external ratings of symptoms, and objective measures such as polysomnography should be incorporated, which have proven feasibility in adolescents in intensive psychiatric care settings (Shahid et al., 2012). Due to reduced recall bias, also sleep diaries might provide more accurate estimates of self-reported sleep than surveys do (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006; Gradisar et al., 2011; Wyatt, 2004), and which have shown high correlations with objective measures of sleep (Wilson, Watson, & Currie, 1998; Wolfson et al., 2003).
Despite of the importance of effective treatments for juvenile depression and symptoms of affective and behavioural dysregulation, chronotherapeutical interventions, such as BLT, are off the list for insurance reimbursement. One might assume that it is the simplicity of treatment that contrasts with high-tech medicine which leads to the fact that they are often not taken seriously (Wirz-Justice, 2010). It is to be highlighted that BLT is a cost-effective, easy-to-apply method, and compatible with other interventions (psychotherapeutic interventions, antidepressant treatment, and wake therapy). Combining different interventions might accelerate improvements, minimize residual symptoms, prevent relapses, and expedite hospital discharges (Wirz-Justice et al., 2009), which is a highly desirable outcome for depressive adolescents.
4 References


for affective disorders. A clinicians’ manual for light and wake therapy (pp.57-60).

Basel: Karger.


5 Abbreviations

ADHD = attention-deficit/ hyperactivity disorder
BDI-II = Beck’s Depression Inventory – II
BLT = bright light therapy
CBT = cognitive behavioral therapy
DLMO = dim light melatonin onset
ITT = intention-to-treat
MEQ = Morningness-eveningness Questionnaire
PSG = polysomnography
RCT = randomized controlled trial
REM-sleep = rapid eye movement sleep
RS = restorative sleep
SAD = seasonal affective disorder
SCN = suprachiasmatic nucleus
SDQ-DP = Strengths and Difficulties Questionnaire – dysregulation profile
SFB/R = revised version of the German sleep questionnaire – version B
SMD = severe mood dysregulation
SQ = sleep quality
SSRI = selective serotonin reuptake inhibitor
TAU = treatment as usual
UV = ultraviolet
6 CV

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7 List of Publications

2011

2012

2013

2014
2015


2016
