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Chronotherapeutics: An alternative treatment of juvenile depression

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ABSTRACT

Chronotherapeutic treatments, such as bright light therapy, sleep deprivation and sleep phase advance have successfully been established for the treatment of adults with seasonal and major depression. Today, sleep deprivation is supposed to be the fastest acting antidepressant we know of. Combined with bright light therapy, the antidepressive effect can be sustained. Notwithstanding, the effect of sleep deprivation and bright light therapy has not yet been studied in adolescents suffering from juvenile depression. However, because of its growing prevalence rates and the insufficient outcomes of established treatments, such as medication and psychotherapy, alternative treatments of juvenile depression are urgently needed. Furthermore, a high percentage of patients suffer from sleep disorders. Along with their large positive impact on sleep patterns and antidepressive effects, chronotherapeutics are thought to be powerful interventions for patients with juvenile depression. The present study investigates the additional benefit of sleep deprivation combined with bright light therapy, as compared to mere bright light therapy. We hypothesize that both therapies have a positive impact on depressive symptoms and sleep parameters, but that a combined therapy enhances and sustains outcomes.

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Introduction

Sleep and depression in youth

Dealing with sleep problems in adolescence is complex and difficult because sleeping behavior and sleep hygiene change rapidly from childhood to adolescence. Sleep phase delay, the preference to sleep at later hours, and other attractive night activities, such as watching TV, telephoning, chatting etc., lead, in combination with early school starts, to sleep deprivation in the healthy adolescent population [1]. In a large epidemiological study, Gangwisch et al. [2] replicated the findings that depressive symptoms and suicidal thoughts are associated with shorter sleep duration and later bedtimes. They point out that strict bedtimes set by parents lead to longer sleep durations and can therefore be a protective factor against juvenile depression. These results are in line with the findings that depressive adolescents often have a different sleep architecture due to delayed sleep onset, reduced sleeping time, shortened latency of REM-sleep and a higher movement rate in sleep [3]. Sleep disturbances are common in patients with affective disorders and even 75% of patients with juvenile depression suffer from insomnia [4–6]. If sleep is considered as a time of recovery, and as a necessary ingredient for cognitive and physical development, depressive adolescents will experience far less benefit from sleep. We have to keep in mind that 47% of adult men and 55% of adult women with a sleep disorder suffer from some kind of depression [7]. Thus, the comorbidity of these two disorders is very high and there might be a bidirectional relationship between sleep and depression. Chronic sleep deprivation is a potential risk factor for depression, while depression is associated with the inability to fall asleep, sleep disturbances, early wake ups and daytime sleepiness [8,9].

Similar to differences in sleep patterns there are also differences in depressive symptoms of adolescents and adults. These depend on the cognitive, social and emotional developmental stages [10–13]. One of the core symptoms of depression is the depressive mood, but children and adolescents frequently display irritable mood instead [14]. Above all, we must note that with a prevalence of 5–6%, juvenile depression is one of the most frequent psychiatric disorders during adolescence and it is alarming that this prevalence rate has been rising up to 4–8% in the recent years [15,16]. The incident rate is highest in mid and late adolescents and twice as high for girls as for boys [17,18]. As in most psychiatric disorders comorbidities are common. It is of great concern that the long-term prognosis is poor: juvenile depression can lead to further symptoms like suicidal behavior and major depression in adulthood with a limited level of functioning [19–22]. The disorder often becomes chronic, recurrent and leads to significant impairments in social life for example in education, family, societal, academic and occupational function [23].

As outlined above, juvenile depression is a major risk factor for the further development of adolescents. Much research has been done in the last few years concerning efficient treatment methods but unfortunately, available and established treatments are insufficient [16]. The need for alternatives is high. Combined medical

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treatment and cognitive behavior therapy is currently the most efficacious acute treatment [24]. But even under intensive psychotherapeutic and medical treatment, the response rate is only about 37% and hence much lower than in adults [25]. Kennard et al. [25] pointed out that 50% of responders to antidepressive treatment still suffer from residual symptoms like mood and sleep disturbance, fatigue and difficulties in concentration. In a 5 year follow up study, Curry et al. [26] found that 42.9% of partial and full responders suffered from a recurrence. Additionally, it should also be considered that children and adolescents have a higher risk of developing self harm, suicidal behavior and suicidal thoughts when medicated with antidepressants such as selective serotonin reuptake inhibitors (SSRIs) [27–30]. A number of studies were conducted to investigate the safety and efficiency of SSRIs [30]. In the UK, most of the SSRIs and other new-generation drugs are not permitted for patients under the age of 18 since 2003 [31]. After discussions about the safety and efficiency of SSRIs were concluded, the prescription of antidepressants decreased. But as alternative treatments are rare the risk of undersupply of patients with juvenile depression is high [31]. In 2004, the Food and Drug Administration (FDA) of the United States published a "Black Box" warning that only for Fluoxetine, the benefits outweighs the risk of suicide in children and adolescents. In adults chronotherapeutics are an established method for treating major depression and they can be combined with medication and cognitive behavior therapy [32]. But as already mentioned, there are almost no randomized controlled studies involving adolescent patients.

Chronotherapeutics

Psychiatric chronotherapeutics are therapies that use circadian principals to treat mood and sleep disorders by changing the circadian rhythm of patients [32]. The application of chronotherapeutics is based on findings in mammals and the knowledge about a so called "circadian pacemaker" located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. It drives and synchronizes body functions such as sleep–wake circles, hormonal output, as well as performance level and mood which all depend on a 24-h rhythm [33]. For this synchronization, external "zeitgeber", especially light, are needed [34]. Light indirectly prompts hormonal processes, for example the distribution of the pineal hormone melatonin, through a non-visual photic input, ranging from special ganglion cells in the retina to the SCN [35]. Light suppresses the segregation of melatonin, and the melatonin level changes drive the sleep–wake rhythm in mammals [36]. When night or darkness last longer, the length of the nocturnal melatonin segregation extends as well. Bright light in the morning advances the melatonin segregation whereas bright light in the evening delays it. That is why patients treated with morning bright light get tired earlier in the evening. In patients with sleep disorders, the internal and external zeitgebers are not balanced, which leads to a shorter sleep duration and a lower sleep quality [32]. Chronotherapeutics like bright light therapy (BLT), sleep deprivation (SD) and sleep phase advance (SPA) take advantage from the dependency of the hormonal rhythms on external "zeitgebers" and use artificial external ones to rebalance internal and external rhythms.

SD, also called wake therapy (WT), is frequently reported as the fastest antidepressant known and several studies proved that this antidepressive effect appears within hours [37–39]. However, the underlying neuronal and hormonal changes are largely unknown and different theories on this topic exist [37]. Unfortunately, the antidepressive effect only lasts until the next sleep phase and already diminishes while taking a short nap. To prevent a relapse, BLT or SPA can be used [32].

The effectiveness of BLT was foremost established for adult patients with seasonal depression, but the same effect sizes as in pharmacological treatments were also found for non-seasonal depression (effect size 0.52, 95%CI 0.18–0.89 m $p < 0.003$) [40,41]. In 2005, an American Psychiatric Association work group decided that BLT can be a first line treatment for seasonal and major depression [42]. In most controlled clinical trials UV-filtered broad-spectrum white light of about 10.000 lux is used with an exposure time varying between 30 and 60 min per morning [32]. Treatment durations of 2–4 weeks were found to be superior to other schedules and are extensively studied. Many clinical trials on adults show that the antidepressive effect of SD decreases fast when the intervention is not combined with other chronotherapeutics [37,43–45].

As previously mentioned, chronotherapeutics have a positive impact on sleep disturbances which are one of the most frequent epiphenomenons in major depression [37] and are also associated with its severity and therapy outcome [46–48]. Sleeping behavior, sleep architecture and depressive symptoms differ between adults, children and adolescents. The comorbidity of sleep disturbances and depression is higher in children and adolescents and we cannot transfer the findings concerning chronotherapeutics from adults to adolescents [8,4,12,11]. We have to research if chronotherapeutics are as effective in adolescents as they are in adults. Furthermore, as an antidepressive effect has been shown in mere BLT and BLT combined with SD, the question arises which treatment is more effective [40,49,37,43]. We currently have no knowledge of any study that compares these two treatments, therefore, we do not know which additional effect SD provides, with the exception of a fast but fragile antidepressive effect.

Hypothesis

Due to the findings mentioned above we assume the following:

1. Both, mere BLT and combined BLT and SD improve sleeping behavior and reduce depressive symptoms in youth.
2. We expect that SD reinforces the effect of BLT.

Evaluation of a hypothesis

Initial evidence suggests that BLT improves sleep disturbances and depressive symptoms in youth. In a randomized controlled study Niederhofer and von Klitzing [50] explored the effect of dim light placebo and BLT in an adolescent setting. The depressive symptoms improved in both conditions, but BLT was superior. It is important to note that the sample size in this study was small ($N = 28$) and that a control group was absent because all patients received dim light and bright light at different times. Swedo et al. [51] treated children suffering from seasonal depression with either 1 h of BLT and 2 h dawn simulation (experimental group) or low intensive dawn stimulation and 1 h wearing clear glasses during sedentary activities. They showed that BLT combined with dawn simulation is an effective treatment for seasonal depression in children. However, it remains unclear if the effect is due to dawn stimulation, BLT or the combination of the different methods. Bogen et al. compared BLT (experimental group) with a dim light condition (control group) in a juvenile inpatient setting lasting 2 weeks [52]. Both groups improved in sleep parameters and depressive symptoms but the BLT group showed a significantly higher sleep recovery and a more stable antidepressive effect 3 weeks after intervention [53]. The designs of afore mentioned studies differ in many points: duration of BLT, intensity of light, control conditions and the diagnoses (seasonal vs. major depression). Furthermore the sample sizes are mostly small. However, these preliminary findings support our hypotheses concerning the effectiveness of BLT. An overview of studies characteristics is given below (Table 1).

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Table 1
Studies concerning bright light therapy (BLT) and wake therapy (WT) in patients with juvenile depression.

Author	Year of publication	Therapy	Lux/duration	Disorder	N	Age
Naylor et al.	1993	WT	–	Major depression, major depression in remission and psychiatric controls	17	12–17
King et al.	1987	WT, medication	–	Major depression	1	12
Detrinis et al.	1990	WT	–	Major depression	4	Adolescents
Niederhofer and v. Klitzing	2011	BLT and dim light placebo	2.500 lux + 50 lux/ 2 weeks	Depressive symptoms	28	14–17
Swedo et al.	1997	BLT, dust simulator, dark glasses and dim light placebo	2.500 lux, 10.000 lux, 250 lux/1 week	Seasonal affective disorder	28	7–17
Bogen et al.	2013	BLT and dim light placebo	10.000 lux, 100 lux/ 2 weeks	Major depression	60	12–18
Niederhofer and v. Klitzing	2011	BLT and dim light placebo	2.500 lux + 50 lux/ 2 weeks	Mild depressive disorder	2	14 + 17
Papatheo-dorou et al.	1995	BLT	10.000 lux/1 week	Bipolar disorder, depressive episode	7	16–22

With regard to SD in juvenile depression there is even less data and to the best of our knowledge there has been no investigation regarding combined BLT and SD in adolescence. Naylor et al. [54] studied the antidepressive effect of one night of total sleep deprivation in adolescent patients with juvenile depression and other psychiatric disorders. They found an antidepressive effect lasting at least 1 day in patients with severe depression. Responding patients had a benefit from sleep deprivation lasting 3–5 days, which is longer than in adults who mostly relapse totally after the next sleeping period or even a short nap.

As outlined above, depression and sleep disorders exhibit a high comorbidity. In order to enhance therapy outcome, both disorders should be treated at once. If the focus was only on either sleep disturbance or depression, the respective symptoms may improve, but residuals would be likely to remain. Chronobiological treatments provide the opportunity to treat depression and sleep disorders simultaneously and optimize outcomes in terms of faster healing and less residuals.

Special needs of adolescents have to be considered when planning the study. Staying awake one night is not unusual in adolescence and treatment compliance could be increased by a group setting. A higher monitoring rate is needed to keep the patients awake and to suspend side effects. Hormonal and chronobiological changes should be controlled. Sleep diaries and the recording of day and night activity levels with actimeters provide a detailed insight into biological changes. A possible study design should be adapted from research on depressed adults proposed by the research group of Wirz-Justice et al. [32], a leading research group on chronotherapeutics. The aim of the present study is to gather more information concerning the efficiency of BLT and initial evidence for the effectiveness of SD and light therapy in juvenile depression.

The idea to investigate the additional effect of sleep deprivation on BLT is novel and we have not found any earlier study on this topic. Staying awake for 36 h as required in SD is exhausting and if there is no lasting additional effect compared to mere BLT, it is arguable that WT is really necessary. On the other hand, SD could lead to a faster and more effective reduction of depression symptoms, and therefore, a systematic comparison of BLT and combined SD and BLT is needed. In view of the preliminary data indicating an antidepressive effect in adolescents of both BLT and SD, we assume that the combined treatment also does. Combined SD and BLT does have a rapid antidepressive effect in adults [55]. Tao et al. [56] showed that a rapid response to treatment is associated with a better treatment outcome. The fast antidepressive effect of SD may stabilize the effect of bright light therapy and lead to faster recovery and a better outcome.

Conclusion

Chronotherapeutics represent a non-invasive treatment with almost no side effects and high compliance [37]. Chronotherapeutic treatments are well established for depressive disorders in adults, but there is a gap concerning the knowledge of its efficiency for adolescents. As mentioned before, alternative treatments for juvenile depression are urgently needed [16]. Chronotherapeutics can be combined with medication and psychotherapeutic treatment and furthermore can be adapted to individual needs and to inpatient and ambulant setting [32]. Considering the high comorbidity rates of depression and sleep disorders, it is incomprehensible that the idea to treat juvenile patients with combined BLT and SD is novel. Furthermore, there is only a small amount of research concerning bright light therapy. In summary, chronotherapeutics could be a powerful weapon against juvenile depression, and an alternative or an addition to pharmacological treatment, which has not been studied until now.

Conflicts of interest

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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