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Antidepressant chronotherapeutics in a group of drug free outpatients

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ABSTRACT

The combination of Total Sleep Deprivation (TSD) and Light Therapy (LT) has been shown to prevent the early relapses characterizing response to TSD. Despite their proved efficacy, TSD and LT are still far from being considered standard therapy in the inpatient units and no study has assessed their efficacy and feasibility in outpatient settings. We studied 27 drug-free out-patients affected by Major Depression, divided in 7 groups according to the date of the wake night. Patients were administered one night of TSD and received LT during consecutive mornings following a predictive algorithm based on Morningness-Eveningness Questionnaire scores. Severity of depression was rated on Back Depression Inventory Scale (BDI) at baseline, one week and three months after the end of treatment. BDI scores significantly decreased during treatment with no difference between the seven consecutively treated groups of patients. Significant differences in BDI scores were confirmed between the baseline and both one week and three months after the end of treatment. TSD and LT caused a significant amelioration of depressive symptoms in an outpatient setting. Similar effects were observed in seven independent groups, suggesting that there is repeatability in findings. Chronotherapeutics confirmed their efficacy in the treatment of depression.

1. Introduction

Despite the wide number of available antidepressant drugs, many depressed patients show only a partial response if any, with a 55% average antidepressant response rate in double-blind, placebo-controlled antidepressant trials (Papakostas and Fava, 2009). It usually takes several weeks to respond to antidepressant drugs, with the delay in response worsening the burden of disease (Moncrieff, 2005). Effective acute antidepressant therapies are then strongly needed. In spite of many fascinating recent advances, new classes of antidepressant drugs (Holden, 2003) are not yet ready for clinical use. On the contrary, a growing number of clinical studies support the usefulness of chronotherapeutic interventions in the treatment of major depression.

Chronotherapeutics are non-pharmaceutical clinical interventions. These techniques, such as Sleep Deprivation (SD) and Light Therapy (LT), consist in controlled exposures to environmental stimuli that act on biological rhythm (Dallaspezia and Benedetti, 2011). Thus, LT was first developed and has been established as the treatment of choice for winter seasonal affective disorder (SAD): subjects affected by SAD, being hypothesised to have abnormal responses to diminishing day length in autumn, could be treated with morning light signalling a spring dawn (Partonen and Pandi-Perumal, 2009). Nowadays, the use of light therapy has then expanded beyond SAD, with different studies providing evidence for the efficacy of bright LT in non-seasonal major depression (Terman, 2007).

SD was first considered a therapy for depression by following up the clinical observations of rapid antidepressant effects after prolonged wake (Wirz-Justice and Van den Hoofdakker, 1999). During the typical antidepressant SD (total sleep deprivation – TSD-), wake is prolonged throughout the night of treatment. It begins with the extension of daytime wake into the night and lasts about 36 h until the evening of the day after. TSD is characterized by an early responsiveness (within 24–48-h), a relatively high efficacy rate ranging from 50% to 80% of treated patients, similar to those observed with antidepressant drugs, and few if any side effects (Leibenluft and Wehr, 1992). Positive antidepressant effects have been reported in different depressive conditions, but better effects have been shown in endogenous major depression compared with secondary depression (Vogel et al., 1975). The clinical usefulness of the treatment was questioned by the short duration of its antidepressant effect, with up to the 80% of SD-responders showing a relapse (though mostly not a complete one) after the recovery sleep. Fortunately, during last years, many strategies for increasing and sustaining the effects of SD over time have been developed and the maintained efficacy of TSD via combinatorial

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strategies have been reported in numerous studies (Benedetti and Colombo, 2011).

The combination of TSD with subsequent LT has been shown to prevent the early relapses. Not only Bright LT during and after SD was shown to stabilise the antidepressant effect of both partial (Neumeister et al., 1996) and total (Colombo et al., 2000) SD, but exposure to bright light during SD was also shown to lead to a more prolonged improvement of responders (van den Burg et al., 1990). This chronobiological combination therapy was shown to be effective also in drug resistant depression with about 44% of patients not responder to traditional antidepressant drugs showing a positive response to chronotherapeutics (Benedetti et al., 2005). Finally, a recent study found that TSD+LT are able to rapidly decrease depressive suicidality in a group of bipolar patients affected by depressive episode. Not only about 66% of patients with a history of suicide acts responded to the treatment with a rapid drop in suicidal symptoms, but also patients, who did not achieve a final response, showed a reduction in suicidality (Benedetti et al., 2014). These results are really interesting and highlight the utility of chronotherapeutics in mood disorders, considering that treating suicidality is a major issue in the treatment of a major depressive episode and the efficacy of antidepressant drugs on suicidality has been questioned (Tiihonen et al., 2006).

The aim of the present study is to investigate the feasibility and the usefulness of TSD and LT in outpatient settings. Indeed, despite their proved rapid antidepressant efficacy, TSD and LT are still far from being considered standard therapy in the inpatient unit and no study has already focused on their usefulness in depressed outpatients.

2. Methods

We studied 27 Dutch outpatients (F=18, M=9), aged between 22 and 52 years (36.67 ± 9.79, mean ± standard deviation) consecutively admitted to the Psychological Center Psychologische Hulpverlening Haastrecht in Oudewater, The Netherland, affected by Major Depression, current single or recurrent episode without psychotic features, (DSM-IV criteria). Patients affected by SAD were excluded. The diagnosis of not SAD was assessed basing on patient history of illness (previous episodes and onset of current episodes).

Patients were administered one night of TSD. During the night, to help the patients to stay awake, there was a short walk around half past midnight and then an excursion to a dairy farm until 3 in the morning. During the five consecutive mornings after the wake night, patients received LT (exposure for 30 min to a 10,000lx light) in the early morning following a predictive algorithm based on Morningness-Eveningness Questionnaire (MEQ) scores (Horne and Ostberg, 1976) and aimed at causing a 2 h phase advance as explained by Terman and colleagues (Terman and Terman, 2005; Wirz-Justice et al., 2009). MEQ consists of 19 questions that ask people to consider their "feeling best" rhythms and indicate preferred clock time blocks for sleep and engagement in various hypothetical situations (e.g., physical exercise, tests, work). MEQ scores can range from 16 to 86, with lower scores indicating evening types and higher scores indicating morning types. High correlations were found between the circadian preference for activities, as rated on MEQ and the rhythm of melatonin production (Mongrain et al., 2004). In our sample 5 patients were evening types, 4 patients were morning types and 18 patients were moderate types.

Severity of depression was rated on Back Depression Inventory Scale (BDI) at baseline, after one week and three months after the end of treatment. The BDI contains 13 questions scored 0–3; the minimum score is 0 and the maximum score is 39. A cut-off score ≥ 11 is considered as depression, with a lower score considered as normal.

All patients were drug free during the study and 20 patients received adjunctive cognitive psychotherapy which had been started before the beginning of the chronobiological treatment.

The treatment was administered in a group of almost three patients in order to facilitate patients. In this way patients were divided in 7 groups according to the date of their consecutive referral to the center. Five patients were enrolled in September, five patients in October, 9 patients in November, four patients in December and four patients in January.

In order to study if the treatment efficacy was linked to photoperiod, correlation analysis between the changing in BDI scores and the basal photoperiod and the changing of photoperiod length during the week of treatment were conducted.

To investigate the influence of factors affecting clinical response, changes in BDI scores over time were analyzed in the context of the General Linear Model (McCulloch et al., 2008; Timm and Kim, 2006) with a repeated measures ANOVA. BDI scores were the dependent variable, time was the within subjects factor, and the presence of adjunctive psychotherapy was the between subject factor.

In order to study if there was repeatability in findings, we did a second analysis in the context of the General Linear Model with a repeated measures ANOVA. BDI scores were the dependent variable, time was the within subjects factor, and the group of patients was the between subject factor.

3. Results

BDI scores (mean ± standard deviation) and photoperiod in minutes (mean ± standard deviation) are shown in Table 1. 10 patients (37%) one week after the treatment and 15 patients (55%) three months after the end of treatment showed a BDI score lower then 11, reaching remission.

BDI scores significantly decreased during treatment in the whole sample (Friedman's ANOVA: $\chi^2=31.26$, $p<0.00001$) Fig. 1A. We did not find any correlation between BDI score changing and both basal photoperiod (Pearson's r=0.173; $p=0.39$) and the changing in photoperiod length during the week of treatment (Pearson's r=0.033; $p=0.87$).

When testing the effect of the chronobiological treatment in the seven different groups of patients in the context of General Linear Model, no difference between the 7 groups of patients (F=0.57; d.f. 2,20; $p=0.85$) was found. Post-hoc Newman-Keuls critical ranges test confirmed significant differences in BDI scores between the baseline and both one week ($p=0.00011$) and three months ($p=0.00012$) after the end of treatment.

When chronotype was considered in the context of General Linear Model as between subject factor.

When adjunctive psychotherapy was considered in the context of General Linear Model as between subject factor, no difference was found between the two therapy groups (F=2.41; d.f. 2,25; $p=0.1$) Fig. 1B. Post-hoc Newman-Keuls critical ranges test confirmed significant differences in BDI scores between the baseline and the other two time points for both patients without (after one week $p=0.005$; after three months $p=0.025$) and with adjunctive psychotherapy (after one week $p=0.001$; after three months $p=0.0001$). No difference in BDI scores was found at each time point between the two therapy groups.

Effect size ($\eta^2 p=0.088$; Observed Power=0.0464) is medium (Cohen, 1988).

4. Discussion

This is the first study about the use of combined TSD and LT in the treatment of major depressed outpatients. We found an efficacy of the treatment in drug free outpatients which lasted for months even after the end of the chronobiological intervention. This result was obtained even without any adjunctive treatment,

Table 1
Characteristics (mean and standard deviation) of the sample and of the photoperiod.

	Mean	Standard deviation
Age	36.67	9.69
BDI at baseline	25.88	7.77
BDI One week after the end of treatment	13.70	7.69
BDI three months after the end of treatment	11.81	10.18
Photoperiod (in minutes) at baseline	556.18	92.19
Photoperiod (in minutes) one week after the end of treatment	533.33	70.63
Photoperiod (in minutes) three months after the end of treatment	680.22	127.37

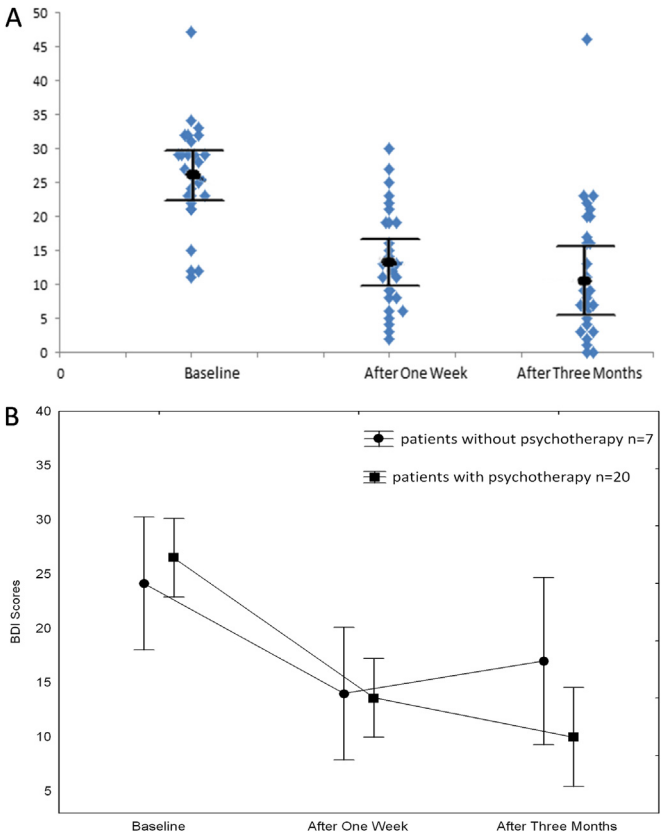

Fig. 1. Distribution of BDI Scores over time. (A) Each point corresponds to a patient and mean scores and standard deviation are plotted. (B) Difference in BDI Scores over time according to the presence of adjunctive Psychotherapy.

both pharmacological therapy and psychotherapy. Every group showed matching results, meaning that there is repeatability in findings.

Unipolar depression was recently reported to be the most important contributor to the burden of mental and neurological disorders in Europe (Wittchen et al., 2011) and it was considered the leading cause of global burden of mental and neurological disorders in terms of Disability Adjusted Life Years (DALYs) (Murray et al., 2012). In everyday clinical practice antidepressant drugs are the mainstay for the treatment of depression, but treatment efficacy is lower than desired (Crown et al., 2002). Moreover, it usually takes several weeks to respond to antidepressants, with the delay in response worsening the burden of disease and patient quality of life and increasing suicidal behavior risk (Moncrieff, 2005). In inpatient units the combination of TSD with subsequent LT have been shown to be effective also in drug resistant depressions (Benedetti et al., 2005) and to be able to rapidly decrease depressive suicidality (Benedetti et al., 2014; Sahlem et al., 2014). In this study chronotherapeutics confirmed their efficacy in the treatment of major depression and showed up as an efficient treatment option in those patients who cannot assume drug therapy. Moreover, we showed the feasibility of TSD + LT also in an outpatient setting. The use of the chronobiological treatment in this kind of setting could mean a reduction of hospitalization and consequently the reduction of the financial, medical and social burden related to hospital admission. Controversially, it could mean an increase in patient quality of life.

The study has two major limitations: the small sample size and the period during which the treatment was administered. In fact, even if patients were not affected by SAD, the treatment was administered in months ranging from September to January in a northern country, period of the year characterized by short day length. At high latitudes, a two hour extension of melatonin secretion was observed in winter, compared with the summer period (Kauppila et al., 1987), meaning that seasonal alterations of the natural photoperiod influence biological rhythms in humans. Even if we did not find any correlation between clinical improvement and the photoperiod length, suggesting that the efficacy of treatment was not linked to photoperiod, in a previous research, focusing on adjunctive LT in major depressed inpatients, we found that season of treatment influence antidepressant response to different LT schedule. When patients were treated during autumn or winter, a better antidepressant effect was found when LT was administered according to MEQ compared to late morning. Otherwise no difference in LT schedule efficacy was found during spring or summer (Dallaspezia et al., 2012). The efficacy of TSD + LT in the present study could then be linked to the season of treatment.

Further research is needed in southern countries, in different season of treatment and in larger samples.

Conflict of interest

The authors do not have any conflicts of interest to report.

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