

# Combination Therapy Using Sertraline with Sleep Deprivation and Light Therapy Compared to Sertraline Monotherapy for Major Depressive Disorder

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## SUMMARY

**Objective:** Bright light therapy is effective and well tolerated in seasonal affective disorder and some studies reported an antidepressant effect of bright light also in non-seasonal depression. On the other hand, total sleep deprivation leads to a rapid and marked improvement of mood in 60% of depressed patients. Combinations of antidepressant medication with those somatic therapies are generally indicated. The aim of this study was to compare the efficacy of the combination of sertraline and partial sleep deprivation or light therapy with sertraline monotherapy in the treatment of major depression.

**Method:** Thirty-seven patients with major depressive disorder were randomly allocated into 3 treatment groups. Thirteen were treated with sertraline and late partial sleep deprivation, 13 with sertraline and bright light therapy and 11 sertraline monotherapy as a control group. Outcome measures included daily (first 15 days) and weekly Hamilton Rating Scale for Depression and biweekly Hamilton Anxiety Rating Scale.

**Results:** Partial sleep deprivation group improved significantly and more rapidly. Accelerated treatment response was shown in sleep deprivation group that improvement was observed after the third day. Bright light and sleep deprivation combinations with sertraline were more effective than sertraline monotherapy for accompanied anxiety in depression.

**Conclusion:** Late partial sleep deprivation in combination with sertraline can accelerate and increase the treatment response in non-seasonal major depressive disorder.

**Key Words:** Sleep deprivation, phototherapy, sertraline, major depression

## INTRODUCTION

After the first experimental sleep deprivation therapy in 1971 (Pflug and Tolle 1971), many studies followed and sleep deprivation therapy was accepted as an effective antidepressant therapy (Papadimitriu et al. 1993, Van Den and van den Hoofdakker 1975). Total sleep deprivation provides improvement in depression features in 60% of cases. Partial sleep deprivation and selective REM sleep deprivation are variants of total sleep deprivation. Especially late partial sleep deprivation therapy which was administered at the second part of the sleep was found as effective as total sleep deprivation (Sack et al. 1988, Schilgen and Tolle 1980). In many cases clinical use of sleep deprivation was limited and its therapeutic effect lasted only until the end of the day which sleep deprivation procedure was employed. As a consequence, sleep deprivation therapy was not considered as an effective monotherapy modality. Concomitant administration of antidepressant medications, phototherapy and sleep phase changes (advance, delay) were employed in order to prolong the effects of sleep deprivation (Colombo et al. 2000, Neumeister et al. 1996, Riemann et al. 1999).

Seasonal affective disorders were reported to improve with bright light therapy (Rosenthal et al. 1984). There were some other studies which revealed that light therapy was effective in non-seasonal depressions (Prasko et al. 2002). But the effect on non-seasonal depressions was controversial (Mackert et al. 1991).

Generally, sleep deprivation or light therapy could not provide adequate antidepressant effect alone. More often, combination with antidepressant medications was needed and combination therapies were shown to increase efficacy (Elsenga and van den Hoofdakker 1982, Benedetti et al. 1997, Kripke 1998, Beauchemin and Hays 1997).

Sleep deprivation and light therapy are not used frequently in our country. Their effects on major depression are well known, but short lasting effect of sleep deprivation and controversial reports about non-seasonal depression wait to be illuminated by additional research. The results of combination studies with antidepressants of these therapeutic modalities which have limits as monotherapy will provide clinicians new horizons.

The aim of this study was to compare the efficacy of the combination of sertraline and sleep deprivation or light therapy with sertraline monotherapy in major depression and to evaluate the effects of partial sleep deprivation or light therapy to accelerate antidepressant response in patients treated with sertraline

## **METHOD**

Forty-nine patients who applied to Psychiatry outpatient clinics of Trakya University Hospital and met diagnostic criteria of DSM-IV for major depression were recruited in the study. They were randomized into three groups; 17 patients received sertraline, 16 patients received sertraline plus light therapy and 16 patients received sertraline and sleep deprivation therapy. The participants were evaluated via Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/CV, First et al. 1997) and patients who had comorbid Axis I disorder, psychotic or seasonal depression, any eye disease or general medical disorder or obtained 18 points or less from 21-item Hamilton Depression Scale (HDS) were excluded from the study. Patients with positive family history for bipolar disorder or known to be resistant to therapy were not included. Resistance to therapy was defined as irresponsiveness despite antidepressant medications which were administered at adequate doses for reasonable period. The study was approved by local ethics committee and written informed consent was obtained from each patient. Patients who received any of antidepressant medications were included after a wash-out period for 4 days. This

wash-out period was determined as 15 days for patients who were using fluoxetine.

Patients in LPSD group received six partial sleep deprivation therapies in first two weeks of hospitalization (Elsenga et al. 1990, Kuhs et al. 1996). These patients were allowed to sleep during 11 pm - 3 am at the days of therapy. Each patient was followed-up during the remaining night and subsequent whole day under the supervision of nurses and interns at inpatient clinics. Time spending activities were provided for them and naps forbidden during the day after sleep deprivation

The patients who were in light therapy group received light therapy for two weeks synchronously with sertraline. Light therapy was started between 7am to 8 am and administered by considering awakening habits of the patients (Deltito et al. 1991, Benedetti et al. 2003). A light box and an active light treatment condition of 10.000 lux white light for 30 minutes was administered (Sadelite, Northern Light Technologies, Montreal, Quebec, Canada).

Sertraline which was found to be effective in some other combination studies was the drug choice (Martiny 2005). Starting dose was determined as 50 mg/day for all patients. The dose was increased maximum 100 mg/day according to clinical response. Benzodiazepines with high potency were used for sleep disorders or anxiety if needed, but their use was limited for two weeks because of potential effects on therapy.

### **Instruments**

Patients were evaluated via Hamilton Depression Scale at the beginning and weekly during 6 weeks. This scale which is administered by the clinician measures the level and severity alterations of depression (Williams 1978). It was translated to Turkish and validity and reliability studies were completed (Akdemir et al. 1996). Patients in sleep deprivation or light therapy groups were evaluated with Hamilton Depression Scale daily for the first 15 days in order to demonstrate a possible early response. Anxiety levels of the patients were evaluated via interviewer rated Hamilton Anxiety Scale (Hamilton 1959) at Weeks 2, 4 and 6. This scale was also adapted to Turkish and its validity and reliability studies were completed (Yazıcı et al. 1998).

**TABLE 1.** Sociodemographic characteristics of the groups.

	Treatment Group			Statistical significance
	Sleep deprivation and sertraline	Light therapy and sertraline	Sertraline	
Gender				
Male	4	3	1	$\chi^2=1.67$ $p=0.43$
Female	9	10	10	
Mean age	40.54 ± 10.33	43.77 ± 15.00	36.00 ± 13.86	F=1.03 $p=0.36$
Educational level				
Illiterate	-	-	-	
Literate	-	-	1	
Primary school	4	7	1	
High school	6	4	4	
University	3	2	2	
			3	
Marital status				
Married	8	8	7	
Divorced, widow	3	2	-	
Single	2	3	4	
Type of depression				
First episode	6	5	4	$\chi^2=0.27$ $p=0.87$
Recurrent	7	8	7	
Occupation				
Employee	5	2	2	
Retired	2	2	-	
Housewife	4	6	7	
Unemployed	1	1	1	
Student	1	2	1	
Mean sertraline doses after treatment	61.53± 21.92	73.07 ± 25.94	72.72 ± 26.11	F=0.89 $p=0.41$

### Statistical analysis

For descriptive statistics means and standard deviations, for group comparisons variance analyses, variance analyses with repetitive measurements and t tests and for evaluation of nominal data chi-square tests were employed. The limit for statistical significance was accepted as  $p < 0.05$  and all tests were evaluated in double tail fashion.

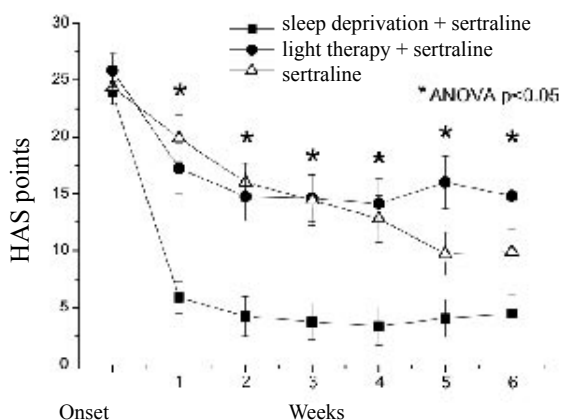
### FINDINGS

Thirty seven patients completed six weeks of the study. Six patients from control group (they did not come back for necessary follow-up evaluations), three patients from sleep deprivation group (two of them did not want to continue and one of them could not comply with sleep deprivation) and three patients from light therapy group (two of them did not want to continue and one of them was shown to have another form of Axis I disorder)

were excluded from the study.

Of the remainder 37 participants, 13 patients were treated with sertraline and sleep deprivation, 13 patients were treated with sertraline and light therapy and finally, 11 patients received only sertraline. Twenty nine patients were females and 8 patients were males. Their mean age was  $40.32 \pm 13.19$  years. Gender and age distributions between groups were similar ( $\chi^2=1.67$ ,  $p=0.43$ ,  $F=1.03$ ,  $p=0.36$ , respectively). Twenty two patients applied for recurrent depression and 15 patients were admitted with the first episode. Of these 15 patients who applied for the first episode, 6 patients were in sleep deprivation group, 5 patients were in light therapy group and 4 patients were in sertraline group and their distribution among groups was similar ( $\chi^2=0.27$ ,  $p=0.87$ ). Mean sertraline doses were  $61.53 \pm 21.92$  mg in sleep deprivation group,  $73.07 \pm 25.94$  mg in light therapy group and

**FIGURE 1.** Changes in depression points of the groups.



\*Statistical analysis was performed via variance analysis of means of weekly Hamilton Depression Scale (HDS) points of the groups.

72.72±26.11 mg in control group. The difference was not statistically significant ( $F=0.89$ ,  $p=0.41$ ) (Table 1).

Weekly changes of groups in Hamilton Depression Scale were presented at Figure 1. The values were similar at the beginning. By the end of the first week, one way ANOVA analysis revealed significant difference between groups. This difference was shown to be sourced from sleep deprivation group by Post Hoc Tukey test. At the end of the study, Hamilton Depression Scale points decreased 82.9% in sleep deprivation group, 38.1% in light therapy group and 60.07% in controls.

When the relationship between therapy weeks and changes in Hamilton Depression Scale points was evaluated with variance analysis (repeated measures), it was shown that all of effect of treatment weeks ( $F_{1,6}=60.13$ ,  $p=0.000$ ), group difference ( $F=11.68$ ,  $p=0.000$ ) and the interaction between therapy week and group ( $F_{1,12}=5.78$ ,  $p=0.000$ ) were significant.

Accompanying anxiety levels were similar at the beginning, but sleep deprivation group showed greatest decrease during following weeks (Figure 2).

## DISCUSSION

This study revealed that combination of sleep deprivation and sertraline was more effective than light therapy and sertraline or sertraline alone in

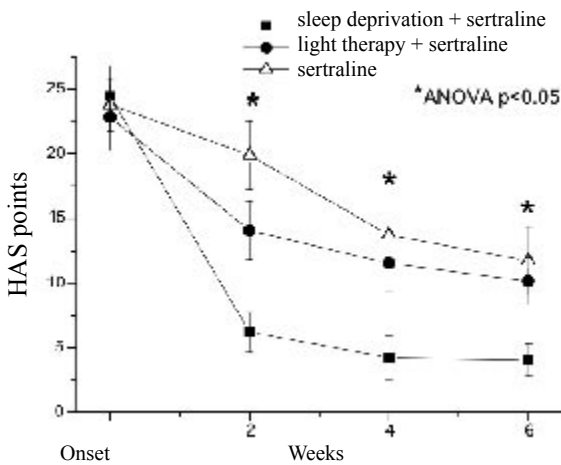
non-seasonal depression. This superiority was present both in efficacy and accelerated antidepressant treatment response. Relatively lower doses of sertraline in sleep deprivation group which were not significant may be explained by synergistic serotonergic effect of these two therapeutic modalities (Salomon et al. 1994, Smeraldi et al. 1999).

Sleep deprivation provides a rapid improvement in depression, but this effect lasts only until the end of the day in which sleep deprivation is administered. After next night sleep or a short nap (Wiegand et al. 1987), relapses are present in 80% of cases who did not use any medication (Giedke and Schwarzler 2002). Wirz-Justice and Van den Hoofdakker reported that general unconcern about sleep deprivation was a consequence of high relapse rates after a recovery sleep (1999). On the other hand, our study revealed that combination of sleep deprivation and sertraline eliminated this problem effectively.

Kuhs and colleagues reported that they could not find any superiority of twice weekly to once weekly late partial sleep deprivation combined with amitriptyline in major depression (1998). We used late partial sleep deprivation three times a week in our study and this frequency might be considered as a high dose. Relatively long lasting effects of sleep might be a consequence of that reality.

It was shown that bright light therapy over 2500 lux provided improvement in patients with seasonal affective disorders (Terman et al. 1989, Wirz-Justice et al. 1993). There was relatively lower number of studies about the effects of light therapy on non-seasonal depression. The results of these studies were controversial; some of them revealed antidepressant effect of light therapy and some of them showed no effect (Mackert et al. 1991, Volz et al. 1990). Kripke and colleagues reported that light therapy had beneficial effects at a level of 12-35% in non-seasonal depression and this administration showed synergism with standard treatment modalities (1998). Yamada and colleagues showed that bright light therapy significantly decreased severity of depression in non-seasonal depression. In contrast, we could not find a beneficial effect of light therapy and sertraline combination over sertraline alone in non-seasonal depression. Our level of light therapy might not be inadequate, because we administered 10.000

**FIGURE 2.** Changes in anxiety points of the groups.



\*Statistical analysis was performed via variance analysis of means of weekly Hamilton Anxiety Scale (HAS) points of the groups.

lux for consecutive 15 days. Different responses of seasonal and non-seasonal depressions to light therapy may be due to different etiology of these two disorders. Similarly, Mackert and colleagues showed that light therapy which was administered two hours a day for a one-week period was not effective in non-seasonal depression (1991). Interestingly, Prasko and colleagues found that bright light monotherapy was more effective than light therapy and imipramine combination (2002).

Bright light therapy was shown to be related with suicide behavior (Praschak-Rieder et al. 1997) and probable switch to mania (Pande 1985, Chan et al. 1994). During the study or follow-up period, we did not meet ant hypomania or mania case. Higher rates for switches to mania were reported in patients with bipolar depression and sea-

sonal affective disorder. The absence of switches to mania in our study may be due to inclusion of unipolar and non-seasonal patients only. We did not meet with any suicidal attempt during our study. But one patient from light therapy group committed suicide one week following discharge with improvement in depression. This suicide was 48 days after the beginning of the treatment and 33 days after the end of last light therapy session. We interpreted that case as a relapse of depression rather than a side effect of light therapy.

In contrast with the findings that sleep deprivation was not effective in anxiety disorders (Joffe and Swinson 1988, Labbate et al. 1997, Labbate et al. 1998), the level of accompanying anxiety decreased in sleep deprivation and light therapy groups when compared with controls. The decrease in anxiety points was parallel with the decrease in depressive features and thought to reflect the improvement in depression.

There were some limitations in our study. The sample size was small and this size decreased the power of the study. The study was not blinded, so it reflected probable patient and investigator subjectivity. Hamilton Depression Scale was administered weekly to controls and daily to patients for the first two weeks and this fashion might provide a non-specific benefit and improvement in depression. Some patients from control group were treated on an out-patient basis and the efficacy of the treatment might be influenced.

As a result, sertraline combination with sleep deprivation was effective in decreasing relapse rates following sleep deprivation. In cases in which early therapeutic response is desired, late partial sleep deprivation may be a combination or augmentation alternative with low side effect profile.

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