May 30, 2013

The seasonal pattern of recurrent episodes of depression has become known as Seasonal Affective Disorder (SAD). The precise pathogenesis of SAD is still uncertain, despite several explanatory theories such as photoperiod and phase-shifted circadian rhythms, neurotransmitter functions, and genetic hypothesis. Given the fact that winter SAD is far more prevalent than summer SAD, the term SAD usually refers to winter SAD and is used accordingly hereafter. Episodes of SAD peak in winter and are characterized by typical and atypical depressive symptoms, i.e. lowered mood, energy loss, excessive sleep with difficulty waking, craving for carbohydrates, weight gain, irritability, social withdrawal, daytime fatigue, and loss of concentration.

The prevalence of SAD varies from 0 to approx. 10% in the general population. Climatological, social and cultural influences, genetic factors and geographical latitude have been reported to have an impact on the prevalence of SAD. SAD is more common among females and younger adults. SAD in females is usually characterized by minor depressive episodes, whereas males more commonly experience major depression.

Many controlled studies have found bright light therapy (BLT) effective in treating SAD. In a systematic review and meta-analysis, the effect size for the reduction of depressive symptoms by BLT in the treatment of SAD was 0.84. The antidepressant effect of bright light is potentiated by early morning administration in circadian time, about 2.5 hours after the sleep midpoint. According to the clinical guidelines, the recommend bright light exposure in treatment of SAD is 10,000 lux for 30 min per day. Although BLT is effective, about 70% of SAD patients complain that sitting in front of the bright light is uncomfortable, and almost one in five SAD patients stop BLT because of that.

The mechanism of action of BLT in the treatment of SAD is still under debate, and it is widely believed that the effect of light is mediated via the eye. However, there is evidence that in mammals significant amounts of light penetrate the skull bone and reach the brain.

Subjects and Methods

Adult persons suffering from seasonal depressive symptoms were recruited through advertisements in a local newspaper and were pre-screened for symptoms of SAD by a phone interview. The procedure of the study is presented in FIG. **12**.

Structured diagnostic interviews were conducted at week 0 and 4 by two trained psychiatrists. Diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for recurrent major depression (moderate or severe) was obtained using the Mini International Neuropsychiatric Interview (MINI). In addition, patients had to fulfil the diagnostic criteria for "seasonal pattern".

The subjects included in the study had to score at least 20 points on the 29-item Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorder (SIGH-SAD, with a 21-item Hamilton Depression Rating Scale (HAMD-21) score of 10 or more and eight-item atypical symptom score of 5 or more. In this study, inclusion scores were analogous with the criteria used for evaluating the response to treatment in patients with SAD in earlier studies. Subjects with lifetime psychotic disorders, bipolar disorders, severe personality disorders, substance abuse or dependence, suicidal ideation during the past month, any psychotropic medications, and other bright-light therapy for the current SAD episode were excluded from this study. Pregnant females were also excluded. Written informed consent was obtained from the subjects after they had been given a full description of the study at the first visit during week 0. The research protocol was approved by the Ethics Committee of Oulu University Hospital, Finland.

The Light Therapy Device

The brain-targeted bright light treatment was given transcranially via ear canals by using the Valkee brain stimulation headset. This device was approved as a medical device in the European Union on 30 Mar. 2010, and since then it has been available for customers in Finland and other EU countries. The light was produced using light-emitting diodes (white LEDs), which were attached to earplugs. The bright light was transmitted to the ear canal by an optical guide. Daily BLT (bright light therapy) was taken during the forenoon at home, and each treatment session lasted 12 minutes.

Grouping of Subjects

The subjects involved in the study were randomly divided into three groups: low dose (group 1), intermediate dose (group 2) and high dose BLT (group 3). The randomization procedure followed a double-blind design. The amount of received light in the three groups was 1 lumen, 4 lumen and 9 lumen, respectively. Lumen is a measure of luminous flux, which is defined as the total amount of visible light emitted from a light source through a solid angle.

Measurement of SAD

The sum score of SIGH-SAD was used to evaluate the severity of SAD. The remission criterion was defined as score of 8 of 29-item SIGH-SAD score at week 4. For further analysis, SIGH-SAD, 14-item Structured Interview Guide for the Hamilton Anxiety Rating Scale (HAMA) and 21-item Becks Depression inventory, BDI were used to evaluate the response to treatment. The criterion for response was fulfilled when the patient had a decrease of 50% or more from the baseline scores in SIGH-SAD. HAMA and BDI. In addition to measuring safety and tolerability, information of bright light-related adverse events was gathered.

Statistical Analyses

All data are presented as percentages or as mean with 95% confidence intervals. Student t-test was used to compare baseline values between genders within light treatment groups. Categorical variables were compared by Chi-Square test or Fisher's Exact test when appropriate. The within-group and between group changes in variables during the study were analysed with repeated measures analysis of variance (ANOVA). Results with 2-sided p values <0.05 were considered statistically significant. Statistical analyses were performed using SAS version 9.2.

Results

Ninety patients with SAD, 68 of whom were females, participated in this study. Of these, one female patient dropped out due to a trip abroad. The mean age of participants was 43.0 years (SD 10.9, range: from 22 to 65 years). Table 1 shows the demographic and baseline variables of the treatment groups in both genders. The groups were similar in most respects, but differed in some variables. Statistically significant differences were found in age and BDI baseline sum score in treatment group 3 and in SIGH-SAD baseline sum score in treatment group 1 between females and males.

TABLE 1

Demographic and baseline variables for treatment groups

	Treatment	Female (N)		Male (N)		
Variables	group	Mean	SD	Mean	SD	p-value
Age	1	42.0 (22)	10.6	43.3 (6)	10.8	0.7952
	2	42.9 (25)	10.1	49.3 (6)	11.3	0.1795
	3	38.4 (20)	10.2	51.0 (10)	11.3	0.0045
SIGH-SAD	1	37.8	5.5	32.0	7.2	0.0414
	2	36.9	6.3	32.5	6.8	0.1407
	3	36.3	6.1	34.4	8.8	0.4092
HAM-A	1	24.0	6.1	22.2	5.7	0.5034
	2	23.0	6.5	21.0	7.7	0.5182
	3	22.2	5.7	20.9	6.3	0.8619
BDI	1	20.5	8.3	17.5	8.0	0.2784
	2	19.7	8.1	15.7	10.4	0.3057
	3	22.2	8.7	13.7	8.7	0.0185

When compared to the baseline (week 0), statistically significant decreases were found in mean SIGH-SAD total scores after adjusting for age and gender in each treatment group (Table 2). The mean SIGH-SAD total scores decreased 17.6 points (47.4%, $p<0.0001$), 17.0 points (45.9%, $p<0.0001$) and 15.9 points (43.7%, $p<0.0001$) in the three treatment groups (1, 4, 9 lumen), respectively. The corresponding values for HAMA were 12.0 (49.9%, $p<0.0137$), 11.4 (49.5%, $p<0.0056$), 10.1 (46.5%, $p<0.0001$) and for BDI 13.7 (67.3%, $p<0.0158$), 13.4 (67.4%, $p<0.1282$), 11.9 (63.2%, $p<0.0013$). Although subjects in each group improved after exposure to bright light treatment, there were no statistical differences between these improvements.

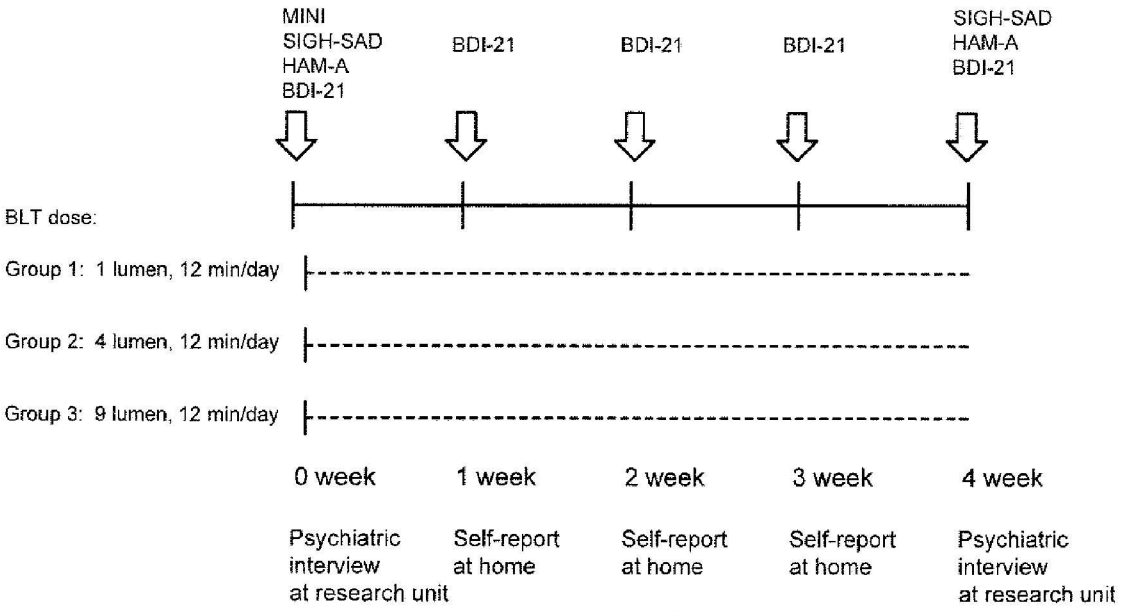
MINI
SIGH-SAD
HAM-A
BDI-21
BDI-21
BDI-21
BDI-21
SIGH-SAD
HAM-A
BDI-21
BLT dose:
Group 1: 1 lumen, 12 min/day
Group 2: 4 lumen, 12 min/day
Group 3: 9 lumen, 12 min/day
0 week
1 week
2 week
3 week
4 week
Psychiatric interview at research unit
Self-report at home
Self-report at home
Self-report at home
Psychiatric interview at research unit

Fig. 12

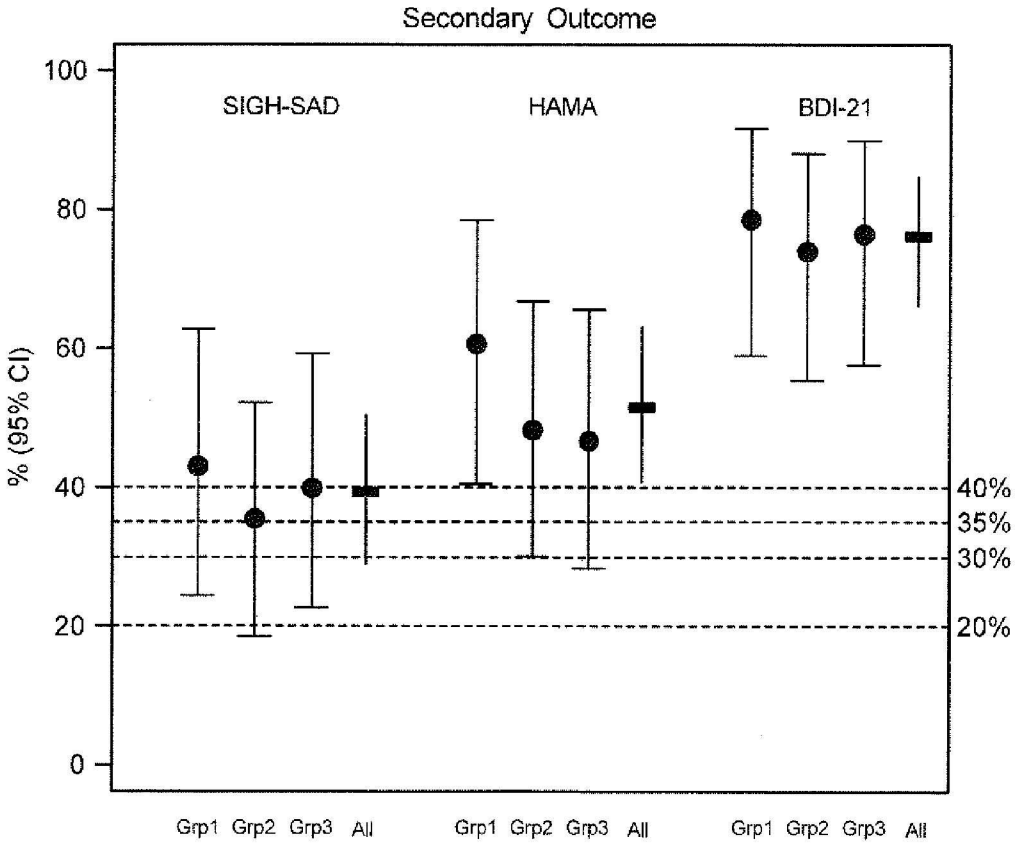
Secondary Outcome
SIGH-SAD
HAMA
BDI-21
% (95% CI)
100
80
60
40
20
0
40%
35%
30%
20%
Grp1 Grp2 Grp3 All
Grp1 Grp2 Grp3 All
Grp1 Grp2 Grp3 All

Fig. 13

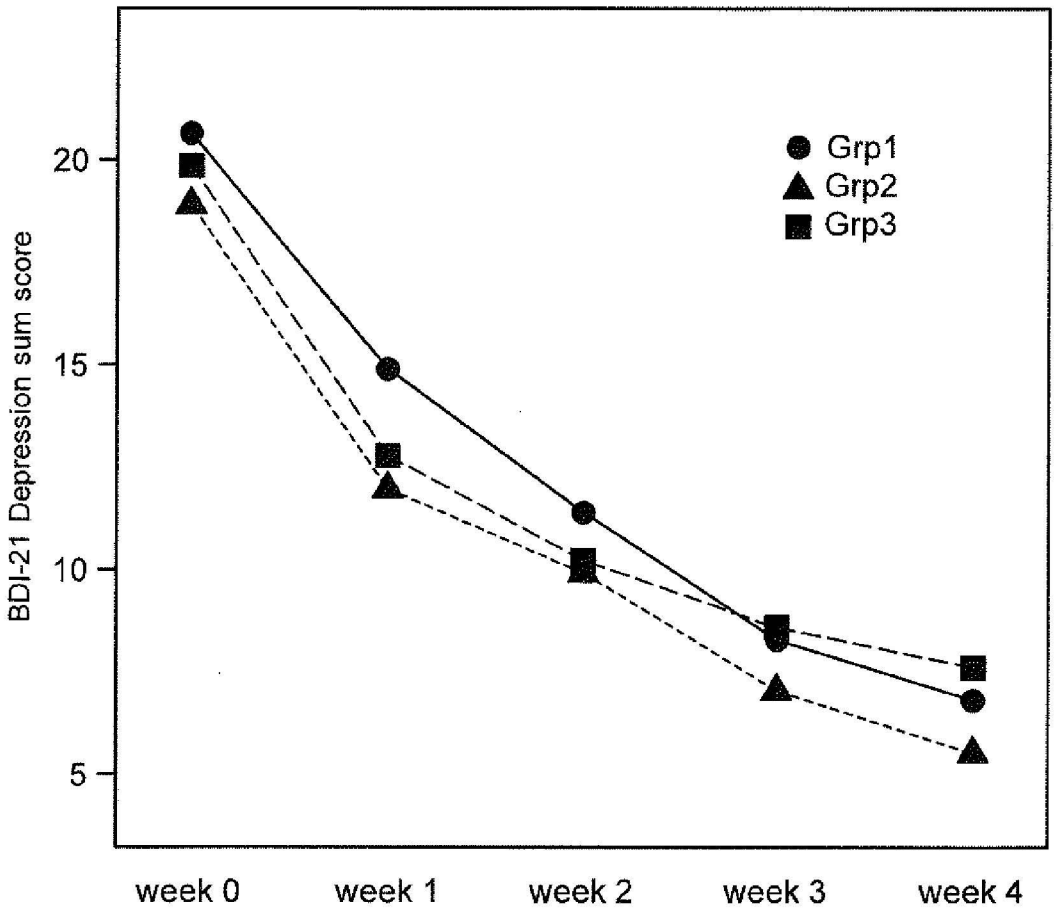
BDI-21 Depression sum score
20
15
10
5
Grp1
Grp2
Grp3
week 0
week 1
week 2
week 3
week 4

Fig. 14

TABLE 2

Depression and anxiety scale measures over four week study period

Measure	Group 1 (N = 28)		Group 2 (N = 31)		Group 3 (N = 30)	
	Mean	95% CI	Mean	SD	Mean	SD
Structured Interview Guide for the Hamilton Depression Rating Scale Seasonal Affective Disorder Version (SIGH-SAD) score						
Baseline	36.6	34.1-39.0	36.1	33.7-38.5	35.7	33.5-37.8
Endpoint	19.0	14.4-23.6	19.1	15.5-22.7	19.8	15.6-23.9
Hamilton Depression Rating Scale (HAMD) score						
Baseline	21.8	20.2-23.5	21.5	19.5-23.5	21.1	19.6-22.6
Endpoint	11.3	8.5-14.1	11.1	9.0-13.1	11.5	8.9-14.0
Atypical Symptom Scale score						
Baseline	14.8	13.1-16.4	14.5	13.2-15.9	14.6	13.2-16.0
Endpoint	7.7	5.3-10.1	8.0	6.2-9.9	8.3	6.3-10.3
Hamilton Anxiety Rating (HAMA) Scale						
Baseline	23.6	21.3-26.0	22.6	20.2-25.1	22.1	19.9-24.2
Endpoint	11.6	8.2-14.9	11.2	8.7-13.7	12.0	9.1-14.8
Beck's Depression Inventory						
Baseline	20.6	17.5-23.7	18.9	15.8-22.1	19.3	15.8-22.9
Endpoint	6.9	3.6-10.1	5.5	3.2-7.9	7.4	4.4-10.4
	%	95% CI	%	95% CI	%	95% CI
SIGH-SAD improvement	47.4	34.9-60.0	45.9	36.0-55.7	43.7	32.7-54.8
HAMA improvement	49.9	34.7-65.2	49.5	38.5-60.5	46.5	35.9-57.2
BDI improvement	67.3	53.0-81.6	67.4	55.5-79.4	63.2	49.9-76.6
	Proportion	95% CI	Proportion	95% CI	Proportion	95% CI
SIGH-SAD score ≦8	28.6	10.7-46.6	16.1	2.4-29.8	13.3	0.4-26.2

The proportions of the patients in each group achieving 50% or greater improvement in SAD symptoms are shown in FIG. **13**. The response rate measured by SIGH-SAD varied from 35% to 45%. Corresponding variations for HAMA were 47-62% and for BDI 74-79%. Although the response rate was remarkable on each measurement, no statistically significant differences were found between treatment groups.

The self-rated BDI was assessed weekly in order to evaluate patients' depressive symptoms throughout the study (FIG. **14**). A statistically significant decrease was found in each treatment group already at week 1 when compared to baseline, and the decrease continued throughout the study, although the decrease in depression scores did not differ between treatment groups.

The proportion of patients who reported potential bright light-related adverse events was 28.1% (n=25). There were no statistically significant differences in emergence of bright light-related adverse events between treatment groups. The most common adverse events were temporary headache, insomnia and nausea, which were reported by 10.1%, 5.6% and 3.4% of the patients, respectively. The other symptoms reported were dizziness, earache, abnormal sensation in the maxillary region, tinnitus, tiredness, irregular heartbeat and irritability.

Discussion

In this study it was found that both self-rated and psychiatrist-rated depressive and anxiety symptoms of SAD patients decreased significantly during the 4-week study period even after controlling for age and gender. However, there were no significant differences in improvement of anxiety or depressive symptoms between groups receiving different intensity of bright light via ear canals.

Bright light therapy has been reported to reduce depression symptoms as measured by the rating scales used in this study. The significant reduction in the symptoms of SAD in the present study parallels earlier two- to four-week studies with bright light therapy using traditional bright light devices. Comparing decreases of symptoms across studies is not optimal, but the comparison may be instructive. In the present study, when measured by SIGH-SAD-29, the decrease of raw scores varied between 15.9 and 17.6 points in three treatment groups, whereas in two earlier studies using same rating scale, the decrease was 10.4 points and 15.1 points. When comparing the percentage improvement, the percentage change in the present study, ranging between 44% and 47%, is in between the improvements seen in two earlier studies, i.e. 57% and over 30%. The SIGH-SAD response-rates observed in the present example are slightly lower than those seen in two earlier bright light studies using the same response criteria, i.e. 50% and 63%.

Researchers have found that bright light exposure also has anxiolytic effects among clinically anxious adults and patients suffering from winter depression. To the best of our knowledge, anxiety measurements have rarely been used in earlier bright light studies even though anxiety symptoms are quite common among patients suffering from depression. In the present study psychiatry-rated anxiety symptoms assessed by Hamilton anxiety scale (HAMA) decreased from

moderate anxiety level to normal level during the four-week study period in each treatment group. The decrease in anxiety symptoms is comparable to the earlier pharmaceutical studies in the treatment of generalized anxiety disorder (GAD). The decrease in the mean HAMA score in the present study ranged from 10.1 to 12.0 points in three treatment groups, whereas in earlier pharmaceutical studies using pregabalin (600 mg/day) duloxetine (60-120 mg/day) and venlaflaxine (75-225 mg/day) the decrease of mean HAMA score was 11.6, 12.8 and 12.4 points, respectively. The response rates in the present study varied from 47% to 62%, while ranging from 39% to 59% in earlier GAD studies using pregabalin, from 40% to 65% with duloxetine, and from 54% to 61% with venlaflaxine. In future studies it would be beneficial to utilize valid anxiety measurements as well when evaluating the effects of bright light in SAD.

When self-reported BDI was used, our findings were in line with bright light groups in earlier studies, showing a decrease of raw scores from moderate depression level to level of minimal depression symptoms. The magnitude of the percentage improvement of depressive symptoms (from 63% to 68%) in the three treatment groups was comparable to the percent change in earlier bright light studies, i.e. 62% (BDI-25), 65% (BDI-21) and 69% (BDI-II). The BDI response rates in the present study are in between the response rates seen in earlier bright light studies, i.e. 58% and 82%.

The proportion of the subjects who met the criterion of remission in the present study varied from 13% to 29% in the three treatment groups, whereas in earlier studies using the same remission criteria, the proportions were 47%, 42% and 28%. On the other hand, it is known that bright light treatment is less sufficient for more severely ill patients and the severity of symptoms at baseline has effects on remission rates; SAD patients who experience more severe symptoms have lower remission rates. In addition, a low atypical balance score may also be a poor prognostic sign for response to bright light therapy. The SAD patients in the present study were more severely ill at baseline than reported in earlier studies. In the present study the baseline SIGH-SAD total scores varied from 35.7 to 36.5, whereas in three earlier SAD studies SIGH-SAD total scores ranged between 26.5 and 30.6 points. In addition, in the present study, the possibility of spontaneous remissions was diminished by excluding patients diagnosed with bipolar disorder not otherwise specified or bipolar II disorder.

The adverse effects of bright light are generally known to be mild and rarely lead to treatment discontinuation. However, 47% of SAD patients are refractory to light therapy, at least partly because of poor long-time compliance with light use. Traditional light therapy requires a considerable daily time commitment from the patient during the symptomatic months, but it has been observed that 58% of patients stopped the light treatment when using the light device become voluntary. In this study, transcranially administered BLT had an equal rate of potential adverse events (28%) when compared to earlier traditional BLT studies (25%). The most common side effects in this study were occasional headache, insomnia and nausea. In an earlier study using traditional BLT the emergence of headache was slightly lower, whereas insomnia and nausea were noted markedly more often. We think that this new bright light innovation might result in better compliance than traditional BLT, because it is convenient, allows moving during treatment, does not irritate the eyes, and the daily treatment times are relatively short.

A limitation of this study is that we did not have a control group. We agree with Meesters and associates that it is impossible to create real placebo condition for visible light. We are also aware of the fact that the bright light used in treatment of SAD is accompanied by a potentially large placebo response ranging from 21% to 41%. It is generally assumed that sham devices have higher response rates than placebo pills used in trials of treatment of depression. However. Brunoni and associates reported in their large review and meta-analysis that repetitive transcranial magnetic stimulation (rTMS) as a non-pharmacological treatment in major depression had a lower placebo response than pharmacological therapy. The placebo-response of the device used in this study has not been explored so far. Since treatment sessions in this study resemble the sessions of rTMS treatment, we believe that the improvement of depression and anxiety symptoms observed in our study are unlikely to be solely explained by the placebo effect. In future studies the size of the placebo response should be carefully scrutinized.

Some methodological limitations deserve discussion. There were older males than females and more severely ill females than males in one subgroup. In addition, the proportion of males (24.7%) was quite low. This may have biased our results, since it is known that the prevalence and severity of SAD may differ in different gender and age groups. Moreover, it is found that males seem to underreport SAD symptoms.

We are aware that the amount of daylight increases towards the spring. However, our study was conducted during the darkest season of the year. All patients lived in Northern Finland, which is located only about 170 km south of the Arctic Circle. In addition, the majority patients were indoor workers who hardly saw daylight during the study period, which is strength of our study.

In sum, this is the first randomized controlled clinical trial to show antidepressant and anxiolytic effect of transcranial bright light therapy on symptomatic SAD patients. We are thus not able to compare our results to earlier studies of transcranial light in the treatment of SAD. These results are however in line with the findings of earlier bright light studies using traditional bright light devices in the treatment of SAD and pharmaceutical studies in the treatment of GAD. In future, studies on neuroimaging, neurobiology and placebo-controlled trials are called for to further assess the efficacy and mechanism of action of transcranially delivered bright light.

The conclusions of this randomized controlled trial where 89 subjects suffering from severe seasonal affective disorder had a 12-min daily Valkee dose at home in three different randomly divided groups of one, four, and nine lumen, are that the response rates in the sub-groups were 74-79% for seasonal depression and 47-62% for anxiety symptoms, and included at least 50% reduction in BDI-21 and HAMA score at week four. The daily administration time was fixed to the morning, after waking up.