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Review

Efficacy of light therapy in nonseasonal depression: A systematic review

Christian Even [a,*], Carmen M. Schröder [b], Serge Friedman [a], Frédéric Rouillon [a]

[a] *Centre Hospitalier Sainte-Anne, Clinique des Maladies Mentales et de l'Encéphale, Université Paris V, Paris, France*
[b] *Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA*

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Abstract

Background: The efficacy of bright light therapy is well established for winter depression but its status in depression without seasonal pattern is unclear.
Methods: We systematically evaluated available data on the efficacy of light therapy in nonseasonal depression.
Results: We identified 62 reports among which 15 met our predefined selection criteria. The available data show evidence for the efficacy of light therapy as an adjuvant treatment to antidepressants. Trials that evaluated light therapy alone (without antidepressants) in nonseasonal depression yielded inconsistent results.
Limitations: Most of the studies extracted poorly controlled the issue of blindness and were limited by small sample sizes. Publication bias may have distorted our estimation of the effect of light therapy.
Conclusions: Overall, bright light therapy is an excellent candidate for inclusion into the therapeutic inventory available for the treatment of nonseasonal depression today, as adjuvant therapy to antidepressant medication. Future clinical trials of light therapy should distinguish homogenous subgroups of depressed patients in order to evaluate whether light therapy may eventually be considered as stand-alone treatment for specific subgroups of patients with nonseasonal depression.

Keywords: Mood disorders; Light therapy; Nonseasonal depression

Contents

* Corresponding author. Centre Hospitalier Sainte-Anne, Clinique des Maladies Mentales et de l'Encéphale, 100, rue de la Santé, 75674 PARIS Cedex 14, France. Tel.: +33 1 45 65 86 39; fax: +33 1 45 65 89 43.
E-mail address: c.even@ch-sainte-anne.fr (C. Even).

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1. Introduction

The therapeutic use of light arose from basic research showing that exposure to light could alter circadian rhythms and could suppress melatonin secretion in humans (Lewy et al., 1980). Given that many seasonal rhythms are mediated through changes in melatonin, light therapy emerged as a logical treatment for seasonal affective disorder (SAD), a condition that consists of recurrent episodes of major depression occurring with a seasonal pattern, most often depression during the fall and winter with full remission during spring and summer. Although the involvement of melatonin in the pathophysiology of SAD is smaller than previously believed (Lam and Levitan, 2000), more than seventy therapeutic trials and two meta-analyses (Terman et al., 1989; Lee and Chan, 1999) have demonstrated the efficacy of bright light therapy as a first-line treatment in SAD (Lam and Levitt, 1999; American Psychiatric Association, 2000).

Today, light therapy is not only considered by the authorities in this field to be "the only treatment in psychiatry that evolved directly out of neurobiological models of behaviour" (Wirz-Justice et al., 2004), it has also emerged as one of the best-studied nonpharmacological biologically oriented treatment approaches in psychiatry (Kasper, 2005). Beyond SAD, other disorders or specific chronobiological malalignments such as circadian sleep phase disorders, shift work (maladaptation) and the jet-lag syndrome similarly benefit from light therapy (Bunney et al., 2005). Besides, because light therapy is well tolerated and safe, it has a very favourable risk-to-benefit ratio (Levitt et al., 1993; Terman and Terman, 1999). Moreover, the long-term follow-up of patients with cumulative exposure durations of up to 1250 h demonstrated the ophthalmologic safety of light therapy, at least in patients without pre-existing ocular abnormalities (Gallin et al., 1995). However, the efficacy of bright light therapy has been much more studied in seasonal than in regular major depression, which, for convenience, we shall refer to as "nonseasonal depression". In this review, we systematically analyzed the available data in the literature to determine whether bright light therapy may be an alternative to antidepressant medication and/or an adjuvant treatment to pharmacotherapy in nonseasonal depression.

2. Methods

2.1. Data sources

We searched the scientific databases Medline and PsychInfo up to June 2006 using "depression", "mood", "light therapy", "light treatment", "phototherapy" and "nonseasonal" as search terms. The computerized search was completed with a manual ascending search on references in the publications initially identified as well as from previous reviews on the subject (Kripke, 1998; Tuunainen et al., 2004; Golden et al., 2005; Terman and Terman, 2005). We additionally searched two reference books in the field of light therapy (Lam, 1998; Partonen and Magnusson, 2001) and contacted the Society for Light Treatment and Biological Rhythms in order to obtain abstracts of its annual meetings for supplementary data.

2.2. Study selection

The selection of studies for this analysis was conducted in two consecutive steps as follows. We first retained all publications that evaluated the efficacy

of light therapy in nonseasonal depression in adults and secondarily selected them according to pre-established criteria which were 1) the use of a controlled parallel group design and 2) the use of light therapy under minimally sufficient conditions previously demonstrated to be efficacious in SAD (duration of trial, intensity/duration of sessions), as detailed below.

Based on the experience of light therapy trials in SAD, we thus discarded studies with cross-over designs, as these are prone to a potential carry over effect, and because the order in which treatments are delivered had previously been observed to influence the therapeutic response to light therapy (Wesson and Levitt, 1998). Additionally, trials that lasted less than a week were excluded, comprising many of those that evaluated light therapy as a means to maintain the effect of sleep deprivation therapy; this aspect of light therapy was furthermore beyond the scope of this review (Neumeister et al., 1996; Colombo et al., 2000). Finally, the combination of light intensity and duration of each light therapy session has been shown to be of particular importance for the efficacy of light therapy on treatment outcome in SAD. As an example, exposure to 2500 lx is efficacious when applied for two hours per day (Wirz-Justice et al., 1987) whereas a daily exposure to 10°000 lx only needs to be performed for 30 min to demonstrate a treatment effect (Terman et al., 1990). Overall, this interaction between the intensity and duration of sessions shows an optimal response above 5000 lx-h. Only studies that fulfilled these minimal duration/intensity criteria (for instance 30-minute sessions at 10°000 lx, 1-hour sessions at 5000 lx or 2-hour sessions at 2500 lx) were retained for further analysis.

3. Results

We identified 62 reports including 46 articles or book sections (Kripke, 1981; Kripke et al., 1983a,b; 1987, 1992; Dietzel et al., 1986; Peter et al., 1986; Yerevanian et al., 1986; Prasko et al., 1987, 1988, 2002; Fleischhauer et al., 1988; Heim, 1988; Mackert et al., 1990, 1991; Stewart et al., 1990; Volz et al., 1990, 1991; Deltito et al., 1991; Levitt et al., 1991; Kjellman et al., 1993; Holsboer-Trachsler et al., 1994; Kasper et al., 1994; Leibenluft et al., 1995; Papatheodorou and Kutcher, 1995; Thalèn et al., 1995; Yamada et al., 1995; Baumgartner et al., 1996; Neumeister et al., 1996, 1997; Beauchemin and Hays, 1997; Muller et al., 1997; Wirz-Justice et al., 1999; Colombo et al., 2000; Sumaya et al., 2001; Loving et al., 2002, 2005a,b; Oren et al., 2002; Benedetti et al., 2003; Epperson et al., 2004; Martiny, 2004; Tsai et al., 2004; McEnany and Lee, 2005; Martiny et al., 2005a,b; Goel et al., 2005), 15 congress abstracts (Kripke et al., 1988, 1989; Deltito et al., 1989; Stewart et al., 1989; Holsboer-Trachsler et al., 1990; Moffit and Ancoli-Israel, 1993; Schuchardt et al., 1993; Prasko et al., 1995; Leibenluft et al., 1997; Loving et al., 1999; Oren et al., 1999; Benedetti et al., 2001; Bloching et al., 2001; Thalèn et al., 2001) and one thesis (Roosli, 1993) that evaluated the efficacy of light therapy in nonseasonal depression. Twenty-two of these reports were excluded because they were duplicate or overlapping reports (Kripke et al., 1988, 1989; Prasko et al., 1988, 1995; Deltito et al., 1989; Stewart et al., 1989; Holsboer-Trachsler et al., 1990; Mackert et al., 1990; Volz et al., 1990, 1991; Kjellman et al., 1993; Schuchardt et al., 1993; Baumgartner et al., 1996; Leibenluft et al., 1997; Muller et al., 1997; Neumeister et al., 1997; Loving et al., 1999; Oren et al., 1999; Benedetti et al., 2001; Thalèn et al., 2001; Martiny, 2004; Martiny et al., 2005b), seven because they were not controlled studies (Peter et al., 1986; Fleischhauer et al., 1988; Levitt et al., 1991; Roosli, 1993; Papatheodorou and Kutcher, 1995; Wirz-Justice et al., 1999; Oren et al., 2002), two because they used a cross-over design (Heim, 1988; Leibenluft et al., 1995), three because they provided no direct comparison between the treated and the control group (Moffit and Ancoli-Israel, 1993; Kasper et al., 1994; McEnany and Lee, 2005) and finally twelve because they did not employ light therapy according to the abovementioned intensity and/or duration criteria (Kripke, 1981; Kripke et al., 1983a,b, 1987; Dietzel et al., 1986; Prasko et al., 1987; Neumeister et al., 1996; Colombo et al., 2000; Bloching et al., 2001; Sumaya et al., 2001; Benedetti et al., 2003; Tsai et al., 2004; Loving et al., 2005b). Overall, we identified 15 studies that fulfilled our selection criteria. However, these 15 studies address different questions and thus cannot be directly compared or pooled in a meta-analytic process. We therefore divided them into three distinct groups. A first group of three studies compared the efficacy of light therapy in seasonal versus nonseasonal depressed patients (Yerevanian et al., 1986; Stewart et al., 1990; Thalèn et al., 1995). These studies answer the question “is light therapy as effective in nonseasonal depression as it is in seasonal depression?”. A second group of 7 studies included nonseasonal depressed patients free of antidepressant medication and compared the efficacy of bright light therapy to that of an exposure to a placebo low-intensity light condition (Deltito et al., 1991; Mackert et al., 1991; Kripke et al., 1992; Yamada et al., 1995; Epperson et al., 2004; Loving et al., 2005a) or to that of a sham air ionization device (Goel et al., 2005). These studies answer the question “has light therapy some

efficacy in nonseasonal depression?". In fact, in one of these studies, about a third of the patients still received their ongoing antidepressant regimen (Loving et al., 2005a) and in another study 2 out of 20 patients received an antidepressant (Goel et al., 2005). A third group of five studies included nonseasonal depressed patients under antidepressant medication and compared the efficacy of light therapy to that of an exposure to a placebo low-intensity light condition (Holsboer-Trachsler et al., 1994; Beauchemin and Hays, 1997; Loving et al., 2002; Prasko et al., 2002; Martiny et al., 2005a). These studies address the question "has light therapy some efficacy as an adjuvant treatment to antidepressants in nonseasonal depression?". In one of these five studies, the patients had also carried out a night with a partial sleep deprivation in addition to antidepressant and light therapy (Loving et al., 2002). We still included this study as the sleep deprivation night was performed in both comparison groups. In another of these five studies, the patients who received antidepressants and light therapy were not compared to patients treated with antidepressants and low-intensity light exposure (placebo) but to a group of patients who only received antidepressants and to another group of patients who received antidepressants in combination with partial sleep deprivations (Holsboer-Trachsler et al., 1994).

3.1. First group of studies: efficacy of light therapy in seasonal versus nonseasonal depression

The general characteristics of theses studies are described in Table 1 (Yerevanian et al., 1986; Stewart et al., 1990; Thalèn et al., 1995). The results of the three studies are unequivocal: they all report a significantly higher efficacy of light therapy in seasonal than in nonseasonal depression, both in terms of improvement in severity scores of depression and in terms of % responders (see Table 1). Moreover, the absolute effect of light therapy appeared more clinically relevant in seasonal patients. Indeed, the absolute difference in Ham-D score reduction between the seasonal and nonseasonal patients was respectively 10 points in the Stewart et al. study, 4 points in the Thalèn et al. study and 15.6 points in the Yerevanian et al. study. Within the nonseasonal patient group, the percentage of those who responded to light treatment varied between 0% and 14% across the three studies, and the Ham-D scores improved by 1.5 and 4.3 points in the Stewart et al. and in the Thalèn et al. respectively while it worsened by 0.9 point in the Yerevanian et al. study.

3.2. Second group of studies: the "light therapy alone" group of studies

3.2.1. Efficacy of light therapy compared to a placebo light in nonseasonal depressed patients without antidepressants

The general characteristics of theses studies are described in Table 2. The studies yielded inconsistent results. Three studies demonstrated that bright light was significantly more efficacious in reducing depressive symptomatology in major depression than the placebo dim light condition (Kripke et al., 1992; Yamada et al., 1995, Goel et al., 2005) whereas four studies reported negative findings (Deltito et al., 1991; Mackert et al., 1991; Epperson et al., 2004; Loving et al., 2005a). To explore the clinical heterogeneity of these studies, we qualitatively examined the impact of several potential confounding factors on treatment outcome, such as inclusion of in- or outpatients, inclusion of bipolar patients or not, blindness of the ratings, timing of light therapy sessions, duration of the trial and sample size. However, none of these variables predicted grouping studies into positive and negative studies in the exact

Table 1
Efficacy of bright light therapy in seasonal versus nonseasonal depression

Study	Yerevanian et al., 1986	Stewart et al., 1990	Thalèn et al., 1995
Subjects	9 SD versus 8 NSD	25 SD versus 8 NSD	68 SD versus 22 NSD
Treatment duration	1 week	1 week	1 week
Diagnosis of depression	DSM-III	DSM-III	DSM-III-R
Definition of "nonseasonal"	Not mentioned	Informal interview	No DSM-III-R seasonal pattern
Depression measure	Ham-D	Ham-D	Ham-D
Results	SD>NSD (% responders: $p<0.001$; Ham-D score: $p<0.01$)	SD>NSD (% responders: $p<0.0001$; Ham-D score: $p<0.001$)	SD>NSD (% responders: $p<0.0012$; Ham-D score: $p<0.001$)

SD = seasonal depression, NSD = nonseasonal depression.
Ham-D = Hamilton Rating Scale for Depression (Hamilton, 1967).

Table 2
Efficacy of light therapy (bright versus dim light) in nonseasonal depressed patients without antidepressants

	Deltito et al., 1991	Mackert et al., 1991	Kripke et al., 1992	Yamada et al., 1995	Epperson et al., 2004	Loving et al., 2005a	Goel et al. 2005
Subjects	$n=17$	$n=42$	$n=51$	$n=27$	$n=10$	$n=81$	$n=20$
Treatment duration	1 week	1 week	1 week	1 week	5 week s	4 weeks	5 weeks
Recruitment	Outpatients	Inpatients	Inpatients	Inpatients	Pregnant women	Older adults	Chronically depressed outpatients
Group randomisation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Time of light sessions	Morning	Morning	Evening [a]	Morning or evening		Morning, midwake or evening	Morning
Blind ratings	Yes	Yes	Yes	Yes	Yes	No [b]	Yes
Diagnosis of depression	DSM-III-R (unipolar, bipolar, dysthymia)	RDC (unipolar or bipolar)	DSM-III (unipolar or bipolar)	DSM-III-R (unipolar or bipolar)	DSM-IV (unipolar or bipolar)	DSM-VI (unipolar)	DSM-IV
Definition of "nonseasonal"	Informal interview	No DSM-III-R seasonal pattern	Informal interview	No DSM-III-R and no Rosenthal criteria for a seasonal pattern	No DSM-IV seasonal specifier	No DSM-IV seasonal specifier	No DSM-IV seasonal specifier and GSS [c] ≤ 6
Depression 2measure	SIGH–SAD	% responders [d]	Ham-D	Ham-D	SIGH–SAD	SIGH–SAD [e]	% remitters [f]
Statistical result	$p>0.05$	$p=0.75$ [g]	$p=0.023$	$p=0.025$	$p=0.88$	$p>0.05$	$p<0.05$ [h]

SIGH–SAD = Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Version (Williams, 1988), RDC = Research Diagnostic Criteria (Spitzer et al., 1978), Ham-D =Hamilton Rating Scale for Depression (Hamilton, 1967).

[a] Few patients received morning and evening light sessions.
[b] Except for a few patients who were rated on the observer-rater version of the SIGH–SAD.
[c] Global Seasonal Score (Rosenthal et al., 1987).
[d] Defined as a 50% reduction in Ham-D scores.
[e] Self-rated version.
[f] Defined as a SIGH–SAD score ≤ 8.
[g] p value for a Yates-corrected χ^2 (computed for this review).
[h] p value for a Fisher exact test (computed for this review).

same way as their results group them (i.e.: the Kripke et al., the Yamada et al. and the Goel et al. studies yielding positive results, the 4 others yielding negative results, see Table 2).

3.3. Third group of studies: the "adjuvant light therapy" group of studies

3.3.1. Efficacy of light therapy compared to a placebo light condition in nonseasonal depressed patients receiving antidepressants

The general characteristics of theses studies are described in Table 3. Four out of five studies reported positive results (Holsboer-Trachsler et al., 1994; Beauchemin and Hays, 1997; Loving et al., 2002; Martiny et al., 2005a). A detailed analysis of the only negative trial (Prasko et al., 2002) did not identify any specific factor (sample size, duration of the trial, geographic latitude of the trial location, time of light sessions, inclusion of in- or outpatients, measure of depression) that would be absent or different in all four positive studies (see Table 3) and thus be able to explain the different outcome.

4. Discussion

4.1. Is there an evidence-based rationale for the use of light therapy in nonseasonal depression?

Or is it merely a random variant of a well tolerated and readily available treatment? Firstly, it is noteworthy that the first light therapy trial in unipolar mood disorders was not conducted in seasonal but indeed in nonseasonal depression (Kripke, 1981). This seminal study by Kripke, though it assessed only the effects of one single session of 1-hour bright light exposure, already yielded promising results. Second, the ability of tryptophan depletion trials, which reduce serotonergic neurotransmission, to suppress the antidepressant effect of light therapy in SAD (Lam et al., 1996; Neumeister et al., 1998) suggests that the effect of light therapy is at

Table 3
Efficacy of light therapy (bright versus dim light) in nonseasonal depressed patients receiving antidepressants

	Holsboer-Trachsler et al., 1994	Beauchemin and Hays, 1997	Loving et al., 2002	Prasko et al., 2002	Martiny et al., 2005a
Subjects	$n=28$	$n=19$	$n=13$	$n=20$ [a]	$n=102$
Treatment duration	4 weeks (but daily sessions only for the 1st week)	1 week	1 week	3 weeks	5 weeks
Recruitment	Inpatients	Inpatients	Outpatients	Inpatients	Outpatients
Group randomisation	Yes	Yes	Yes	Yes	Yes
Time of light sessions	Morning	Morning	Morning	Morning	Morning
Blind ratings	Yes	No	No	Yes	Yes
Diagnosis of depression	DSM-III-R	DSM-IV	DSM-IV	DSM-III-R	DSM-IV
Definition of "nonseasonal"	Not mentioned	No DSM-IV seasonal specifier	Informal interview	No DSM-III-R seasonal pattern	No DSM-IV seasonal specifier
Antidepressant	Trimipramine	Ongoing antidepressant	Ongoing antidepressant	Imipramine 150 mg/J	Sertraline

Depression measure	% response [b]	% remission [c]	POMS	Ham-D [d]	Ham-D	% remission [c]	% response [b]	% remission [c]	Ham-D scores
Statistical result	$p=0.053$ [e]	$p=0.007$ [e]	$p=0.02$	$p=0.025$ [f]	$p>0.05$	$p=0.74$ [g]	$p=0.006$	$p=0.015$	$p<0.01$

Ham-D = Hamilton Rating Scale for Depression (Hamilton, 1967), SIGH–SAD = Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Version (Williams, 1988), POMS = Profile of Mood States (McNair et al., 1988).

[a] Sample size for the 2 subgroups of interest.

[b] Defined as a 50% reduction in Ham-D scores.

[c] Remission was defined as a score below 8 on the Ham-D.

[d] Self-rated version.

[e] p value for the χ^2 computed by us for the patients under trimipramine alone versus trimipramine+bright light therapy.

[f] The authors excluded an outlier.

[g] p value for a Yates-corrected χ^2 for the patients who achieved remission (computed for this review).

least partly mediated through the serotonergic system, and may thus be relevant for the treatment of other types of depression. Longitudinal data on the course of seasonal affective disorder also implicitly support the use of light therapy in nonseasonal depression. A specific bibliographic search to identify long-term follow-up studies of patients with SAD (based on the abovementioned sources) enabled us to find five studies with at least a 2-year follow-up (Leonhardt et al., 1994; Sakamoto et al., 1995; Thompson et al., 1995; Schwartz et al., 1996; Graw et al., 1997). These longitudinal observational studies all come to a similar conclusion. After a few years after having been diagnosed with SAD, 1/3 of patients are in remission from mood disorders, 1/3 still display SAD and 1/3 have a mood disorder that is no longer seasonal. Interestingly, among the patients included in the therapeutic trials of light therapy, positive outcomes are reported for an overall 2/3 of the patients, while only 1/3 of SAD patients, according to the longitudinal studies, eventually have more permanent (and thereby "genuine"?) SAD. Thus, among the responders to light treatment in SAD trials, there may be some patients who are in fact not genuine SAD cases but who, casually or for other reasons, fell within the criteria of SAD at this point of their history. These findings therefore suggest that the diagnostic criteria for SAD are too loose and/or that light therapy is potentially efficacious in at least some forms of nonseasonal depression. As there is currently no clear rationale for the use of light therapy in all types of nonseasonal depression, some subgroups of patients may bear specific circadian disturbances or other symptoms potentially within the reach of light therapy.

4.2. The limitations of the two previous meta-analyses

The two previous meta-analyses that have been performed to assess the efficacy of light therapy in nonseasonal depression bear limitations which constrain any interpretations drawn from these studies (Tuunainen et al., 2004; Golden et al., 2005). The meta-analysis by the Cochrane collaboration combined studies that assessed the efficacy of light therapy alone with studies that assessed light therapy as an adjuvant treatment as well as with studies that assessed the ability of light therapy to maintain the effect of sleep deprivation

(Tuunainen et al., 2004). The significant variability among these included studies is prone to attenuate the significance of any outcome, and is thus unlikely to lead to support strong conclusions. The meta-analysis by Golden et al. more judiciously separated the studies according to their purpose (Golden et al., 2005). The authors split the studies into two groups, one for light therapy alone (without antidepressants) and one for light therapy as an adjuvant treatment. The three studies in their "light therapy alone" group comprised two studies that enrolled the same patients (Volz et al., 1991; Baumgartner et al., 1996). We excluded both of these studies because their patient population also overlapped with a third study that we had selected (Mackert et al., 1991). Conversely, we included five studies that Golden et al. had not included, two due to differences in selection criteria (Deltito et al., 1991; Yamada et al., 1995) and three because they had been published more recently (Epperson et al., 2004; Loving et al., 2005a; Goel et al., 2005). In their "adjuvant treatment" meta-analysis, Golden et al. included 5 studies: two of them had studied the same patient sample (Holsboer-Trachsler et al., 1994; Muller et al., 1997), another had tested the ability of light therapy to maintain the effect of sleep deprivation (Neumeister et al., 1996) and another had only tested whether the response to sleep deprivation predicted the response to light therapy (Fritzsche et al., 2001). Additionally, this latter study also included depressed patients with a seasonal pattern. Finally, the largest study of light therapy in nonseasonal depression (Martiny et al., 2005a) was published only later than the Golden et al. meta-analysis.

The heterogeneity of the methodology used in the various trials (as demonstrated in Tables 2 and 3) renders any inclusion of the results in a meta-analytical computation tentative. As a general rule, the soundness of meta-analyses decreases with increasing differences in study design/methodology and with a decreasing number of available trials (Thompson, 1994). Finally, given the small number of studies included, the conclusions of any meta-analysis may be reversed as soon as new trials appear (Terman, 2006).

4.3. First group of studies: light therapy in seasonal versus nonseasonal depression

One of the three studies in this group included very few patients and may have thereby been hindered by a sampling bias (Yerevanian et al., 1986). Another study opposed two groups of patients who differed not only by their seasonal pattern, but also by the duration of the current episode which was 142 months in the nonseasonal group, far longer than in the seasonal group, whose episodes, by essence, only last a few months (Stewart et al., 1990). This long duration of the current depressive episode in the nonseasonal group may thus be an indicator of treatment resistance, i.e. patients in this group could have been more prone to treatment failure in general, without this being specific for light therapy. Moreover, as patients with SAD are not blind to their own seasonal periodicity, they may have more positive expectations about light therapy than nonseasonal depressed patients. Difference in expectation may partly account for the observed difference of outcome. However, all studies in this group support a higher efficacy of light therapy in seasonal than in nonseasonal depression. Moreover, in two of the three studies, the severity of depression was measured with the Hamilton Depression Rating Scale (Ham-D), an instrument that does not assess atypical symptoms (increased sleep, increased food intake, weight gain) and should have therefore unfavourably affected any perceived improvement in seasonal patients.

In sum, only a limited number of studies so far have compared light therapy in seasonal and nonseasonal depression, and these exhibit significant methodological limitations (low number of patients, noncomparability between groups, nonblind assessments, no assessment of the patients' expectations) that render their results tentative. However, all available studies support a higher efficacy of light therapy in seasonal compared to nonseasonal depression.

4.4. Second group of studies: "light therapy alone"

The described discrepancy of findings in the "light therapy alone" studies (Table 2) suggests that at least subgroups of nonseasonal depressed patients may respond to light therapy. However, no predictor of response has yet been identified in nonseasonal depression. A recent case report suggests that a comorbid night eating syndrome may be a predictive factor for a positive response to light therapy in nonseasonal depression (Friedman et al., 2004). To identify subgroups of patients who respond to light therapy, we propose two approaches based on previous findings.

The first approach would be to refer to the predictors of response to light therapy already identified in SAD, and to conduct therapeutic trials with nonseasonal patients who display these predictive characteristics. A specific bibliographic search on this topic (based on the above-mentioned computerized databases and book references) enabled us to find six studies that investigated predictive factors of response to light therapy in SAD (Stinson and

Thompson, 1990; Nagayama et al., 1991; Oren et al., 1992; Krauchi et al., 1993; Lam, 1994; Terman et al., 1996). Table 4 summarizes these predictors, which are mainly atypical characteristics (hypersomnia, hyperphagia with carbohydrate craving, and weight gain).

The second approach to identifying light responsive patients would be to recruit depressed patients with symptoms that may reflect individual chronobiological characteristics such as increased diurnal variation of mood, early awakenings, etc. This approach would furthermore allow for assessment of the timing of light sessions in relation to the patient's circadian phase (e.g.: evening sessions to induce a circadian phase delay in patients with early awakenings). Consistent with the phase delay hypothesis proposed as the underlying pathophysiology of SAD (Lewy and Sack, 1988; Lam and Levitan, 2000; Murray et al., 2003), it is acknowledged that light therapy is more efficacious when prescribed in the morning so to induce circadian phase advance (Lewy et al., 1987, 1988, 1998). Furthermore, the magnitude of the therapeutic effect of light treatment in SAD has been correlated to the magnitude of the induced phase advance (Terman et al., 2001). In contrast to SAD, however, it is highly unlikely that a single phase disturbance may underly nonseasonal depression. Nonseasonal patients probably have heterogeneous chronobiological patterns, with some patients displaying phase delays of some circadian rhythms, while others may exhibit phase advances or no phase disturbance at all. Indeed both, theoretical models of phase advance (Kripke, 1983; Gwirtsman et al., 1989) as well as phase delay in circadian rhythms (Teicher et al., 1988) have been proposed for depression. On a clinical level, difficulty falling asleep in nonseasonal depressed patients raise the possibility of an underlying phase delay of their circadian system, which would support morning light sessions. Conversely, patients with early morning awakenings can be suspected to be phase advanced, which would support evening light sessions. One way of determining a patient's circadian phase position physiologically and thereby recruiting chronobiologically homogeneous subgroups of depressed patients would be to measure the Dim Light Melatonin Onset (DLMO). The DLMO is the timepoint when melatonin secretion rises over a predefined threshold in the evening, under experimental dim light conditions. This procedure allows to unmask the melatonin profile from confounding parameters, and has been validated to provide a relatively reliable estimate of the circadian phase position. Thus, we believe that the inconsistent results from previous studies on the effects of light therapy alone in nonseasonal depression may indicate that the heterogeneous group of depressed patients included in these studies may have masked a potential therapeutic effect for a relevant subgroup of patients. For future investigations, the selection of patient subgroups according to the predefined clinical and/or chronobiological criteria described above may thus significantly further our knowledge of the therapeutic properties of light therapy in nonseasonal depression.

Another limitation of the six studies in our "light therapy alone" group is the poorly controlled issue of blindness. Some patients probably guessed that they had been allocated to the placebo light condition when exposed to a device that only delivered a few hundred lux or less. Conversely, patients in the treatment arm probably guessed they were under the purportedly active therapy when receiving thousands of lux per session. The difficulty of creating a valid placebo condition is one of the main difficulties in light treatment trials. It has only been overcome in 1998 when two distinct studies (Lewy et al., 1998; Terman et al., 1998) first used a credible placebo by exposing the subject to bright light (10°000 lx) at an inappropriate time of the day (evening). With respect to nonseasonal depression, it is more difficult to predetermine an appropriate or an inappropriate (placebo) time for light sessions as long as no single chronobiological phase alteration (phase advance or phase delay) has been associated with depression. It is thus virtually impossible to define a placebo time for light sessions in nonselected samples. As we suggested above, the selection of subgroups of chronobiologically homogeneous patients may resolve both limitations: knowledge of patient chronotypes that respond to light treatment and protection of blindness

Table 4
Predictive factors of response to light therapy in seasonal depression

Stinson and Thompson, 1990	Atypical scale on the SIGH–SAD
Nagayama et al., 1991	Atypical scale on the SIGH–SAD
Oren et al., 2002	Atypical symptoms (hypersomnia, weight gain, carbohydrate craving), Ham-D score
Lam, 1994	Hypersomnia, increased food intake, younger age
Krauchi et al., 1993	Intake of sweets during the second half of the day
Terman et al., 1996	Melancholic features and atypicity ratio[a] <30% predict nonresponse.

Ham-D = Hamilton Rating Scale for Depression (Hamilton, 1967), SIGH–SAD = Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Version (Williams, 1988).

[a] Atypicity ratio = atypical scale divided by the total SIGH–SAD score (8 "atypical" items + Ham-D 21-item).

(by defining an appropriate as well as a placebo timing of light sessions). Furthermore, such studies may in turn contribute to a better understanding of how chronobiological characteristics may contribute to the etiology/pathophysiology of depressive illnesses. A variant of this approach consists in a broad recruitment of depressed patients which are then phase-typed subsequently. This design would allow for individual and prospective selection of the timing of light sessions for each patient. With the exception of one trial which compared light treatment in seasonal and nonseasonal depressed patients (Thalèn et al., 1995), only the Loving et al. study (see Table 2) strived to phase-type nonseasonal depressed patients before initiating light therapy (Loving et al., 2005a). In an elderly sample of depressed patients, these authors individualized the timing of light sessions according to clinical and actigraphy (recording of the rest–activity cycle over an extended period of time) criteria. The results were disappointing since bright light was not superior to dim light placebo. However, in this study, the effect of light treatment on melatonin phase had been weak, suggesting either that compliance had been low or that this elderly sample was resistant to the circadian effects of light (and thereby to its potential therapeutic effects). Another way to address the placebo issue has been developed by Eastman et al. for seasonal depression (Eastman et al., 1998). They used a deactivated air ionization generator as a placebo control and checked 1) that the daily behavioural commitment was equal to the one for light treatment and 2) that the expectations of the patients were also similar. This method has also been used for nonseasonal depression in one of the studies included in this review (Goel et al., 2005).

4.5. Third group of studies: "adjuvant light therapy"

The majority of the "adjuvant light therapy" studies support the efficacy of light therapy in conjunction with antidepressants, except the study by Prasko et al. However, in this negative trial, only 11 patients received bright light and imipramine and 9 patients received dim light and imipramine. All were inpatients and displayed a Ham-D (Hamilton, 1967) baseline score above 20 while other studies included inpatients or outpatients with Ham-D scores as low as 13 (Martiny et al., 2005a) or even 10 (Loving et al., 2002). The Prasko et al. trial may thus have been underpowered and may have included more severe and/or treatment resistant patients. The recent study by Martiny et al. is the largest (102 patients) and longest (5 weeks) trial investigating light therapy in nonseasonal depression to date. In this trial, bright light therapy was found efficacious as an adjuvant treatment to sertraline on all outcome measures including the 6-item version of the Ham-D, an instrument that assesses the depression core symptoms (depressed mood, self-depreciation and guilt feelings, work and interests, psychomotor retardation, psychic anxiety and general somatic) (Bech et al., 1975). Indeed, the depressive symptomatology comprises core depressive symptoms and a large number of symptoms often present in other disorders. In the 17-item Ham-D, some items measure the core symptoms of depression, while the remaining items cover less specific symptoms such as sleep disturbances, anxiety and somatisation. Although they are often part of the depressive syndrome, these latter items may be the therapeutic target of drugs lacking specific antidepressant properties. Some authors therefore even suggest that an antidepressant label should be given only to drugs improving the core symptoms, in addition to improving the global symptomatology (Lecrubier and Bech, 2007). Over the years, the 6-item Ham-D appears as the most consistent measure of the core symptoms of depression (Bech et al., 1981; O'Sullivan et al., 1997; Lecrubier and Bech, 2007). In the study by Martiny et al., the 6-item HAM-D scale was the most sensitive in discriminating between bright and dim light treatments (Martiny et al., 2005a). It suggests that the adjuvant effect of light therapy is, as the authors say, a "genuine core depressive effect". However, the studies in our "adjuvant light therapy" group are also hampered by the poorly controlled issue of blindness, as described above. Finally, future studies in this field should consider light therapy as an adjuvant treatment to the entire spectrum of commonly used antidepressant medications.

5. Conclusion

Recent studies provide evidence for the efficacy of bright light therapy as an adjuvant treatment to antidepressant pharmacotherapy in nonseasonal depression. Considering the insufficient remission rate of depression with pharmacotherapy alone and the safety of light therapy, larger multicenter trials should be conducted to ascertain whether adjuvant light therapy should be recommended and made available for the complementary management of depressed patients at large.

However, investigations on the efficacy of bright light therapy alone, i.e. without concomitant antidepressant medication, for the treatment of nonseasonal depression have yielded inconsistent results to date. Studies suggest that bright light therapy alone is more efficacious for SAD than it is for nonseasonal depression. Future therapeutic

trials should investigate specific and homogeneous subgroups of nonseasonal depressed patients. The selection of these subgroups could be based on predictors of response to light therapy already identified in SAD. Alternatively, as bright light therapy has been suggested to exert its antidepressant effect through its effects on the circadian system, subgroups of patients could be selected with regards to their chronobiological characteristics, either clinically defined (chronotypes) or based on their circadian phase position according to physiological paradigms such as the DLMO.

Overall, bright light therapy is an excellent candidate for inclusion into the therapeutic inventory available for the treatment of nonseasonal depression today, as adjuvant therapy to antidepressant medication, or eventually as stand-alone treatment for specific subgroups of depressed patients.

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