



TITLE: **Phototherapy for the Treatment of Seasonal Affective Disorder (SAD)**

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PHOTOTHERAPY FOR THE TREATMENT OF SEASONAL AFFECTIVE DISORDER

“In the dark time of the year the soul’s sap quivers”

TS Eliot

INTRODUCTION

The California Assessment Technology Forum has received requests to review the published data regarding the efficacy and safety of phototherapy for treatment of seasonal affective disorder (SAD).

BACKGROUND

Depression is common, disabling and often unrecognized or inadequately treated in general medical practice. Epidemiological studies demonstrate a lifetime prevalence of major depression in 7-12% of men and 20-35% of women. The point prevalence of major depression in a community sample is 2.3-3.2% for men and 4.5-9.3% in women. Numerous studies report a 5-10% prevalence of major depression in primary care settings with a substantially higher rate (20-40%) in patients with co-existing medical problems (Cole et al 2003). It is clear that depression has a significant adverse impact on patient’s functioning and well-being. In addition, the societal cost of depression—including cost of impaired job performance, direct cost of medical, psychiatric, and pharmacological care, and cost stemming from depression related suicide—has been estimated at more than \$43 billion in the United States (Feldman 2000).

The most severe form of depression, major depression, is associated with considerable disability, morbidity and mortality. In fact, it is associated with as much, and often more, physical and social disability as other chronic illnesses such as diabetes, coronary artery disease and arthritis. Major depression represents a heterogeneous group of disorders, most probably arising from a host of etiological determinants. Because no clear anatomic, biochemical or physiological lesions have been found to explain major depression, most investigators agree that it is a complex psychobiological syndrome that can be diagnosed only on clinical, syndromal criteria. Some promising studies, however, suggest etiological possibilities as well as therapeutic interventions.



BACKGROUND, continued

For example, it is increasingly recognized that both genetic makeup and family experiences contribute to an individual's vulnerability to developing major depression. In addition, numerous biological markers of depression have been identified. These biological markers (e.g. cortisol, norepinephrine and serotonin) can reliably differentiate groups with and without major depression, but no marker is specific enough to be used diagnostically (Cole et al 2003).

The DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, 1994) criteria are listed below. Five of nine symptoms must be present most of the day nearly every day for at least a two week period; one of these symptoms must be a either a depressed mood or pervasive anhedonia (loss of interest or pleasure in usual activities).

DSM-IV Criteria for Major Depression

Five or more of the following symptoms—one of which must be depressed mood or anhedonia—must be present for at least two weeks.

1. Depressed mood
2. Anhedonia (loss of pleasure in usual activities)
3. Feelings of worthlessness or inappropriate guilt
4. Inability to concentrate
5. Fatigue or loss of energy
6. Sleep disorder (insomnia or hypersomnia)
7. Psychomotor retardation or agitation
8. Significant weight loss or gain
9. Recurrent thoughts of death or suicide

Depression is often a chronic problem with remissions and recurrence over the patient's lifetime. About one-third of patients with a single episode of major depression will have another episode within one year of discontinuing treatment and more than half will have another episode in their lifetime. Patients with 3 or more episodes have a 90% risk of recurrence (Whooley and Simon 2000). Other mood disorders include chronic depression or dysthymia, minor depression, adjustment disorder with depressed mood, mood disorders due to a general medical condition and bipolar disorder. Other mental disorders often present with symptoms similar to depression and may, therefore, lead to misdiagnosis. In addition, depression often presents in combination with other mental disorders.

BACKGROUND, continued

Evidence from randomized trials demonstrates that antidepressant medication and structured psychotherapy are effective for the treatment of major depression and probably dysthymia. Treatment of minor depression (defined as 4 or fewer DSM-IV criteria for less than two years) generally consists of “watchful waiting” coupled with supportive counseling. More than 80% of depressed patients have a response to at least one medication, although individual antidepressants are effective in only 50-60% of patients (Whooley and Simon 2000). Antidepressants generally take from 4-6 weeks to have a full therapeutic effect. Treatment is recommended for at least 6 months following remission of symptoms to prevent relapse. Patients with chronic depression or with multiple prior episodes or high risk of relapse should be offered more prolonged treatment of at least two years.

Seasonal Affective Disorder

Seasonal affective disorder (SAD) was first described by Rosenthal et al (1984) as “a condition characterized by recurrent depressive episodes that occur annually”. The DSM-IV diagnostic criteria for Recurrent Mood Disorder with Seasonal Pattern includes the following:

- A. There has been a regular temporal relationship between the onset of Major Depressive Episodes in Bipolar I or Bipolar II Disorder or Major Depressive Disorder, Recurrent, and a particular time of the year (e.g., regular appearance of the Major Depressive Episode in the fall or winter). Note: Do not include cases in which there is an obvious affect of seasonal-related psychosocial stressors (e.g., regularly being unemployed every winter).
- B. Full remissions (or a change from depression to mania or hypomania) also occur at a characteristic time of the year (e.g., depression disappears in the spring).
- C. In the last 2 years, two Major Depressive Episodes have occurred that demonstrate the temporal seasonal relationships defined in Criteria A and B, and no non-seasonal Major Depressive Episodes have occurred during that same period.

BACKGROUND, continued

Seasonal Affective Disorder, continued

- D. Seasonal Major Depressive Episodes (as described above) substantially outnumber the non-seasonal Major Depressive Episodes that may have occurred over the individual's lifetime.

The symptoms of SAD can be identical to those of other depressive episodes, but tend to include those features associated with an atypical major depression including low energy, irritability, weight gain and overeating, particularly food high in carbohydrates (Rosenthal et al 1985). The average duration of the symptoms is five months, generally commencing in November. As with other depressive disorders, women are affected disproportionately to men. The epidemiology of SAD is not fully characterized, though the risk of seasonal mood swings is clearly associated with northern latitudes. The prevalence of SAD is estimated to be 0.5%-1.5% in northern European populations, but up to 10%-20% of these populations report milder, recurrent episodes consistent with sub-syndromal SAD (Leppamaki et al 2002).

Explanations for the phenomenon of SAD tend to focus on biological models. The shorter photoperiod and decrease in sunlight exposure experienced by people living in temperate and higher latitudes during the winter is hypothesized to be the main trigger for SAD (Eastman et al 1998). Biological theories of SAD and the effects of phototherapy generally are grouped under four main headings: the melatonin hypothesis, circadian hypotheses, photochemical hypotheses and neurotransmitter theories (Dalglish et al 1996). Melatonin seems to modify the hypothalamic control of a number of hormones and is important in regulating seasonal change in animals. Light suppresses the length of time that melatonin is secreted by the brain which may affect the emergence of seasonal mood patterns. The circadian theory states that the short photoperiod of winter days delay circadian rhythms, and that by reversing this "phase shift" with morning phototherapy the symptoms of SAD could be alleviated. The photochemical hypothesis postulates that SAD sufferers differ in the amount of light perceived by the retina, so the most important variable is the intensity and duration of supplemental light. Finally, several neurotransmitters have been implicated in SAD including dopamine, serotonin, and norepinephrine. Not surprisingly, much current research is focusing on the role of serotonin in the mediation of seasonal affective changes (Dalglish et al 1996).

BACKGROUND, continued

Phototherapy

Phototherapy is based on the principle that the presentation of artificial light at a similar strength to natural sunlight will prevent the biological changes that mediate SAD during the winter. The intensity of a light source is measured in lux. Normal night-time lighting is around 250-500 lux, while a bright sunny day on the Equator is around 80,000 lux. A gray afternoon in Northern Europe is around 10,000 lux (Czeisler et al 1999). Phototherapy for SAD tends to use 2500-10,000 lux delivered via a commercial light box or a portable head mounted unit (light visor). Full spectrum fluorescent is used with the omission of UV wavelengths; some light boxes also come equipped with a filter to eliminate harmful UV wavelengths. Phototherapy is recommended to commence within 2 weeks of the start of symptoms and to continue through the winter months. Patients are instructed to sit approximately 18 inches away from the light box for 30 minutes up to several hours once or twice per day for a minimum of one week. Patients are generally permitted to engage in another activity (e.g. reading) so long as they do not close their eyes and periodically pass their gaze over the lights. There has been some interest as to whether the timing and delivery of phototherapy influences its efficacy. Some research has concluded that morning light is more efficacious than evening light (Lewy et al 1998) but other studies have found that the timing of light treatment is not critical (Meesters et al 1995). Other research has concluded that “dawn simulation” (the gradual increase in illuminance before the subject awakens) is associated with a greater clinical response than bright light alone (Avery et al 2001).



TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

There are many light box and light visor devices being marketed for seasonal affective disorder. These devices are considered medical devices by the FDA and therefore require pre-market clearance. An extensive search of the FDA website and the Internet was conducted for several devices. FDA pre-market clearance was not found for any of the devices searched.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

To date, there have been at least 20 randomized trials comparing light treatment to some sort of placebo, either photic (e.g. dim light) or non – photic (e.g. a negative ion generator). In addition, trials have randomized subjects to different active treatments (e.g. dawn simulation vs. bright light; morning vs. evening light), and one study examined the efficacy of light applied to the popliteal fossa vs. placebo. Many of these studies are small with less than 10 patients in each arm. Patients were generally recruited for these studies from media and advertising with the stated expectation that light treatment is an accepted treatment for seasonal depression. Patient expectations were considered in some, though not all, of the studies. A significant methodological issue in all depression trials is the significant placebo effect.

The Hamilton Depression Rating Scale (HDRS) (Hamilton 1967) is the measure most often used as the measure of change of severity of depression in studies of phototherapy and SAD. It can be used as a self-report measure or be scored for severity by the rater. More recently, several additional items were added to the HDRS to account for the atypical symptoms that predominate in SAD patients. This scale is called the Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorders Version (SIGH-SAD). The SIGH-SAD is comprised of the 21 item HDRS and eight supplementary items concerning the atypical symptoms commonly seen in winter depression such as hypersomnia, increased appetite and weight gain.



TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes (continued)

Most studies assess the efficacy of phototherapy by reporting on the patients who achieve a response as evidenced by a decrease of 50% or greater on the SIGH-SAD scale or a remission as shown by a final SIGH-SAD score less than or equal to 8. Other outcomes assessed include improvement on other standardized measures of depression such as the Beck Depression Inventory. Broader outcomes such as impact on quality of life, function at home and work, economic cost of the disease and cost offset of treatment, and impact on other medical illness are rarely considered in the SAD treatment literature.

Level of evidence: 1, 3, 5

TA Criterion 3: The technology must improve the net health outcomes.

Patient Benefits

Randomized trials

Bright light vs. placebo

Rosenthal et al (1984), Rosenthal et al (1985) and James et al (1985) were influential in establishing SAD as a significant disorder and gaining acceptance for phototherapy as an effective treatment. These studies all recruited patients from newspaper ads to participate in a randomized, crossover design consisting of 1-2 weeks of bright light treatment (2500 lux) followed by a one week washout period and then exposure to dim white or yellow light at 100-300 lux. They found a significant difference in response to treatment (as measured by HRSD) between the bright light and dim light subjects with virtually all of the bright light subjects responding and about half of the dim light subjects responding to treatment. There are several methodological issues that cast doubt on these early studies, however, including method of recruitment (patients responded to ads that reported the beneficial effects of light treatment), lack of follow-up of patients who failed to complete the study, and small overall numbers.



TA Criterion 3: The technology must improve the net health outcomes (continued)

Bright light vs. placebo, continued

Several studies closely followed on these earlier investigations; most failed to find a significant difference between dim light and bright light. Wirz-Justice et al (1986) recruited 22 patients from newspaper ads and physician offices into a randomized crossover design of 5 days of light therapy (2500 lux) followed by a 1 week washout and then 5 days of treatment. They found no significant difference in pre and post-HRSD scores between dim and bright light. Similarly, Joffe et al (1993) evaluated 105 subjects across 5 centers with three intensities of light delivered by a head visor: 60 lux, 600 lux and 3500 lux. Using a 2-week randomized parallel design they found no significant difference in antidepressant efficacy of the three intensities of light as measured by % reduction in HRSD-SAD scores. Eastman et al (1992) used a deactivated negative ion generator as a non-light placebo as compared to bright light in a randomized study of 32 patients. They found no difference between placebo and bright light treatment in response to treatment with a significant decline in SIGH-SAD scores for both groups. Stewart et al (1991), Brainard et al (1990), Isaacs et al (1988) and Grota et al (1989) all used a randomized, crossover design to compare bright light treatments to a control condition of dim light, red light, or filtered bright light. Overall, while some patients in the bright light treatment groups responded more favorably or remained in remission longer, there was not a significant difference found between placebo and treatment groups in these studies. Rosenthal et al (1993) conducted a randomized parallel treatment study of 55 patients treated with 6000 lux vs. 400 lux for 1 week and found no significant difference between the two groups. Levitt et al (1994) randomly assigned 43 subjects to receive 2 weeks of treatment with either bright light (mean of 4106 lux) or dim red light (mean 96 lux) using a head mounted unit. They found no significant difference in response rates between patients receiving bright light (67%) as compared with patients receiving dim light (68%).



TA Criterion 3: The technology must improve the net health outcomes (continued)

Bright light vs. placebo, continued

Two small controlled trials did show a clear advantage to bright light over dim light. Lam et al (1991) recruited 11 patients from a seasonal mood clinic and randomized them to a triple cross-over design consisting of three treatments: bright light at 2500 lux for 2 hours, bright light with UV block (2500 lux with filter in place) and dim light (500 lux). They found a significant difference in HRSD change score between bright and dim light. Magnusson et al (1991) randomized 10 patients into a crossover design consisting of bright white light (10,000 lux) and dim red light (400 lux) each for 40 minutes per day. They found a significant difference in post-HRSD scores between bright and dim light.

Several studies conducted in the past five years have used more rigorous methodology than many of the earlier studies discussed above. Overall, these studies have failed to convincingly demonstrate a significant difference between bright light and dim light or other placebo. Three negative studies are reviewed first. Teicher et al (1995) randomized 57 patients across two sites to receive, over a two week period, 30 minutes of morning phototherapy with a light visor that emitted either a dim (30 lux) red light or a bright (600 lux) white light. Response was assessed using the structured SIGH-SAD scale. Hamilton depression scores declined by 34.6% for subjects given bright white light and by 40.9% for subjects given dim red light. Overall, 39.3% of patients who received red light and 41.4% of patients who received bright white light showed a full clinical response.

Levitt et al (1996) conducted a double-blind controlled trial in which 43 subjects were randomly assigned to receive one of four treatments: active light box (5,000-10,000 lux), placebo light box (the lamps emitted no light but did produce a hum), active head mounted unit or HMU (with 2 LED's mounted on a cap and light beams directed at the eyes) and a placebo HMU. Patients were treated for 2 weeks. Response was defined as a 50% or greater reduction in both the 17 item "typical" score and 8 item "atypical" score on the SIGH-SAD. They found no significant response rate between the four cells and no significant difference in response rate between patients who received light (48%) versus patients who received no light (41%).



TA Criterion 3: The technology must improve the net health outcomes (continued)

Bright light vs. placebo, continued

The authors acknowledge that the inability to find a difference between the active and placebo treatments may be due to the small sample size.

Wileman et al (2001) recruited subjects from primary care practices in Scotland during January over two years. Fifty-seven participants were randomly allocated to 4 weeks of bright white (10,000 lux) or dim red (500 lux) light for 4 weeks. Patients completed the SIGH-SAD at baseline and weekly during the 4 weeks of treatment and at 2 and 6 weeks after treatment. Patient expectations of treatment were assessed prior to treatment. The primary outcome variable was response to treatment at 4 weeks. They found that both groups showed a marked decrease in SIGH-SAD scores with no clear differences between the groups. The proportion of responders in treatment and control groups was around 60%. No significant correlation was found between patient expectations and SIGH-SAD scores.

Three recent studies, Eastman et al (1998), Terman et al (1998) and Lewy et al (1998) are said to “provide the best evidence that light is an effective antidepressant in seasonal affective disorder (SAD)” (Wirz-Justice 1998). These will be reviewed below. Eastman et al (1998) found that bright light therapy had a specific anti-depressant effect beyond its placebo effect, but it took at least 3 weeks for a significant effect to develop, and the difference between the groups was limited to one criterion. They recruited patients through advertisements and local media who met criteria for SAD but also had atypical symptoms of increased appetite or weight and increased sleep. All were free of psychotropic medications and none had ever used light treatment. Patients were randomly assigned to morning light (6000 lux), morning or evening placebo and evening light. Placebo consisted of a sham negative ion generator that consisted of shiny black cylinders, 32 cm high, with 3 small lights in front that changed rapidly between red and green and emitted a humming sound. Patients were given pamphlets before the study with information from “scientific and lay literature” promoting negative ion and light treatment for SAD. Ninety-six patients completed the study and 25 dropped out during the 5 week protocol.



TA Criterion 3: The technology must improve the net health outcomes (continued)

Bright light vs. placebo, continued

Expectation ratings showed that all groups expected their treatment to be very successful. Patients were classified as responders if their 24-item SIGH-SAD score decreased to 50% of baseline. The percent responders for the morning light, evening light and morning placebo groups were 55%, 56%, and 52% after 3 weeks of treatment, and 67%, 75%, and 48% after 4 weeks. There were no statistically significant differences at treatment week 3 or 4. Significant differences emerged when patients were classified as responders by “strict joint criteria” designed to identify those with complete or nearly complete remissions (a decrease in SIGH-SAD of 50% and a score less than or equal to 8). Using these criteria, at week 4, the percent responders for the morning light, evening light and morning placebo groups were 61%, 50%, and 32%, statistically significant differences between light and placebo. Several methodological issues are apparent with this study. First, there is no discussion of attempted follow-up with the 25 patients who dropped out or information given on which group they were originally assigned to and when they dropped out. Second, although the negative air ionizer is a creative idea for a placebo, it does not resemble a light box. Third, significant differences between placebo and light were only found when responders were classified most strictly, and then only by week 4 of treatment.

Terman et al (1998) recruited subjects 18-65 years by advertising/media and physician referral. During 6 years, from November to March, 158 subjects entered the study and 145 completed it. They used a morning-evening crossover design balanced by parallel group controls and a non-photic control, negative air ionization. Patients were randomly assigned to 6 groups for 2 consecutive treatment periods, each 10-14 days. Light treatment sequences were morning-evening, evening-morning, morning-morning, and evening-evening (10,000 lux for 30 minutes). A negative air ionizer was set to deliver either high or low ions per cubic centimeter. They found that at least half the subjects undergoing light or high-density ion treatment in period one improved by 50% or more. Fewer subjects met the remission criterion of a post-treatment SIGH-SAD score of 8 or less. Within period one, the remission rate for morning light was 54.3%, evening light 33.3%, high-density ions 20% and low-density ions 10.5%. Remission rates for high-density ions continued to improve with an additional 2 weeks of treatment after period 1; no corresponding changes were reported for the parallel light groups.



TA Criterion 3: The technology must improve the net health outcomes (continued)

Bright light vs. placebo, continued

The authors conclude that light therapy, particularly morning light, and high-density negative air ionization have a specific antidepressant effect in SAD. As with Eastman et al (1998) discussed above, no information is provided on subjects who did not complete the study. In addition, they report that patient expectations of treatment efficacy when assessed at baseline were slightly higher for light therapy than the air ionizer (expected “significant” rather than “moderate” improvement). It is not clear if this had an impact on the response to treatment.

The third study is not a placebo-controlled trial. Instead, it compares morning with evening light administration. According to the phase-shift hypothesis for winter depression, morning light (which causes a circadian phase advance) should be more antidepressant than evening light (which causes a delay). Although no studies have shown evening light to be more antidepressant than morning light, investigations have shown either no difference or morning light to be superior. Lewy et al (1998) assessed morning vs. evening light in both crossover and parallel-group comparisons. Fifty-one patients and 49 matched controls were studied for 6 weeks. After a pre-baseline assessment and a light/dark and sleep/wake adaptation baseline week, subjects were exposed to bright light at either 6 to 8 AM or 7 to 9 PM for 2 weeks. After a week of withdrawal from light treatment, they were crossed over to the other light schedule. Dim-light melatonin onsets were obtained 7 times during the study to assess circadian phase position. Morning light phase-advanced the dim-light melatonin onset and was more antidepressant than evening light, which phase-delayed it. However, the absolute impact of light treatment on the subject’s depression scores in this study was unimpressive and significantly worse than placebo in most other studies. They found that with the usual remission criteria of a greater than 50% decrease in SIGH-SAD scores, 37% of patients exposed to morning light and 6% of patients exposed to evening light met remission criteria.



TA Criterion 3: The technology must improve the net health outcomes (continued)

Extraocular light vs. placebo, continued

Koorengeval et al (2001) conducted a double blind placebo controlled trial of extra-ocular light therapy for patients with SAD. Based on research that purported to demonstrate that light applied to the popliteal fossae induced phase shifts of the human circadian pacemaker, these researchers hypothesized that extra-ocular light may be therapeutic in SAD and would be more amenable to a placebo-controlled trial than visible light. 29 patients were randomized to receive illumination of the popliteal fossae by fiberoptic light or no light in a manner undetectable by the subject. They found that both conditions showed a progressive improvement of clinical state over time, but there was no statistically significant difference between them. According to the SIGH-SAD criteria for remission, (defined as a decrease of greater than 50% on the SIGH-SAD and a final SIGH-SAD score of less than or equal to 8), 27% in the active treatment group and 21% in the placebo group were remitted

Dawn simulation vs. bright light

Foreland et al (1998) randomized 61 patients with SAD to receive either lightbox treatment with 1500-2500 lux white light for 2 hours in the morning for 6 days or dawn simulation (DS) with 60 or 90 minutes of light augmentation time to 100-300 lux for 2 weeks. Patients in the DS group had a 40% reduction in depressive symptoms while the lightbox patients had a 57% reduction in symptoms by 2 weeks. At 10 weeks the two groups were identical with about an overall reduction of 40%.

Avery et al (2000) randomized 95 patients with SAD to one of three conditions: bright light therapy (10,000 lux for 30 minutes over 6 weeks), dawn simulation (DS) (1.5 hour dawn signal peaking at 250 lux) and a placebo condition (a dim red light 1.5 hour dawn signal peaking at 0.5 lux). Over 6 weeks the subjects were blindly rated by a psychiatrist using the SIGH-SAD scale. Remission was defined as SIGH-SAD less than or equal to 8 and response as a greater than or equal to 50% decrease in SIGH-SAD scores. They found that DS was associated with greater remission and response rates compared to the placebo and bright light. Bright light did not differ significantly from the placebo.



TA Criterion 3: The technology must improve the net health outcomes (continued)

Phototherapy for Other Depressive Disorders

There have been a number of small studies that have examined the efficacy of phototherapy in depressive disorders other than SAD. Oren et al (2002) conducted an open trial of bright light therapy in 16 pregnant patients with major depression. Patients were instructed to use a 10,000 lux light box for 60 minutes daily for at least 3 weeks. After 3 weeks they found that mean depression ratings improved by 49%. The lack of a control group makes the significance of these findings unclear. Sumaya et al (2001) investigated the efficacy of morning light treatment on depression among older adults residing in a long-term care facility. They enrolled 10 patients with an average age of 84 in a placebo controlled crossover design to 1 week (5 days) of bright light (10,000 lux), or dim light (300 lux) or placebo (no treatment). There was a 1 week washout period between treatments. They found that Geriatric Depression Scale scores decreased significantly in the bright light treatment group (from a mean of 15 to 11), but remained unchanged in the other two conditions.

Case series

Levitt et al (2002) evaluated 3 weeks of open treatment with light therapy for patients with SAD and sub-syndromal SAD. 46 patients enrolled and 44 completed at least 2 weeks of treatment with 5000 lux for 30 minute daily increased to 60 minutes after 2 weeks at the discretion of the physician. The SIGH-SAD was administered weekly. Response rates were similar in SAD and sub-syndromal SAD patients with response rates of 62%-69%.

Nonrandomized, comparative trials

Wirz-Justice et al 1996 compared “natural light” treatment of 20 patients (obtained while patients engaged in a one-hour morning walk) and artificial light therapy of 2800 lux for 30 minutes per day over 3 weeks for 8 patients. Patients were given a choice of treatment. According to the SIGH-SAD scores, 25% of patients remitted after the light box treatment and 50% after the walk. They conclude that ‘natural’ light is as efficacious as artificial light in treating SAD. The potential confounding effects of the exercise are raised but thought not to be significant as “our subjects did not exert themselves physically”.



TA Criterion 3: The technology must improve the net health outcomes (continued)

Patient Risks

Light therapy has been considered a benign treatment with few side effects or risks. One study (Labbate et al 1994) examined the frequency of adverse effects of bright light treatment for SAD in 30 patients treated for one week with 2 hours of 2500 lux bright light. They found that side effects were mild and remitted with time. Side effects consisted of agitation, hypomania (in one patient), sleep disturbance and visual side effects such as eye strain and headache. There was no control group for comparison. In another uncontrolled study, (Terman and Terman 1999) reported on side effects of phototherapy in 83 patients with SAD treated with 10,000 lux for 30 minutes for 10-14 days. They reported several mild side effects including :”jumpiness/jitteriness” in 8.8%, headache (8.4%), and nausea (15.9%). A theoretical risk of phototherapy is the potential for prolonged bright light exposure to produce harmful effects on the retina. This has led some investigators to call for routine ophthalmological examinations prior to initiating light therapy (Reme and Terman 1992). At the current time, there is insufficient evidence to support this recommendation.

Many patients report that they find it inconvenient and difficult to find the time to sit in front of the light box, leading to a relatively high drop-out rate in many of the studies. One study found that about 19% of patients stop light treatment because of the inconvenience (Schwartz et al 1996).

TA Criterion 4: The technology must be as beneficial as any established alternatives.

The alternatives to phototherapy for Seasonal Affective Disorder consist of the established treatments for major depressive disorder such as pharmacotherapy and psychotherapy, specifically cognitive behavioral therapy or interpersonal therapy. There is little research on these treatments for SAD. Ruhrmann et al (1998) conducted a randomized, parallel design comparing 5 weeks of treatment with fluoxetine (20mg/day) and a placebo light condition vs. bright light (3000 lux at 2 hours/day) and a placebo drug. 40 patients were enrolled and 35 completed the study.

TA Criterion 4: The technology must be as beneficial as any established alternatives (continued)

They found no significant difference in response to treatment (70% of patients in light group vs. 65% in fluoxetine group responded) or in remission rates (50% in light group and 25% in fluoxetine; P=NS)

Ghadirian et al (1998) examined the therapeutic effects of tryptophan vs. light therapy in 13 patients with SAD in a parallel crossover design. Light therapy (10000 lux for 30 minutes over 2 weeks) was compared with tryptophan (2 grams bid-tid for 4 weeks). They concluded that both tryptophan and light had significant therapeutic effects, and that tryptophan was equally effective to light in treating SAD.

Thorell et al (1999) conducted a placebo-controlled double blind pilot study in 8 women with SAD; 4 were randomized to citalopram 40 mg plus 2 weeks of light treatment, and 4 were randomized to placebo plus light. By week 34, one patient dropped out of the celexa group due to side effects and 2 from the placebo plus light group switched to treatment with celexa due to worsening symptoms. They report that patients in the celexa arm of the study had improved depressive outcomes at 34 weeks as compared to light plus placebo and conclude that their results should encourage further research on the benefits of combining SSRI's with light therapy.

Kaspar (1997) found that 900 mg of hypericum (St Johns Wort) was associated with a significant reduction in the total HDRS over 4 weeks in patients with SAD, and there was no additional improvement with the addition of bright light. Lam et al (1995) found no difference between fluoxetine and placebo over 5 weeks of treatment (though again both groups showed significant improvement).

Other agents studied for the treatment of SAD include atenolol (Rosenthal et al 1988), Ginkgo biloba (Lingjaerde et al 1999), alprazolam (Yamadera et al 2001), melatonin (Wirz-Justice et al 1990) metergoline (Turner et al 2002) and reboxetine (Hilger et al 2001). There is no convincing evidence to support the use of any of these agents in the treatment of patients with SAD.



TA Criterion 5: The improvement must be attainable outside the investigational settings.

The published data are not sufficient to conclude that the efficacy of the phototherapy for Seasonal Affective Disorder procedure has been established in the investigational setting, let alone under conditions of usual medical practice.



RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The Blue Cross Blue Shield Association reviewed this topic in May 1995 and concluded “phototherapy for the treatment of seasonal affective disorder does not meet Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria”.

Centers for Medicare and Medicaid Services (CMS)

CMS does not have coverage policy regarding the use of phototherapy for seasonal affective disorder on the national or local level.

California Psychiatric Association

The Association has been asked to provide a position statement and representation at the meeting.

CONCLUSION

Since the first empirical work on SAD almost 20 years ago (Rosenthal et al 1984), light therapy has become accepted as the treatment of first choice for this disorder. A rigorous evaluation of the empiric literature, however, leaves considerable uncertainty as to the efficacy of this practice. In spite of over 20 randomized trials of light therapy for seasonal affective disorder since 1984, it is not possible to conclude that this treatment is significantly superior to placebo for most patients with SAD.

There are a few methodological issues that consistently stand out in the SAD treatment literature. One significant issue is the powerful impact of placebo in the treatment of depression. It is well known that there is a high response rate to placebo in most major depression drug trials, generally on the order of 15%-50% (Appleton and Davis 1973). To determine the efficacy of phototherapy for the treatment of SAD, it is necessary to demonstrate the incremental benefit of light therapy above that of placebo. While many studies found that bright light is more effective than dim light in the treatment of SAD, few show a significant difference between these treatments. While it is possible that the placebo response could create a type II error in these studies and obscure the benefits of light treatment, it is also possible that most of the benefit seen with light therapy is primarily due to its being an effective placebo for patients with SAD.

In addition, it has been difficult to construct an appropriate placebo in SAD trials. Dim light, typically at around 300 lux (the winter indoor light intensity), has been used most frequently as the placebo control for bright light. Dim light is easily distinguished by patients from bright light, which may influence the placebo response. Negative ion generators have been used in more recent studies but are easily distinguished by patients from light emitting boxes.

Another related issue has to do with the method of recruitment of most of these studies and the link with patient expectations. The vast majority of SAD treatment studies recruited their patients through media and advertising, the content of which often touted the purported benefits of light for seasonal depression. This self-selection of patients is problematic, especially when paired with the issue of it being impossible to blind patients to the intervention. Even in the earliest studies, most patients predicted that bright light would be helpful.



CONCLUSION, continued

Because expectations for improvement are believed to account for a component of placebo effects, and there is a significant influence of placebo effect in all depression trials, it has been difficult to show definitively that phototherapy has an antidepressant effect beyond its placebo effect. However, in spite of the fact that patients generally have higher expectations for bright light than dim light or other placebo treatments, patient expectations have not always correlated with response.

On a final note, it has been suggested that there may be different sub-populations of patients who meet criteria for SAD but respond differently to light treatment. Patients with SAD may have either unipolar or bipolar depression. In the early studies of light treatment (e.g. Rosenthal et al 1984) the majority of patients enrolled were bipolar, and generally had a better response to light. This suggests that closer attention should be paid to this and other co-factors that may predict a better response to light for patients suffering from SAD.

In conclusion, most of the more rigorously conducted placebo-controlled trials of light treatment for SAD have found no significant differences between placebo and light treatment. Although SAD is a relatively low cost and safe treatment, it is impossible to conclude from the existing literature whether phototherapy is significantly more effective than placebo for the treatment of SAD.

Thus, TA criteria 1-5 are not met.



RECOMMENDATION

It is recommended that phototherapy for the treatment of Seasonal Affective Disorder does not meet California Technology Assessment Forum technology assessment criteria.

June 11, 2003



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