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Review article

Natural treatments for seasonal and non-seasonal depression: a review of literature and comparison of antidepressant responses

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ABSTRACT

The symptoms of depression might be alleviated by such non-pharmacological interventions as sleep deprivation, bright light exposure, and physical exercise. Some strategies of non-drug treatment for seasonal and non-seasonal depression seem to be very effective, but the involvement of specific biological mechanisms in the observed beneficial response still remains to be clarified. A present literature review was combined with a brief summary of the results of a set of author's investigations that provided a possibility to compare the antidepressant effects of several one-week treatments in 268 female subjects with either winter depression or non-seasonal depression or without depression (n=118, 64 and 86, respectively). It was demonstrated that a total night sleep deprivation failed to improve mood in non-depressed subjects, whereas in seasonally and non-seasonally depressed subjects the significant improvements of similar magnitudes were observed. Furthermore, any type of one-week treatment (i.e., 6 or 7 days of bright light, physical exercise, melatonin or placebo intake, and vocation in a south region) administered either alone or in combination with one night of sleep deprivation produced a notable reduction of depression scores in both depressed and non-depressed subjects. Such treatments prevented relapse after sleep deprivation. Mood further improved after visual treatments, such as bright light and physical exercise, rather than after blind intake of ether melatonin or placebo. The

studies of natural antidepressants highlighted the possibility that they often work as powerful placebos, and that, compared to the biology of depressives; their psychology is the most important mediator of clinical response. Further research might be aimed on testing the predictions based on evolutionary explanation of depression and antidepressant responses to natural treatments.

1. A review of antidepressant responses to natural treatments

1.1. Depression and conventional antidepressant medications

Depression is characterized by the presence of several of the following symptoms for, at least, two weeks: low mood most of the day, loss of interest in usual activities, gain or loss of weight, too little or too much sleep, fatigue, thoughts of death or suicide, inability to concentrate, and guilt or feeling of worthlessness. Depression is much more common than other mental disorders. It ranks fourth in the world in terms of the global burden of disease (Murray, Lopez, 1996; Üstün et al., 2004). Therefore, it is of importance to study the clinical benefits offered by its treatment with antidepressants (i.e., Andrews, 2001).

Some recent findings have aroused concern among researchers and the lay public about efficacy of the conventional antidepressant medications. For instance, the general negative view that the public have about the benefits of pharmacological interventions (Jorm et al., 1997) was supported by a number of their clinical trials suggesting that they act non-specifically and are not distinctly superior to placebo treatments (Joffe et al., 1996; Moncrieff et al., 1998; Antonuccio et al., 1999; Khan et al., 2000; Kirsch et al., 2008; Moncrieff, 2002; Walsh et al., 2002).

1.2. Sleep deprivation

Since Pflug and Tölle's (1971) initial demonstration of the antidepressant effect of sleep deprivation, there has been considerable interest in the examination of its possible therapeutic benefits. At present, it is a well-established fact that sleep deprivation (wake therapy) produces rapid improvement of mood in 40-60% of depressed patients, and that this improvement is usually short-lasting, because 50-80% of responders suffer a complete or partial relapse after recovery sleep (Kuhs & Tölle, 1991; Riemann et al., 1993; Wirz-Justice, Van den Hoofdakker, 1999; Geidke & Schwarzler, 2002).

The mechanisms of the antidepressant effects of sleep deprivation remain unclear (Wu & Bunney, 1990). One group of most often discussed hypotheses postulates that depression is associated with a pathological increase in some aspects of physiological and emotional arousal and that sleep deprivation works by "de-arousing" or "de-inhibiting" depressed patients (Szuba et al., 1991; Van Den Burg et al., 1992; Bouhuys et al., 1995; Gillin et al., 1995; Wu et al., 1992, 1999; Clark et al., 2006).

Various methods have been proposed to stabilize the improvement of mood in sleep-deprived depressives. Such stabilization can be achieved by the administration of conventional antidepressant medications. For instance, Wu and Bunney (1990) reported a relapse rate of 59% in those patients who received pharmacological treatment after sleep deprivation, and a rate of 83% in those patients who were not subsequently treated with antidepressants.

There are also unconventional antidepressant treatments which show benefits similar to the pharmacological interventions, but without notable side effects. Among those treatment alternatives, such natural interventions as bright light and physical exercise were proposed to be the promising stabilizers of mood after successful action of sleep deprivation (Neumeister et al., 1996; Pinchasov et al., 1998; 2000; Poljakova et al., 1998; Putilov, 2001; Putilov et al., 2004, 2005a). The question arises whether such treatments can be recommended as safe, cheap, rapid and effective antidepressants, for, at least, those depressives who do not respond to drug medications, who prefer non-pharmacological treatments, and who have depression in mild or moderate rather than severe, chronic or recurrent forms.

1.3. Bright light

Almost 30 years ago, Kripke pioneered the research of bright light treatment for depression by forwarding the hypothesis that light might work as an effective antidepressant during the procedure of sleep deprivation (Kripke, 1981; Kripke et al., 1983ab). Two experiments designed to compare the effects of total sleep deprivation in dimly and brightly lit rooms showed that, from one hand, light at night is not necessary for the antidepressant action of sleep deprivation, but, from another hand, it was found to trigger earlier and more long lasting antidepressant effects compared to the effects obtained in dim light condition (Wehr et al., 1985; Van den Burg et al., 1990).

The clinical efficacy of combined treatment consisted from sleep deprivation and light therapy was demonstrated in the studies conducted by several research groups (Neumeister et al., 1996; Bloching et al., 2000; Pinchasov et al., 2000; Colombo et al., 2000; Loving et al., 2002; Benedetti et al., 2005; Putilov et al., 2005a).

Soon after Kripke's studies (Kripke et al., 1983ab), bright light therapy was suggested to be the effective treatment for a newly described form of depression, seasonal affective disorder (Rosenthal et al., 1984). Unlike other affective diseases, the depression with seasonal pattern (winter depression, summer depression, etc.) has not been discovered by medical practitioners. Rather, winter depression was predicted and discovered by the research in the field of chronobiology (Lewy et al., 1982). The prediction of antidepressant action of bright light for winter depression was based on the assumption that deprivation of light in wintertime is a key factor for its development (Rosenthal et al., 1984).

Since the first description of this condition, the predicted effect of bright light therapy to reverse its symptoms has been demonstrated in numerous studies and confirmed by their meta-analyses (Terman et al., 1989; Lee et al., 1997; Lee, Chan, 1999; Golden et al., 2005; Terman, Terman, 2005). The general conclusion was that the symptoms of this depression may remit after just one or two weeks of 2 to 4 hour daily exposure to bright light (2500 lux or more).

Some researchers argued that treatment in the morning is more beneficial than evening treatment (Lewy et al., .1987, 1998a; Terman et al., 1990, 1998; Avery et al., 1990), but many reported results can be interpreted as indicating that the timing of light administration is not critical for antidepressant response (i.e., Wehr et al., 1986; Jacobsen et al., 1987; Wirz-Justice et al., 1993; Lafer et al., 1994; Meesters, 1995; Meesters et al., 1995).

The earlier comparisons of bright light treatment with placebo (i.e., dim red light or a negative ion generator) either showed an advantage of bright light over dim light (Rosenthal et al., 1984, 1985; Lam et al., 1991; Magnuson, Kristbjarnarson, 1991) or failed to demonstrate such advantage (Wirz-Justice et al., 1986; Grota et al., 1989; Brainard et al., 1990; Joffe et al., 1993; Rosenthal et al., 1993). Some of more recent studies provided evidence for superiority of morning bright light over either evening bright light or placebo (Michalon et al., 1997; Eastman et al., 1998; Lewy et al., 1998a; Terman et al., 1998). However, many other studies did not find clear differences between bright light and placebo (Levitt et al., 1994, 1996; Teicher et al., 1995; Avery et al., 2001; Wileman et al., 2001).

Although for several decades bright light has been regarded as the treatment of choice for winter depression (Terman et al., 1989; Lam et al., 1997; Wirz-Justice et al., 2005), recent clinical trials failed to provide evidence for its superiority over either antidepressant medications (i.e., Pjrek et al., 2005; Lam et al., 2006; Westrin, Lam, 2007; Howland, 2009) or cognitive behavior therapy (Rohan et al., 2007, 2009).

The neurobiological basis of winter depression and of the antidepressant action of bright light has been studied by many research groups. The vast majority of the proposed explanations were focused on biological mechanisms (reviewed by Rosenthal, Wehr, 1992; Lee et al., 1997; Lam, Levitan, 2000; Sohn, Lam, 2005; Rohan et al., 2009). However, after more than two decades of extensive experimental research, no causal relationship has been drawn between the incidence of winter depression and the relative shortage of light. Although bright light exposure has been used in treatment of this condition, its cause is not inevitably a lack of light (Putilov et al., 1999, 2005b). The questions that still remain to be open include the following: 1) is winter depression a photoperiodically induced condition?; 2) is any specific component in the light treatment for winter depression?; 2) is any specific physiological system responsible for alleviation of the symptoms of this depression?; and 3) is any causal link between the physiological and mood responses to bright light treatment? (Putilov, 2009).

In contrast to the general acceptance of bright light as an excellent treatment for patients with winter depression, the benefits of such treatment for depression without seasonal pattern are unclear (Lam et al., 1989; Kripke, 1998; Even et al., 2008). Among earlier reports, there were both positive (Kripke et al., 1983ab, 1992;

Yamada et al., 1995) and negative findings (Stinson & Thompson, 1990; Mackert et al., 1991), as well as the results indicating that the clinical response in non-seasonally depressed patients is modest compared to that in patients with winter depression (i.e. Yerevanian et al., 1986; Deltito et al., 1991; Thalen et al., 1995).

Meta-analyses of the reported trials mostly supported the usefulness of bright light as an antidepressant for non-seasonal depression (i.e., Tuunainen et al., 2004, Golden et al., 2005). However, the inconclusiveness of findings might be exemplified by several most recent publications. In the study of Prasko et al. (2002), the bright light with imipramine-like placebo was found to be insignificantly better than either bright light with imipramine or dim red light with imipramine. In a placebo-controlled crossover study, Sumaya et al. (2001) demonstrated that bright light treatment decreases depression in institutionalized old adults. However, one of the methodologically most rigorous trials comparing bright light with dim light (Loving et al., 2005ab) in non-seasonal old depressives did not find that bright white light is a statistically superior to red dim light. Prior to the light administration, some of these depressives were successfully deprived from late night sleep, but showed only little improvement of mood (Loving et al., 2005a). Furthermore, in a study purposed on comparing bright light with dim light in responders to sleep deprivation (Fritzsche et al., 2001), a significant advantage of bright white light over dim red light was not observed in patients with major depression.

1.4. Physical exercise

It seems that wakefulness itself rather than changes in physical activity and posture is involved in the mechanism of antidepressant action of sleep deprivation (Baumgartner & Sucher, 1990). At the same time, physical activity is also able to treat depression (i.e., reviewed by Lawlor, Hopker, 2001; Stathopoulou et al., 2006; Martinsen, 2008; Mead et al., 2009)

The first attempts to apply physical exercise treatment for winter depression were based on the suggestion that it must work due to circadian phase advance. In the pioneer study of Koehler et al. (1993), 50% improvement of mood was reported following 2 weeks of training on a stationary bicycle between 6:00 and 8:00. In another investigation (Kurz et al., 1995), similar 50% improvement was reported in depressed seasonals following 12-day aerobic treatment from 07:00 to 8:00. In contrast, no mood effect was found in those depressed subjects who just listening music and reading magazines during the same hours, and even negative mood effect was found in healthy subjects treated with aerobic. However, no evidence was so far provided for phase shifting nature of antidepressant action of physical exercise in winter depression.

Partonen et al. (1998) reported the results of comparison of the effects of physical exercise under bright and ordinary light on mood of healthy indoor employees. This and later reports (Partonen et al., 1998; Leppämäki et al., 2002, 2004) indicates that physical exercise combined with exposure to bright light was significantly more effective in improving mood than exercise under ordinary room light or relaxation training.

1.5. Walking and sleep phase advance

Two more natural treatments for depression include the exposure to natural light and advance of sleep phase.

In a study of Wirz-Justice et al. (1996), a “natural light” obtained by a one-hour morning walk was compared with artificial bright light for 30 min per day. It was found that more patients remitted after the walk than after the artificial light (Wirz-Justice et al., 1996).

Such chronotherapeutic intervention as advance of sleep schedule was suggested by Riemann et al (1999) for prevention of the relapse after sleep deprivation. The results of their study of depressed patients indicated that an advance of sleep time is a more effective stabilizer of the antidepressant effect of sleep deprivation than a delay of sleep (Riemann et al., 1999, 2002).

It was also demonstrated (Wu et al., 2009) that adding such interventions as sleep deprivation, morning bright light and phase advance as adjunctive treatment to lithium and antidepressants can accelerate and sustain antidepressant response.

A phase advance of the circadian system might be induced by either morning light or late afternoon/early evening melatonin administration (Lewy et al, 1998b). The phase shift hypothesis of winter depression predicts that an antidepressant effect might be achieved by afternoon or evening treatment with melatonin (Lewy et al, 1987, 2006). If afternoon melatonin is capable to improve winter depression due to pharmacologically induced advance shift of circadian phase, this treatment may be used to prevent further relapse after sleep deprivation as

more tolerated procedure compared to the phase advancing by means of alteration of patient's sleep-wake schedule (Putilov et al., 2000, 2004).

2. Comparison of antidepressant responses to natural treatments

2.1. Antidepressant responses

The objective of our open trials of natural antidepressants for seasonal and non-seasonal depression was to evaluate the clinical usefulness of non-drug treatments and to detect the relationship between clinical and physiological responses. In this section, I review major clinical results of the studies completed between 1988 and 2000 and reported in a number of separate publications (Putilov et al., 1991, 1996abc, 1999, 2000, 2004, 2005ab; Danilenko et al., 1991, 1994; Danilenko, Putilov, 1993, 1995, 1996, 2005; Palchikov et al., 1997; Pinchasov et al., 1998, 2000, 2002; Poljakova et al., 1998; Putilov, 1998, 1999, 2001, 2009; Pinchasov, Putilov, 1999; Putilov, Danilenko, 1999, 2005ab).

A total sample included 268 female subjects with winter depression, non-seasonal depression and without depression (n=118, 64 and 86, respectively). Thirty six of these subjects were left without antidepressant therapy for a week (n=10, 11, and 15, respectively). The one-week monotreatments for 151 participants were either 1-hr physical exercise from 13:00 (n=9, 9, 9) or 2-hr 2.500 lux cool-white incandescent light. Light administration was started either at 8:00 (n=29, 0, 16) or at 14:00 (n=9, 9, 9) or at 16:00 (n=24, 0, 14) or at 18:00 (n=8, 0, 6). The combined treatments for 81 subjects included a night of total sleep deprivation followed by 6-7-day treatment with either 2-hr bright light from 14:00 (n=8, 12, 0) or with 1-hr physical exercise under ordinary room light from 13:00 (n=0, 12, 0) or with 1-hr physical exercise under bright light from 12:00 (n=5, 11, 0) or with 0.5 mg melatonin at 16:00 (n=8, 0, 8) or with 0.5 mg placebo at 16:00 (n=8, 0, 9). Most participants were studied at the hospital of the Siberian Branch of Russian Academy of Medical Sciences, Novosibirsk, Russia. Only two evening-treated groups spent their treatment week at home.

Additionally, the subsets of light-treated winter depressives were restudied before and after night flight and one-week vocation in Firuza resort (south of Turkmeniya, 38 degree North) (n=19, 0, 0), in summer (n=42, 0, 18) or during the following winter, before and after a week of home based administration of dim red light (<50 lux from head mounted unit, "Light Cap", Health Light Inc., Canada) for 30-min in the morning hours (n=9, 0, 0).

The 21-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967) was mostly administered twice, with one-week interval. In the case of the combined therapy, the scale was administered three times: before and after total sleep deprivation and after consecutive 6-7-day treatment with either light or exercise or melatonin or placebo. The scores are presented in Figure 1. The same as in Neumeister et al. (1996) criterion was applied for determination of mood response to sleep deprivation: 40% reduction of 16-item HDRS (with omitting 5 items concerning sleep, weight loss and diurnal variation, ## 4, 5, 6, 16 and 18).

Two-tailed paired Student's t-test was employed to detect the differences between pre- and post-treatment conditions, and unpaired Student's t-test was used to compare two diagnostic groups (i.e., seasonal vs. non-seasonals) or two different treatments on the reduction of depression score (i.e., bright light vs. physical exercise).

Neither clinically nor statistically significant mood improvement was detected in untreated groups (Figure 1).

Total night sleep deprivation did not improve mood in non-depressed subjects, whereas the improvements were significant in seasonally and non-seasonally depressed subjects ($t=5.5$ and 9.9, $p<0.001$). There was no difference in reductions of the HDRS score between these two diagnostic groups (37% and 44%, respectively; between subjects comparison gave $t=-1.0$, $p=0.330$). It was noted that, among non-seasonal depressives, the responders to sleep deprivation had significantly lower baseline HDRS score than non-responders (20.0 vs. 25.4, $t=-3.521$, n= 22/13, $p=0.001$). By contrast, the baseline scores were similar in responders and non-responders with winter depression (21.4 vs. 22.3, $t=-0.447$, n= 14/15, $p=0.658$).

Any type of one-week treatment produced significant reduction of depression score in both depressed and non-depressed subjects (Figure 1). Winter depression responded better than non-seasonal depression to monotreatment with bright light (65% vs. 30%, $t=4.8$, $p<0.001$). Moreover, the tendency for better response to physical exercise was noted (68% vs. 57%, $t=2.0$, $p=0.063$). However, the responses were similar for combination of sleep deprivation with physical exercise under bright light (60% vs. 65%, $t=-1.0$, $p=0.351$).

In non-seasonal depression, the physical exercise alone or in combination with sleep deprivation was a significantly better treatment compared to bright light monotreatment ($p<0.001$ for both). Besides, the

combination of sleep deprivation with exercise was better treatment than its combination with bright light (71% vs. 44%, t=2.7, p=0.013).

In winter depression, bright light was an effective treatment irrespective of the time of the day (from 65% to 70%). Besides, all combined treatments for winter depression, including placebo, prevented relapse after sleep deprivation. However, further marked reductions of the HDRS score were observed after bright light exposure and exercise, while they were less notable after blind administration of either melatonin or placebo (i.e., the final HDRS reductions were 66%, 60%, 34% and 54%, respectively).

Despite similarity of the antidepressant effects of melatonin and placebo, the patients' reports suggest that they experienced the expected chronobiological action of these substances. For instance, only the patients treated with melatonin complained on early morning awakening. Compared to the patients from the placebo-treated group, they showed 4-fold higher frequency of complains on the acute soporific effect of this treatment.

Compared to the response of inpatients with winter depression to 2-hr bright light, their next winter response to home based administration of 30-min dim red light was significantly worse (36% vs. 68%, paired t=-3.3, p=0.01).

Regarding the within group variability of the antidepressant response, non-seasonal depressives showed higher variation in HDRS response. Considerable difference was shown for the combined treatment with light: the variation was significantly higher in non-seasonal depression compared to winter depression (SD=35.7% vs. 7.3%, F=25.1, n=12/8, p<0.001).

The improvement observed in winter depressives after one week in Turkmeniya (Figure 1) was non-significantly better than the effect of one-week treatment with bright light (81% vs. 70%, paired t=1.7, p=0.124).

The drop of psychiatric score between winter pre-treatment condition and summertime reexamination was closed to the drop caused by one week of bright light treatment (77% vs. 72%, paired t=0.7, p=0.488, respectively).

In sum, the results suggest that a total night sleep deprivation failed to improve mood in non-depressed subjects, whereas the significant improvements of similar magnitudes were observed in seasonally and non-seasonally depressed subjects. Any type of one-week treatment produced a notable reduction of depression scores in both depressed and non-depressed subjects. The results also indicate that the midday treatments seemed to be as beneficial as are the treatments in other times of day. It was found that winter depression responded better than non-seasonal depression to the treatments with physical exercise, bright light and combination of sleep deprivation with bright light. Besides, it was documented that all used treatments, including placebo, prevent relapse after sleep deprivation in winter depressives. However, further significant reduction of depressive scores was obtained after bright lighting and after physical exercising rather than after blind administration of either melatonin or placebo. When the excellent response to monotreatment or to combination of sleep deprivation with one-week treatment was observed, there was no further improvement from the combining all three treatments (sleep deprivation, physical exercise and bright light).

In general, the results of the investigational non-drug trials suggest that non-seasonal depression demonstrates excellent response to the combination of sleep deprivation with physical exercise, and that winter depression can be equally well-treated with physical exercise and bright light. Somewhat better improvement was seen only when one-week vocation was spent in the south region, but this difference failed to reach a statistically significant level (see Putilov et al., 2005, and Putilov, Danilenko, 2005ab, for the detailed discussion of these results in the light of the findings reported by other groups).

2.2. Time course of sleepiness and mood

Time course of sleepiness and mood during 36-hour sleep deprivation was examined in the melatonin trials (Putilov et al., 2000; Danilenko KV, Putilov, 2005; Putilov, Danilenko, 2005b). Sleepiness and mood were assessed on Karolinska Sleepiness Scale (Åkerstedt, Gillberg, 1990) and 10-cm visual analog scale, respectively, with 3-hr interval in 16 female patients with winter depression and 17 age-matched female controls. Data of this study were also compared with data on 33 age-matched female controls subjected to a shorter interval of experimental sleep deprivation (Putilov et al., 2009ab).

The time courses in 8 responders and in 8 non-responders to sleep deprivation, as well as the time courses in these 16 patients and 17 healthy controls were compared using repeated measure ANOVAs. The significance of main effect pointed on the difference in the mean level between the groups, and group by time of day interaction indicated the difference in time course.

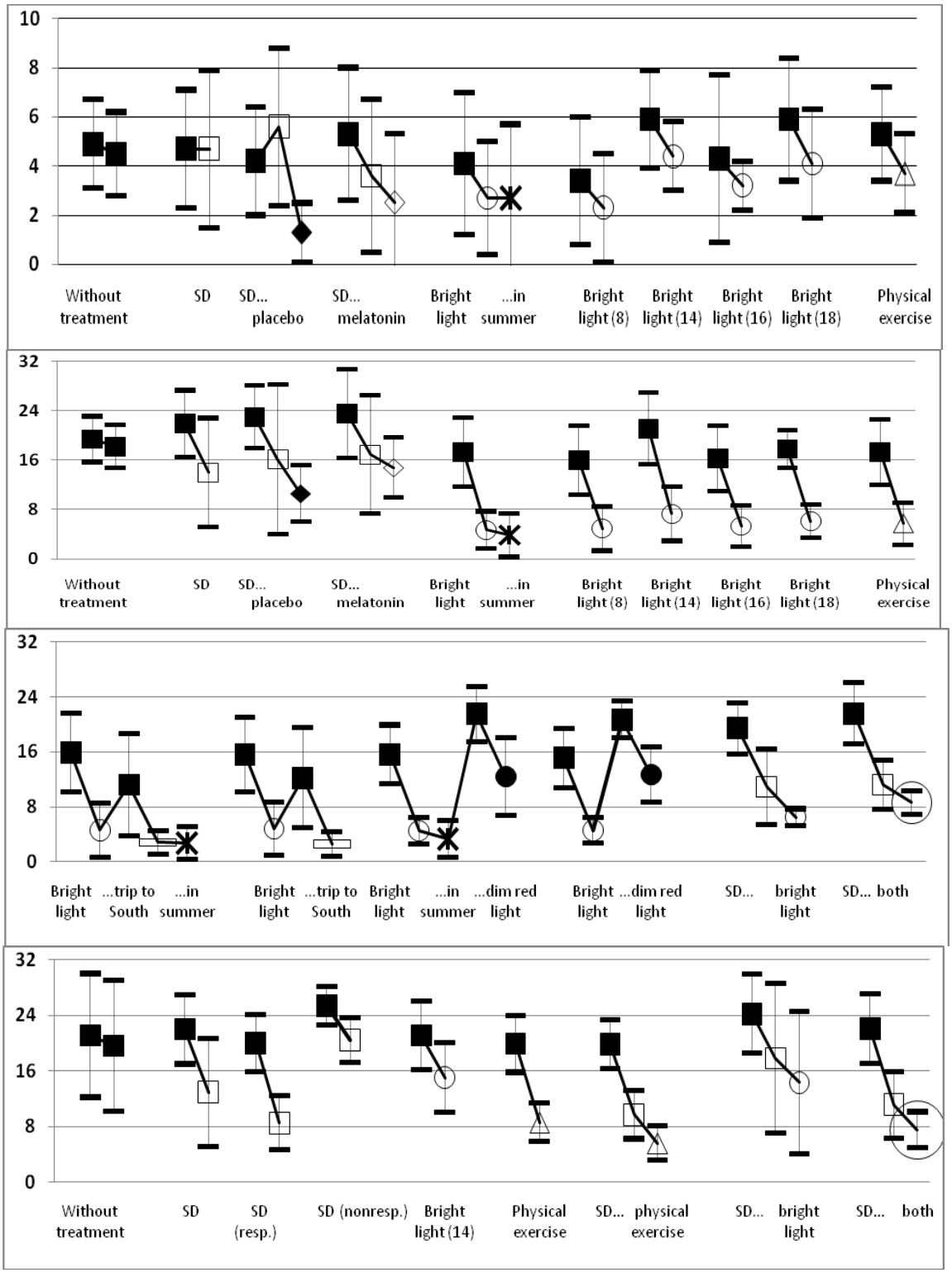

Fig. 1. Hamilton Depression Rating Scale scores in female subjects with winter depression, non-seasonal depression, and without depression.

Top: subjects without depression, middle: subjects with winter depression, bottom: subjects with non-seasonal depression. Treatments: Without treatment: before and after a week without treatment, SD: before and after one night of sleep deprivation, SD… placebo: before and after one night of sleep deprivation, and then after 6-day treatment with 0.5 mg placebo at 16:00, SD… melatonin: before and after one night of sleep deprivation, and then after 6-day treatment with 0.5 mg

melatonin at 16:00, Bright light… in summer: before and after one week of 2-hr bright light (2500 lux) either in the morning or in the late afternoon, and during reexamination in summer, Bright light (8): before and after one week of 2-hr bright light in the morning, Bright light (14): before and after one week of 2-hr bright light in the early afternoon, Bright light (16): before and after one week of 2-hr bright light in the early afternoon, Bright light (18): before and after one week of home treatment with 2-hr bright light in the evening, Physical exercise: before and after one week of 1-hr physical exercise. SD… bright light: before and after one night of sleep deprivation and after subsequent week of 2-hr bright light, SD… physical exercise: before and after one night of sleep deprivation and after subsequent week of 1-hr physical exercise, SD… both: before and after one night of sleep deprivation and after subsequent week of 1-hr physical exercise under bright light, Bright light… dim red light: before and after one week of 2-hr bright light in one winter and before and after 30-min dim red light (<50 lux from head mounted unit, "Light Cap", Health Light Inc., Canada) in the next winter, Bright light… in summer… dim red light: subset of subjects restudied between treatments in summer, Bright light… trip to South: before and after one week of 2-hr bright light and then before and after one week vocation in south region, Bright light… in summer… trip to South: subset of subjects restudied in summer, SD (resp.): subgroup of responders to sleep deprivation, SD (nonresp.): subgroup of non-responders to sleep deprivation. Filled squares: Before treatment in winter. All other: after treatment or follow up, including open squares: after one night of sleep deprivation, rhombs: after subsequent treatment with either placebo (filled) or melatonin (open), triangles: after physical exercise as monotreatment or as subsequent treatment (after sleep deprivation), circles: after light, either dim red (filled) or bright (open) as monotreatment or as subsequent treatment (after sleep deprivation), large circles: after subsequent treatment with physical exercise under bright light, asterisks: follow up in summer, open rectangle: after return from one week vocation in south region.

Figure 2 illustrates the time courses of sleepiness and mood throughout sleep deprivation of healthy female subjects and female subjects with winter depression. Patients significantly differed from healthy controls on the level and time course of sleepiness ($F=9.9$, $df=1/31$, $p=0.004$, and $F=2.5$, $df=10/310$, $p=0.007$, respectively). However, responders to sleep deprivation did not differ from non-responders ($F=0.0$, $df=1/14$, $p=0.968$, and $F=1.2$, $df=10/140$, $p=0.329$, respectively). By contrast, patients did not differ significantly from healthy controls on time course of mood ($F=1.3$, $df=10/310$, $p=0.219$), but, as expected, they self-reported lower mean level of mood ($F=8.2$, $df=1/31$, $p=0.007$). There was no difference in mean level of mood between responders and non-responders ($F=0.2$, $df=1/14$, $p=0.699$), whereas these two groups significantly differed on the time course of mood ($F=4.7$, $df=10/140$, $p<0.001$). Thus, there is nothing special in the level and time course of sleepiness in responders, and the only notable difference between them and other groups was in time course of mood. When compared with the course of mood in non-responders, it showed a gradual increase throughout the second part of the experimental period.

Data from another sleep deprivation experiment indicate even more pronounced differences between healthy controls and depressives in sleepiness and mood (Figure 2), but, again, it seems that neither mean level nor time course of sleepiness account for the differences in time course of mood in responders and non-responders.

Generally, the observed dynamics of sleepiness and mood suggest 1) the lowered levels of alertness and mood in patients compared to controls, 2) the increase in sleepiness during and after sleep deprivation in both patients and controls, and 3) the increase in mood level in responders when compared to non-responders which is notable in the second part of night and which is still persistent in the afternoon. These results are consistent with the findings of the previously reported studies (i.e., Szuba et al., 1991; Wu et al., 1992; Beutler et al., 2003).

3. Unresolved issues of antidepressant responses to natural treatments

3.1. Association between physiological and antidepressant responses

The special role of the factors of physical and biological nature in such conditions as winter depression remains to be unclear. In biomedical research of winter depression, these factors cannot be easily separated from the psychosocial factors. For instance, brain neurotransmitter regulation might be directly altered by both annual physical cycles and negative social input associated with unpleasant feelings, such as sadness, loneliness, luck of interest, withdrawal from participation in normal activity and the like (Putilov et al., 2005b).

Depression is often accompanied by typical or atypical neuro-vegetative symptoms which, however, do not necessary reflect the actual deviations of the physiological state from the normal range. The real physiological disturbance might be surprisingly small, if any (Putilov et al., 1999; Putilov, 2004c, 2005b). The comparison of self-reported symptoms with objective measurements indicates that patients with winter depression exhibit the

tendency to overestimate their summer-winter neuro-vegetative variations in retrospective reports and clinical interviews. This discrepancy was revealed by comparison of the retrospectively reported and objectively measured amplitudes of seasonal variations in such variables as sleep length and body weight (i.e., Putilov, 2004c, 2005b; Putilov et al., 1999).

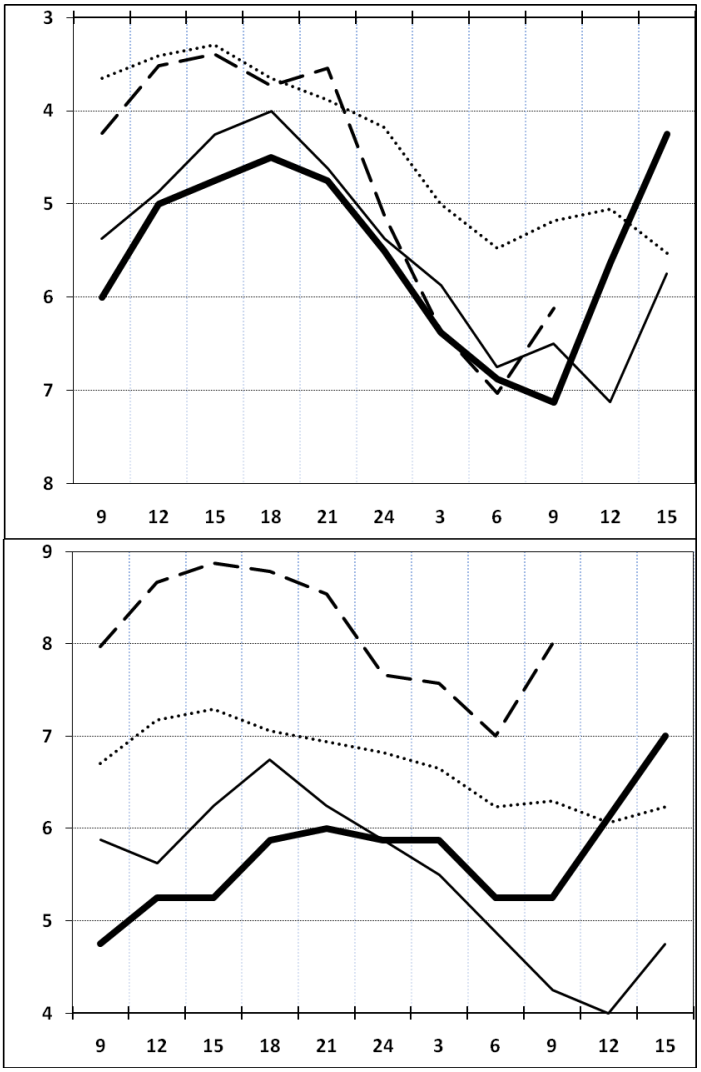

Fig. 2. Time course of sleepiness and mood in sleep deprived winter depressives and healthy controls.
Top: time course of sleepiness self-assessed on 9-step Karolinska sleepiness scale, bottom: time course of mood self-assessed on 10-centimeter visual analog scale. Solid line: 8 responders to sleep deprivation, thin line: 8 non-responders to sleep deprivation, dotted line: 17 age-matched healthy controls (data from the study by Putilov, Danilenko, 2005b), dashed line: 33 age-matched healthy controls (data from another deprivation study of shorter duration: Putilov et al., 2009ab).

For example, when retrospective reports suggest 1-to-3-hr difference between sleep duration in summer and winter, the average winter-summer difference in EEG sleep duration did not exceed several minutes (although it often was statistically significant; Putilov et al., 1996a; Palchikov et al., 1997; Putilov, 2004c, 2005b). This observation supports the earlier published report on systematically recorded sleep timing which also indicates that the deviation of sleep in winter depressives from the normal range is far from being as dramatic as retrospectively reported estimates (Shapiro et al., 1994).

Our investigational antidepressant trails were mostly aimed on a search for the associations between clinical and physiological responses to the treatments (Putilov, 1998; Pinchasov et al., 2000). In general, the results suggest that, from one hand, all physiological indexes in depressed patients tended to shift toward those observed

in controls. From the other hand, most of physiological systems responded to the treatment independently one from another. Moreover, no solid evidence was found for a strong dependence of an antidepressant response from such four particular physiological responses as advance of circadian phase, increase in energy expenditure, activation of sympatho-adrenal system, and intensification of non-rapid eye movement sleep (Putilov, 1998). Although highly significant correlation was noted between the number of these physiological responses and the number of clinical responses to the treatment, the results of this correlational analysis do not prove the causal relationship between the physiological and clinical responses (Putilov, 1998). The latter can depend upon the former, but the opposite causal relationship also cannot be excluded (Putilov, 1998, 2009; Putilov et al., 2005ab). Besides, the relationship between physiological and clinical responses can be more complex. For instance, patients can more likely to believe that they are getting the treatment that really helps when they experience physiological changes as the side effects of their treatment with natural antidepressants.

3.2. Association between immunological and antidepressant responses

Unlike different physiological responses that always positively correlated with clinical responses, the opposite pattern of correlation was found for an index representing the immune response to the treatment (Putilov, 2000).

Namely, the lymphocytes were enumerated before and after one-week trial of non-drug therapy in 115 participants of our studies. A decreased total number of lymphocytes, or lymphopenia, was detected in several groups of seasonally depressed patients before but not after a certain treatment. However, in contrast to our expectations, a reduction of depressive symptoms and an augmentation of the total lymphocytes number were found to be negatively correlated in each of these groups (Pinchasov, Putilov, 1999; Putilov, 1999, 2000).

It seems that this paradoxical result can be better understood in the light of the hypotheses suggesting the evolutionary roots for a specific link between the immune system and depression symptoms. They were mentioned in the last section of this review, but the first thing that has to be done in future studies is to confirm the negative association between the immune and clinical responses. The problem is that, although similar findings were independently obtained by several other groups (i.e., Leu et al., 2001), most of them were not then fully reported since were regarded as negative results.

3.3. The issues of non-specific effects

Sometimes, depressives receiving a placebo improved nearly as much as those receiving the antidepressant drugs. In the majority of these cases, the drugs fail to show superiority over placebo simply because they are not very powerful compared to the improvement in placebo group (Andrews, 2001; Gelenberg et al., 2008). At least, meta-analyses of modern literature on antidepressant medications shows that, in the vast majority of investigational trials, the depressed patients assigned to one- to four-week placebo treatment exhibit substantial symptom reduction (i.e., Joffe et al., 1996; Khan et al., 2000; Walsh et al., 2002). Moreover, meta-analyses indicate that the improvement in drug-treated group is strongly predicted by the improvement in placebo group. For moderate and mild forms of depression, the difference between drug and placebo groups is so small in magnitude (i.e., less than 2 points on HDRS) that, being statistically significant, it might not be regarded as clinically important. The small difference between drug and placebo group might be not only explained by pharmacological action of the drugs on patients' mood, but also by the side effects of the drugs which encourage patients to believe that they are receiving a beneficial treatment (i.e., Moncrieff et al., 1998, 2004; Kirsch et al., 2008).

Therefore, the important question of one-week natural trials is to which extent the antidepressant action can be attributed to non-specific effects. Such effects can include placebo and psychotherapeutic responses, the positive interactions with the research stuff, pre-treatment expectations of benefits from innovative treatment, spontaneous remission, natural fluctuations in severity (they suggest that mood is likely to be improved when next assessed), and so on.

Although psychotherapeutic mechanisms can contribute to the antidepressant effect of sleep deprivation, they do not provide a complete explanation for the observed improvement of mood (Wu & Bunney, 1990; Wirz-Justice, Van den Hoofdakker, 1999). Moreover, the early studies ruled out the possibility to explain the antidepressant effect of sleep deprivation by the influence of such psychological factors as patients' positive expectations and attitudes, because favorite clinical responses were also documented when patients were told that this intervention served an aim of either diagnostic (Pflug, Tölle, 1971) or biological rhythm assessment (Gerner et al., 1979).

By contrast, the studies of such natural treatments as bright light and physical exercise highlighted the numerous issues related to placebo effects, patients' expectations, patient-psychiatrist interactions, spontaneous remission, and so on. Below I review these issues by mostly using the light treatment studies for their illustration.

It is well-known that placebo response is dose-dependent (i.e., see examples provided in Eastman, 1990). Therefore, the placebo effect is hardly controlled in comparisons of presumably less and more effective non-drug antidepressants. Indeed, patients cannot be "blind" to the majority of such treatments due to their visibility. It is plausible to suggest that bright light or physical exercise can provide a better antidepressant response compared to active or placebo pills, because it is easy for patients to recognize that, in accordance to their beliefs, this is a real antidepressant. The patients also easy recognize what is a weaker antidepressant, if it is supposed to be lower intensity or shorter duration or inappropriate timing. For instance, patients distinguish the difference between dim and bright light emitting boxes or between negative ion generator and light emitting box.

In depression, seeking help and expecting the receiving a beneficial treatment is likely to instill hope of improvement. Many results of comparison of the effects of light with other treatments point on the importance of pre-treatment expectations as powerful modulators of antidepressant response to the non-drug treatments. Most patients predicted that bright light will help. When their expectations of treatment efficacy were assessed at baseline, they often where higher for bright light than for placebo treatment (i.e., Rosenthal et al., 1984; Eastman et al., 1998), and for the morning light than for evening light (i.e. Sack et al., 1990). As a rule, the treatment responses were also similar when expectations for bright light and placebo were similar (i.e., Loving et al., 2005a).

In the trials with light emitted by lamps (Terman et al., 1989), it is rather easy for a patient to make conscious or unconscious prediction on which of the treatments would be most effective. By contrast, in the studies of the antidepressant effects of visor, the prediction seems not to be so simple, because one might expect that both bright and dim light (or green or red) are similarly effective due to closeness of light source to the eyes. This uncertainty appears to complicate the distinguishing between different lights in "placebo-counting" manner. The evaluations of initial expectancy scores in the visor studies indicated that, indeed, patients had the same expectations for therapeutic effects of proposed active and placebo treatments (i.e. Teicher et al., 1995). Again, the clinical outcome in the studies with head-mounted devices was in the agreement with the pattern of patients' expectations: no relationship to intensity, color or duration was found (Teicher et al., 1995).

Nobody has been tested the researchers' expectations that may also modulate the antidepressant response in patients. It is very natural for the researchers and physicians to stimulate a placebo response in the patients when their own believes in the treatment efficacy coincide with patients' hopes. One of contrast examples are the results of Eastman and our groups which were different on the attention paid to the placebo outcome.

Eastman was most concerned by the placebo action of bright light (Eastman, 1990). In the investigations of her group the extremely careful attention was devoted to controlling placebo effects in assessing treatment benefits of morning and evening lights. Several years of regular trials passed before this group finally found the significant but very small benefit of morning bright light (Eastman et al., 1993, 1998). Compared to this benefit, much bigger and faster improvements were reported by the majority of earlier investigators who, as can be guessed, were less skeptical.

Unlike the Eastman group, most of our studies (Danilenko, Putilov, 1993; Putilov et al., 1996ab; Putilov, 1998, 1999; Pinchasov, Putilov, 1999; Pinchasov et al., 2000, 2002) did not focus on the differences between clinical effects of active and placebo treatments. Instead, the main question was whether the objective physiological measures correlate with treatment response (i.e. Putilov, 1998). Consequently, the antidepressant responses in these trials were found to be among the highest.

Many earlier reports on the efficacy of light therapy were not based on the rigorous study designs. Not surprisingly, the highest and most rapid improvement of mood was reported in short open trials when patients were not cross over for another treatment (i.e. Wirz-Justuice et al., 1993; Meesters, 1995; Meesters et al., 1995, Putilov, 1998; Putilov et al., 2005a). These antidepressants responses seem to be bigger not due to the effectiveness associated with specific effects of the treatment, but rather because such treatment is not concerning the patient's mind by the necessity of guessing which is an active treatment and which is a placebo treatment. This conclusion is complemented by the reports on close correlation between positive pre-treatment expectations and beneficial antidepressant action of bright light for winter depression.

Such factors as spontaneous remission and natural variation in severity cannot account for the considerable amount of the improvement in the case of long antidepressant trials. For instance, Kendler et al. (1997) reported a median time of recovery of 6 weeks in a population sample of women. Hence, it is unlikely that spontaneous

remission and natural variation in severity can significantly contribute to the antidepressant response observed in the short open trials applying a parallel design. Nevertheless, these responses were found to be stronger compared to the responses in longer trials, especially when the longer trials applied crossover or placebo-controlled designs.

The light treatment literature indicates that, when the applied methodology was most rigorous, the antidepressant effect was found to be either very modest (i.e., Eastman et al., 1989) or indistinguishable from the effect of placebo treatment (i.e., Loving et al., 2005a). Therefore, if one takes into account only most rigorously conducted placebo-controlled trails, the clinical data do not support the assumption that bright light is more effective antidepressant than other antidepressants or placebo for the treatment of seasonal and non-seasonal depression (see also the first section).

An order effect suggesting the superiority of a supposedly more effective treatment as the first treatment was noted in the cross-over studies comparing light of different color, intensity, and timing (reviewed by Terman et al., 1989; Rafferty et al., 1990). Possibly, the placebo effect of any first treatment mimics the differences between more and less optimal treatment. As for the following (second) treatment, its effect might be modulated by the previous treatment effect. For instance, the success of the first treatment which is supposed to be more effective might encourage a patient to develop an expectation that this first effect must differ from the effect of the following, supposedly less effective, treatment. Consequently, the second treatment is evaluated more critically in order to support this expectation.

Due to influence of psychological factors on the clinical benefits of the innovative antidepressant trials, one has to be cautious with the interpretation of their results. There are no doubts that the placebo patients in such trials were not really left untreated. The placebo substance was pharmacologically inert, but it had symbolic value for those depressed subjects who hoped to improve. Additionally, the patients received information on their symptoms and possibility to verbalize their problems. They also obtained psychological support from physicians, research assistants and other participated subjects, and, at least, some of them might be very sensitive to the encouragement that comes from being studied and treated. Therefore, the mood improvement may be largely attributed to the psychotherapeutic action of the treatment.

Notably, Geerts et al. (1995, 1996) reported that non-verbal behavior and communication between physician and patient during pre-treatment interview has a predictable value for future therapeutic benefits of bright light therapy. In another study (Boenink et al., 1997), a high-pitched voice with small variation in this pitch was found to be a predictor of light treatment benefits. It was suggested that bright light treatment gives extra comfort in "tense" patients, who become rapid responders to this treatment. Thus, psychosocial component of natural (physical in nature) treatments for depression seems to play an import role in clinical response and, therefore, it requires further elaboration.

The results reported by Koorengeval et al. (2001) can serve an illustration of the role of non-specific effects in the clinical response. In a double blind placebo controlled trail, a progressive improvement of clinical state over time was observed after treatment with extra-ocular light administered in the bend of both knees, and no significant difference was found between two indistinguishable for a patient treatments, either placebo (no light) or extra-ocular light by fiber-optic illumination (Koorengeval et al., 2001).

A difference in expectations for the effects of these treatments might be suggested for patients with and without seasonal pattern. Indeed, the comparison of the effects of bright light with the effects of physical exercise or sleep deprivation supports this suggestion. It was found that sleep deprivation was equally effective for seasonal and non-seasonal mood disorder (Putilov et al, 2004, 2005a). Furthermore, physical exercise was also found to be an effective treatment for both, while the response to light was weaker in non-seasonals (see previous section). The results also indicate that, in general, non-seasonally depressed patients tended to respond worse to any treatment compared to winter depressed patients (Putilov et al, 2004, 2005a).

The differences in the antidepressant response between the seasonally and non-seasonally affected patients may be attributed, at least in part, to the differences between these diagnostic groups in heterogeneity of clinical symptoms, rate of spontaneous remission, and vulnerability to have comorbid psychic and somatic illnesses. Another important reason would be the differences in psychological aspects of the responses to non-drug treatments in winter depression and non-seasonal depression (Putilov et al, 2005ab).

The facts indicating that patients with winter depression benefit more from non-drug therapy than those with non-seasonal mood disorder might be, in particularly, explained by the difference in the magnitude of placebo response. It is likely that the positive expectations for antidepressant action of bright light are much

stronger in seasonal depressives who, unlike non-seasonal depressives, associate their depression with winter season, and, therefore, light might have a symbolic value for these patients. Given that depression in general is highly related to patients' beliefs about treatment, the difference in antidepressant response might be attributed to the differences in the beliefs and to the differences in personalities of patients with seasonal and non-seasonal depression.

At least, the published reports of the double-blind pharmacological studies support such explanation, because they suggest very high responsiveness to drug placebo in seasonally depressed patients (i.e., Oren et al., 1994).

Possibly, winter depressives mostly belong to a psychologically distinct subgroup of depressives. Their comparison with patients without seasonality on the personality characteristics (Bagby et al., 1996) revealed a significant difference on one of five dimensions of the five-factor model of personality. Namely, winter depressed patients scored higher than non-seasonally depressed patients on the openness dimension. They seem to be more imaginative, more emotionally sensitive and they more likely to entertain unconventional ideas (Bagby et al., 1996). Hence, it is reasonable to suggest that this personality trait may account for higher responsiveness of the individuals with winter depression to innovative non-grug treatments. Such a treatment provides a novel and interactive experience that might increase the positive pre-treatment expectations and stimulate a strong placebo effect.

Sometimes, the contribution of psychological factors in seasonality of depression might be unconsciously hidden by a patient. In particular, it was found (Beratis et al., 1996) that the depressive episodes can be anniversary reactions associated with intense traumatic experiences in childhood, adolescence or adulthood. The time and the place of the traumatic event can act as triggers eliciting the clinical symptoms. Therefore, anniversary reactions may constitute a subgroup of seasonal mood disorders, which are precipitated primarily by psychological factors rather than climatic conditions (Beratis et al., 1996).

Furthermore, patients might unconsciously replace the real but psychosocial cause of their depression by more neutral but less traumatic physical cause, such as winter darkness (Putilov et al., 2005b). For instance, a patient can readily associate low mood in winter with difficulty to wake up in the dark morning hours rather than with the numerous psychosocial problems, such as a lack of desire to come at time in the office due to negative feelings associated with this job (i.e., salary perceived as insufficient, interpersonal problems with a boss and colleagues, etc.).

It has to be emphasized, however, that most cases of seasonal depression cannot be explained by seasonality of psychologically traumatic events, because, unlike statistics for other mental disorders, hospital admission statistics for depression and mania shows significant seasonal patterns with the incidence of depression being highest in fall and winter (i.e., Suhail and Cochrane, 1998).

Many paradoxical facts were collected by the investigators of light treatment effects for which the contribution of psychological rather than biological factors in antidepressant action might be considered as the most plausible explanation. Several of them are listed below.

It was noted (i.e. Sher et al, 2001) that the extent of reduction of depressive symptoms after the first hour of treatment predicts the final therapeutic outcome. It is unlikely that such a short exposure to bright light may produce immediate effect on mood via alteration of the patients' physiology. More plausible explanation of the rapid antidepressant response to light is the impact of psychological factors (i.e., positive pre-treatment expectations in the therapeutic outcome).

The placebo explanation looks reasonable for a paradoxical fact reported by Richter et al., (1992). They compared the effects of real light treatment and imaginary light treatment. During the hypnotic session patients were made to imagine that they perceived bright light. No statistical differences in treatment outcomes were found. A significant difference was detected only at day 10 after the treatment: the effects of the imaginary light were gone, while the effects of real light treatment were still observed (Richter et al., 1992).

The conflicting data on the duration of relapse after successful light treatment is another paradoxical fact of light treatment studies. Some researchers stated that relapse occurs within 3 to 4 day after withdrawal (i.e. Rosenthal et al., 1985; Terman, Terman, 1992), while other groups observed remission that lasted longer (i.e. Yerevanian et al., 1986; Grota et al., 1989). Besides, solid data were provided on the increase in response percentages at 10th day after treatment compared to the 3rd day (Meesters, 1995). These discrepancies resemble the above-mentioned contradicting reports on treatment outcomes for bright light. They do not support the suggestions of a certain strong physiological background for the antidepressant response.

In sum, the antidepressant drugs are effective, but not necessarily due to their pharmacological action on low mood. As for natural treatments, the remission rate for them might be rather high compared to that reported in pharmacological studies. In the light of reviewed above observations, the most reasonable explanation for this fact is a high level of therapeutic hopes in the studies using the parallel design and visible antidepressants that, albeit the pills in the blind cross-over trials, do not include a placebo or include a less active treatment for a given patient. In general, there is no evidence that the rapid and considerable antidepressant action of one-week natural trials can be attributed to the specific rather than placebo effect.

3.4. Evolutionary psychological explanation of antidepressant responses

The specific feature of depression is that there is no other illness in which the placebo effect is so large, either in absolute terms or as a proportion of the change in the treatment group (Andrews, 2001). For instance, placebo groups make 60% of the progress recorded in the drug-treated groups, whereas it is only 23% in agoraphobia, 21% in obsessive-compulsive disorder, and no progress at all in schizophrenia (Andrews, 2001). Patients treated with drug antidepressants report feeling better, but it is questionable whether this is due to pharmacology of the drugs. Improvement of depressive symptoms is highly influenced by the patients' beliefs that they are receiving an effective treatment. The nature of depression seems to be very sensitive to encouragement that comes from being involved in treatment. Such specificity of the response to the treatment in depressive disorders requires explanation.

Evolutionary thinking can provide account of the origin and function of most important human traits. Several hypotheses conceptualizing depression and its response to antidepressant treatment as the evolved psychological features of human beings were proposed within the meta-theoretic framework of evolutionary psychology (see Nettle, 2004, for review). In general, all these explanations postulate the useful functions of apparently negative emotional states which work as the defense mechanisms (Thornhill, Thornhill, 1989; Suarez, Gallup,1991; Price et al., 1994; Gilbert, Allan, 1998; Hagen, 1999, 2002; Nettle, 2000, 2004; Nesse, 2000, 2006; Sloman et al., 2003; Watson, Andrews, 2002; Allen, Badcock, 2006; Gilbert, 2006; Andrews, Thompson, 2009).

Some of these explanations consider low mood as an adaptation to the threatening circumstances where life goals cannot be achieved, and they tend to interpret clinical depression as a kind of dysregulation of adaptive mechanism (i.e., Henderson, 1974; Gilbert, Allan, 1998; Nesse, 2000, 2006; Sloman et al., 2003). Other hypotheses claim that depression does not arise from any defects in the body, because it itself is an adaptation from an evolutionary viewpoint (i.e., Price et al., 1994; Hagen, 1999, 2002; Watson, Andrews, 2002; Andrews, Thomson, 2009). The later hypotheses usually postulate that it serves to signal the need for more fitness-enhancing investment from the depressive's kin and allies, and, at least, in the ancestral environment, it had really provoked the increase in such investment (discussed in Nettle, 2004).

There was also an attempt to provide an evolutionary account of the particular forms of depression. Such condition as postpartum depression was interpreted as an adaptation by which the mothers extort greater investment from their social network by making themselves unable to cope with child's care without such investment (Hagen, 1999). This explanation predicts that psychosocial risk factors, especially those related to the perceived social support, play the critical role in manifestation of depression. Indeed, the particular findings on postpartum depression fit well in this prediction (Hagen, 1999, 2002; Hagen, Barrett, 2007).

Notably, similar to the biological basis of winter depression, the biological basis of postpartum depression was accounted by several hypotheses and it was intensively examined by a large amount of empirical research.

For instance, many studies tested the suggestion that perinatal depression can be triggered by massive hormonal changes that accompany the peripartum period (i.e., Harris, 1994; O'Hara, 1995). The fluctuations in hormones observed during pregnancy and following childbirth would affect mood. However, there are still no definitive studies to prove this. Many research results are negative or contradictory for most of the hormonal variables, and evidence for a reproductive hormone abnormality in postpartum depression is scant (i.e., O'Hara et al., 1991; Harris et al., 1996; Hayes et al., 2000). Generally speaking, the idea of a causal relationship between hormonal variables and postpartum mood has not yet been empirically supported, and the empirical studies do not prove that the biological factors are the causes of postpartum depression.

As it was noted by Hagen (1999), fathers are not undergoing dramatic hormonal changes, but also suffer from postpartum depression. Indeed, a national survey of 2089 two-parent families showed the prevalence of postpartum depression is 14% for mothers and 10% for fathers (Paulson et al., 2006). The depression in these

families is more than twice more common than in general population (i.e., compare with results reported by Blazer et al., 1994).

Because biological causes of seasonal affective disorder were in the focus of experimental research for many years, the contribution of such psychosocial risk factor as poor social support has not been tested in earlier studies. The first reports have been published only in this century. They provided evidence for association of the perceived social support with seasonality of mood (Michalak et al, 2001, 2003) or with diagnosis of winter type of seasonal affective disorder (Putilov, 2003, 2004ab, 2005a; Pilkova et al., 2004ab). The association of mood seasonality with poor social support is unpredicted finding for biological theories of seasonal depression (Michalak et al, 2001, 2003), but it is in agreement with evolutionary psychological explanations of depression (Putilov, 2002, 2003, 2004ab, 2005a; Pilkova et al., 2004ab).

It seems that, similar to other depressions, winter depression can be seen as an adaptive emotional response to negative psychosocial factors (Putilov, 2002, 2003, 2004ab, 2005a; Putilov et al., 2005b). Some specific features of this form of depression would require a bit more complex explanation, because it might result from the combined action of negative psychosocial factors and seasonal variations in physical environment. However, the former factors seem be of the most importance than the latter factors. The effects of psychosocial and physical environments would meet at the level of biochemical mechanisms, because they would be either the same or related or interact in additive manner to produce similar brain reactions in response to these distinct external factors (Putilov, 2003, 2004ab, 2005a; Putilov et al., 2005b).

In more detail, depression causes psychic pain and distress. Similar to physical pain, it might have an evolved function to inform the organism that it faces danger in current situation. Feeling such emotional pain as sadness in the worse season of the year might help to conserve energy and to draw attention to a possible threat to fitness of such life circumstances as the combination of poor social support with unfavorable seasonal worsening in physical environment. An affected individual might unconscientiously perceive a threat to her/his chances to enhance fitness (i.e., to succeed rather than loose in terms of survival and reproduction), if, in despite of the changes in environment from bad to worse, the previous social and physical activities will be simply continued. Low mood and withdrawing from usual activities allow to conserve energy and, simultaneously, to signal to the closest social environment (i.e., family, friends and allies) about genuine need of help and assistance (i.e., in initiation of fitness-enhancing life changes).

Indeed, it is well-known (Schieffenhövel, 1995) that in different situations people living in different cultures all show very similar facial, gestural, postural, and physiological signs of pain and sadness. The behavior signals of bad feeling, such as physical and psychic pain, grief, despair, and sadness, are universal rather than cause- and culture-dependent. They remind those of infants and children. The response to these conspecific signals from the members of kin group is similar to a parental response, and it is usually aimed on termination of the painful stimulus or, if it is not possible, on consoling, comforting and giving help and support (Schieffenhövel, 1995).

Specifically, such emotions as sadness, grief and despair might be understood as the evolved non-verbal signals aimed on alarming social environment about subjective experience of considerable lose, failure to attain a significant goal, conflicts in interpersonal relationships, and other events associated with either real decrease or threat of decrease in inclusive fitness of a suffering individual. The mental state diagnosed as depression might be conceptualized as a response to insufficiency of feedback signals from a small community of kin and allies. In other words, the suffering person when exposing his/her emotional pain unconsciously expects to see the appropriate reaction from his/her close social surrounding (i.e. the members of extended family and other members of hunter-gatherer community in which we evolved). The development of full-blown depression might be a secondary response to lack of unconsciously recognized signs of support along with calming, consoling, expression of empathy, sympathy, protection, etc. (Putilov, 2003, 2004ab, 2005a; Putilov et al., 2005b).

When such depression developed in one of the members of a small ancestors' group of highly mutually dependent hunter-gatherers, it imposed significant burden not only on the sufferer, but also on her/his social partners (i.e., close relatives, friends, and co-workers). Fitness of the group members was also put at risk, because their fitness was positively correlated with fitness of the sufferer. The bargaining hypothesis of depression (Hagen, 2002, 2003) proposes that depression is sometime analogous to a labor strike. In ancestral communities, it imposed considerable costs on family, friends, and co-workers to force them to make changes that are in interest of the sufferer. This society was not like a modern company that can easy hire another employee instead of the depressed one. Rather, when the sufferer stopped to participate in the usual physical and social activities of the group, other group members cannot simply leave her/him and hire someone else.

Insufficiency of supporting response from the surrounding members of modern society forces the sufferer to search for support from a psychiatrist who symbolizes the last member of the extended family by providing a scientifically proved help in the form of antidepressant treatment.

It seems that the disruption of extended family in the industrial societies led to the considerable deficiency of psychosocial mechanisms that evolved to protect people from the development of full-blown depression. Now it is maladaptive to get depressed expecting that others in response will readily offer their support. As a result, different forms of depression increase in their rate in modern times compared to the traditional societies or to the same societies just several decades ago. The psychosocial components of different types of antidepressant therapy can, at least partly, counteract to this mood lowering deficiency. Such interpretation assumes that any kind of newly established treatment can elicit a favorable response that is, however, associated with placebo rather than specific effect (Putilov, 2003, 2005a).

Nevertheless, it is expected that medical scientists will further succeed in producing the effective treatments for depression, when they simply continue their efforts to create the new brand treatment options that they believe to work better than the earlier established antidepressant medications.

In the evolutionary psychological framework, seasonal forms of depression are not exceptional in the respect of their dependency upon psychosocial factors. Winter and summer forms of seasonal depression differ on their neuro-physiological features, but, as any other depression, they tend to be brought on by the problems associated with social rather than physical environment. In contrast to this view, seasonal depression has been mostly understood as a specific affective disorder that develops in response to periodical changes in physical environment. Therefore, the hypothetical influence of physical periodical factors on bodily functions has been considered to be the primary and most important cause of seasonality of mood. Following this paradigm, the researchers have not focused their studies upon non-periodic psychosocial risk factors as possible causes of seasonal depression. However, the accumulating knowledge about the involvement of psychosocial factors in winter depression indicates that any pure biological theory that stresses the disturbances in physiological and neurotransmitter systems is too limited for theoretical understanding of this condition and its successful treatment with conventional and unconventional antidepressants (Putilov, 2002, 2003, 2005a; Putilov et al., 2005b).

To resume, a better understanding of mood regulation in treated and untreated individuals can be achieved by considering depression as the evolved feature of human response to negative psychosocial factors modulated by the feedback response from the other members of small ancestral societies. Further research is required to include psychosocial aspects in the theoretical framework of seasonal depression and the therapeutic action of natural antidepressants.

3.5. Evolutionary explanation of some of depressive symptoms

Different evolutionary psychological explanations of depression suggest that either the extremely negative emotional states have certain adaptive functions or, at least, a low mood state is an adaptation whereas clinical depression is a kind of dysregulation of adaptive mechanism. However, some of other evolutionary explanations suggest that only certain depressive symptoms were actually advantageous to our ancestors, whereas there was nothing good in depression itself and it seems to be incredibly maladaptive for psychological interactions of our depressed ancestors with their social environment. For instance, some explanations suggest that, although depression is a devastating illness, it evolved to better resist infectious agents in our ancestors' societies (i.e., McNally et al., 2008; Kinney, Tanaka, 2009; Raison, Miller, 2013). Therefore, the authors of these hypotheses (i.e., Raison, Miller, 2013) proposed that some of depressive symptoms, such as social withdrawal, lack of energy, and a loss of interest in once enjoyable activities can be actually advantageous to our ancestors because they likely protected them against pathogens, and this, of course, was the most important advantage since, until the last century, these agents were the major causes of human death. Evolution can also favor depression because the immune system of depressed individuals operates under a "smoke-detector principle" (Raison, Miller, 2013). Although a smoke detector often react to false alarms, if it was removed, the consequences could be severe. Similarly, immune responses associated with depression can be typically not necessary, but an ancestor might die from only one infection and, hence, that particular depressive episode can become a critical defense against the only infection if it was able to initiate an immune response that finally allowed to better fight off it (Raison, Miller, 2013).

In the framework of such evolutionary thinking, seasonality of depression can be better understood as an adaptation to seasonality of infection diseases. Therefore, depression can be regarded as an adaptive response

when was developed during a season of the highest risks of getting and transmitting infections. It is reasonable to expect that the depressed individuals suffer from acute stress associated with higher than usual risks of infection disease, but their depressed state can both jump-start their immune system and manifestation of some particular symptoms can better protect them from getting and transmitting this disease. Indeed, such symptoms as lack of energy and a loss of interest in once enjoyable activities lead to energy conservation that is highly crucial, because immune activation against infections is relatively costly (Kinney, Tanaka, 2009). Moreover, such symptom as social withdrawal was recognized among the most typical symptoms of winter seasonal affective disorder (i.e., Rosenthal et al., 1984). In accord with our unpublished epidemiological results on seasonality of depressive symptoms in normal and clinical populations of the former Soviet Union (Putilov, 1999, unpublished doctoral thesis), this symptom was self-reported synchronously with the majority of neuro-vegitative depressive symptoms and approximately two weeks earlier than the symptom of bad mood that was usually reported with a four-week delay relative to photoperiod. The interpretation of depression symptoms as a defense against infections (i.e., Kinney, Tanaka, 2009; Raison, Miller, 2013) can help in understanding the negative correlations between immune and clinical responses to natural antidepressant treatments (i.e., Putilov, 2000), but, as it was already abovementioned, future experimental research and full reports of earlier collected observations are required for empirical support of the paradoxical relationship between seasonal depression and immune response to its treatment.

4. Conclusion

It seems that sleep deprivation is the only antidepressant which is proven to work efficaciously and rapidly, and which cannot be purely explained as being a placebo response. However, the clinical use of sleep deprivation for depression is limited due to the transient nature of its antidepressant effect. The relapse can be prevented by the combination of sleep deprivation with other antidepressants. In the open trial, one-week administration of such non-drug treatments as bright light or physical exercise was found to stabilize the antidepressant effect of sleep deprivation. Furthermore, each of these interventions produces further improvement of mood. However, if at least one of two treatment modalities ensures excellent response (i.e., in the case of winter depression), there is no additional benefit when they are combined. The mechanisms of action of the pharmacological and non-pharmacological treatments for depression are still unclear. Placebo effect seems to account for a large portion of the therapeutic response. Although the changes in patients' physiology correlate with the changes in patients' mood, the beneficial physiological responses are not necessarily involved in beneficial clinical response. They, however, can contribute to the patients' beliefs about the treatment.

Generally speaking, patients' psychology rather than their physiology might be the major mediator of the action of pharmacological and non-pharmacological antidepressants. It seems that etiology of seasonal and non-seasonal depression and the benefits of one-week natural treatments cannot be fully explained without accounting for the factors of psychosocial nature, such as expectations, motivation, cognitions, personality traits, patient-physician communication, perception of social support, etc. It is important to understand the nature of depression in order to understand which treatment may be most beneficial. Such understanding might be provided by the conceptualizing seasonal and non-seasonal depression in the evolutionary psychological framework.

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