Effect of controlled-release melatonin on sleep quality, mood, and quality of life in subjects with seasonal or weather-associated changes in mood and behaviour

Sami Leppämäki, Timo Partonen, Olli Vakkuri, Jouko Lönnqvist, Markku Partinen, Moshe Laudon

Abstract

This study aimed to explore the effects of melatonin on sleep, waking up and well being in subjects with varying degrees of seasonal or weather-associated changes in mood and behaviour. Fifty-eight healthy adults exhibiting subsyndromal seasonal affective disorder (s-SAD) and/or the negative or positive type of weather-associated syndrome (WAS) were randomised to either 2 mg of sustained-release melatonin or placebo tablets 1–2 h before a desired bedtime for 3 weeks. Outcome measures were changes from baseline in sleep quality, sleepiness after waking, atypical depressive symptoms and health-related quality of life by week three. Early morning salivary melatonin concentrations were measured at baseline and treatment cessation in all subjects. Melatonin administration significantly improved the quality of sleep ($P < 0.03$) and vitality ($P < 0.02$) in the subjects with s-SAD, but attenuated the improvement of atypical symptoms and physical parameters of quality of life compared to placebo in the subjects with WAS, positive type.

Keywords: Circadian; Melatonin; Mood; Quality of life; Sleep

1. Introduction

Melatonin, or $N$-acetyl-5-methoxytryptamine, is a hormone principally produced and released by the pineal gland. It may mediate sleep induction and regulation of circadian time-keeping by activation of melatonin mt1 and mt2 receptors of the circadian clock, and by enhancing $\gamma$-aminobutyric acid A (GABA$_A$) receptor function (Wan et al., 1999; for review see Brzezinski, 1997). The onset of melatonin secretion from the pineal gland is phase locked to the primary sleep gate or the increase in sleepiness that routinely occurs in the late evening hours and links to the start of a period with high levels of sleep propensity (Shochat et al., 1997).

Administration of 1–80 mg of melatonin orally has been documented using polysomnographic recordings to accelerate sleep initiation, increase sleep propensity, and improve sleep maintenance in trials on healthy people (Waldhauser et al., 1990; Dollins et al., 1994; Tzischinsky and Lavie, 1994; Attenburrow et al., 1996). Interestingly, no effect on sleep was found in one of the earliest trials with oral administration of 1 or 5 mg melatonin (James et al., 1987), but later studies have shown that even low doses of melatonin have hypnotic-like effects when administered in the early evening (Zhdanova et al., 1995; Stone et al., 2000).
Daytime melatonin administration has been shown to shorten the latency of sleep onset and promote sleep by heat dissipation, leading to lowering of core body temperature (Reid et al., 1996; Cagnacci et al., 1997; Hughes and Badia, 1997; Mishima et al., 1997). In addition, melatonin administration shifts the phase of circadian rhythms, which can be phase advanced when melatonin is given in the afternoon and phase delayed thereafter (Lewy et al., 1992; Zaidan et al., 1994; Yang et al., 2001). No effects on mood have been reported with orally administered doses of 0.1–240 mg of melatonin in healthy subjects (Lieberman et al., 1984; Dollins et al., 1994).

Treatment of insomnia with melatonin has resulted in conflicting findings. Oral doses of 0.5–5 mg of melatonin have not lengthened total sleep time as assessed with polysomnographic recordings, but improved the subjective quality of sleep and sleep promotion (James et al., 1990; Hughes et al., 1998). However, there is reasonable evidence of the efficacy of 1–2 mg of sustained-release melatonin on the initiation, maintenance and quality of sleep as monitored by wrist actigraphy among the elderly (Haimov et al., 1995; Garfinkel et al., 1995). Moreover, melatonin administration has been suggested as a useful hypnotic for depressed or medically ill patients with sleep disturbances (Dolberg et al., 1998; Dalton et al., 2000; Andrade et al., 2001). In patients with seasonal affective disorder (SAD; for review, see Partonen and Lönnqvist, 1998), melatonin treatment has achieved slight improvements in sleep (Wirz-Justice et al., 1990) and mood (Lewy et al., 1998).

Our aim was to study the effects of sustained-release melatonin on the quality of sleep, sleepiness after wake-up, mood and health-related quality of life. A secondary objective was to explore these effects in subjects with a varying degree of seasonal, weather-associated or circadian changes in mood and behaviour.

2. Experimental procedures

This double-blind trial was carried out in the capital area of Finland, a northern European country with approximately 5 million inhabitants, from February to March over 3 years (1997–1999). We set out to enrol employees and their families from a population of approximately 2000 working adults. A leaflet was delivered to employees in co-operation with occupational health care centres by the principal investigator, whom they were advised to contact for further information. The covering letter invited volunteers to take part in a trial focusing on the effects of melatonin on the duration and quality of sleep, and on melatonin secretion.

Target subjects were healthy adults with subsyndromal SAD and/or weather-associated syndrome (WAS, negative and positive types). The latter subjects routinely show negative or positive weather-associated changes in mood and behaviour. Subjects with subsyndromal SAD regard themselves as normal, have no severe medical condition or history of major affective disorder in winter, but do routinely experience some difficulties during the winter months (Kasper et al., 1989).

The exclusion criteria were known hypersensitivity to melatonin, known or suspected pregnancy, breast feeding, suicidal ideation requiring precautions against suicide, and a general medical condition or substance use disorder needing close medical attention or immediate medication which might limit participation in the trial. None of the participants took any psychotropic medication during the study. All eligible subjects who showed interest in the trial were included. They were not paid for participation.

2.1. Trial medication

Fifty-eight eligible subjects were randomised to either 2 mg of controlled-release melatonin (Circadin®, Neurim Pharmaceuticals, Israel) (group A), or placebo tablets (group B) once per day in the evening for 3 weeks (days 1–21). They were advised to take the tablets 1–2 h before a desired bedtime, and to avoid eating for 30 min before and 60 min after the ingestion.

2.2. Melatonin assessment

Subjects took their own saliva samples prior to the start of medication (day 0) and immediately after cessation (day 22). Collections were made at 06:00, 06:30 and 07:00 h for analysis of the concentration of melatonin. Subjects were advised to avoid drinking caffeine-containing beverages and using toothpaste until the collection was completed each morning, and to stand in a dark room while taking each sample. Samples were immediately frozen and stored at −20°C until assayed for melatonin by radioimmunoassay with an iodinated melatonin tracer and a melatonin-specific antiserum (Vakkuri et al., 1984; Vakkuri, 1985). The lowest detectable concentration by the method was 1.3 pg/ml (5.7 pmol/l), and the intra- and inter-assay coefficients of variation were from 6.7 to 9.5% and from 9.8 to 12.5%, respectively.

The passive secretion of melatonin into saliva reflects closely the changes in serum melatonin (Vakkuri et al., 1985), and simple and noninvasive saliva sampling is of clinical value in monitoring circulating levels of melatonin. The use of salivary melatonin measurements is established for phase typing of the melatonin rhythms (Voultsios et al., 1997).

2.3. Ratings

Subjects filled in the 15-item Groningen List of Sleep Complaints (GLSC, Department of Biological Psychiatry, University Hospital of Groningen, The Netherlands; unpublished) in the morning soon after waking, three times at
baseline (days −2 to 0) and six times around the end of the trial (days 19 to 24). The sum of this scale gives a global score of sleep quality ranging from 0 to 14, the maximum indicating good sleep quality. Levels of subjective sleepiness and alertness were also measured with a 10-cm visual analogue scale (VAS) ranging between ‘extremely tired’ (0 cm) and ‘extremely alert’ (10 cm). In addition, ten items concerning the waking-up process, such as ease of waking and inertia against waking were assessed with a structured questionnaire each morning.

The subjects also completed the 8-item addendum (ATYP) of a revised version of the Structured Interview Guide for the Hamilton Depression Rating Scale—Seasonal Affective Disorders Version Self-Rating Format (Williams et al., 1991), and the RAND 36-item Health Survey 1.0 (RAND; Hays et al., 1993) at baseline and at the 3-week follow-up. The ATYP has a self-rated format for scoring atypical depressive symptoms such as increased duration of sleep, increased appetite, weight gain, and carbohydrate craving. The RAND generates eight dimensions of health-related quality of life and is sensitive to changes in state of health among general populations (Hemingway et al., 1997).

2.4. Seasonal and circadian patterns

In addition, subjects filled in the Seasonal Pattern Assessment Questionnaire (SPAQ; Rosenthal et al., 1987), and the Morningness–Eveningness Questionnaire (M-EQ; Horne and Ostberg, 1976) at baseline. The SPAQ measures mood and behavioural changes with the seasons, and general well-being in relation to weather conditions. The sum of a six-item subscale gives the Global Seasonality Score (GSS), ranging from 0 to 24. The severity of weather-associated symptoms can be assessed with a 10-item subscale, the sum ranging from +1 to +30 for the positive type, being zero for the neutral type, and ranging from −30 to −1 for the negative type. The SPAQ criteria for subsyndromal SAD require that subjects have a GSS of 10 or more and experience seasonal change as no more than a mild problem, or a GSS of 8 or 9 and experience seasonal change as at least a mild problem (Bartko and Kasper, 1989). The M-EQ measures time patterns of daily behaviours and preferences, yielding five types (definitely morning or evening types, moderately morning or evening types, or neither morning nor evening type) with characteristic behavioural patterns based on the endogenous clockwork. In this study, a tripartite division into morning, evening and neutral types was used.

2.5. Ethics

The study was approved by an ethics committee of the University and by the National Agency for Medicines, Finland. All the questionnaires had been translated into Finnish and then back into English to verify their linguistic accuracy. All subjects gave their written informed consent to the participation after full explanation of the procedure. This study was conducted in full conformity with the principles of the Declaration of Helsinki and its amendments.

2.6. Statistics

The calculation of the sample size was based on the expected reduction in atypical depressive symptoms measured on an interval scale. Our estimate of the standard deviation (5 points) on the ATYP was based on the results of an earlier study (Kasper et al., 1989). We accepted the risk of committing type I and type II errors of 5% each, and were not willing to overlook a difference of 8 points between the means in the two groups. Hence, the minimum number of subjects required in each group was 10.

Our setting used the absolute changes in mean scores on the GLSC, the VAS, the ATYP, and the RAND as the outcome measures. Multiple regression models were computed for each outcome measure, allowing for group, age, sex, and the baseline values as covariates. The final models were formed with stepwise selection. The distributions were analysed using the Shapiro–Wilk test of normality, and the error variances using Levene’s test of equality. To study associations between baseline measurements, partial correlation coefficients were calculated, after controlling for sex and age.

3. Results

Of the 58 participants, 37 (28 women, 9 men) were randomised to melatonin (group A), and 21 (16 women, 5 men) to placebo (group B). In group A the mean age (S.D.) was 36.0 (9.5) years, range 24–60, and in group B, 42.6 (10.8) years, range 20–55. All subjects entered the trial, and 55 (95%) completed it, of whom two (one woman from each group) subjects returned the questionnaires only, and two (men from group A) collected the samples only. Three (two women from group A, one man from group B) dropped out because of busy social and occupational schedules. Finally, there were complete data on 32 and 19 subjects from groups A (25 women, 7 men) and B (15 women, 4 men), respectively.

Of the subjects, 13 exhibited subsyndromal SAD, 21 the negative type of WAS (of whom 7 also had subsyndromal SAD), 24 the positive type of WAS (of whom 3 also had subsyndromal SAD), and 6 neither type of WAS (of whom 2 had subsyndromal SAD; see Table 1). The frequency of subsyndromal SAD among WAS- and non-WAS typed subjects was not significantly different ($\chi^2=2.8$, d.f. = 2, $P=0.3$).
Table 1
Subgroup classification (n) by trial group

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Trial group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
</tr>
<tr>
<td>SPAQ</td>
<td></td>
</tr>
<tr>
<td>Without subsyndromal SAD</td>
<td>25</td>
</tr>
<tr>
<td>With subsyndromal SAD</td>
<td>7</td>
</tr>
<tr>
<td>WAS</td>
<td></td>
</tr>
<tr>
<td>Negative type</td>
<td>13</td>
</tr>
<tr>
<td>Neither type</td>
<td>5</td>
</tr>
<tr>
<td>Positive type</td>
<td>15</td>
</tr>
<tr>
<td>M-EQ</td>
<td></td>
</tr>
<tr>
<td>Morning type</td>
<td>5</td>
</tr>
<tr>
<td>Neither type</td>
<td>24</td>
</tr>
<tr>
<td>Evening type</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviations: SPAQ, the Seasonal Pattern Assessment Questionnaire; SAD, seasonal affective disorder; WAS, weather-associated syndrome; M-EQ, the Morningness–Eveningness Questionnaire.

3.1. Baseline assessment

At baseline, scores on the ATYP were associated with those on the GLSC ($r=-0.38, P=0.007$), on the GSS ($r=0.30, P=0.04$), and on the M-EQ ($r=-0.39, P=0.007$). In addition, scores on the M-EQ were associated with those on the GLSC ($r=0.35, P=0.02$), and on the VAS ($r=0.49, P=0.001$). The baseline values on these scales did not differ between the trial groups A and B. At baseline, the mean GLSC (S.D.) was 10.7(2.0) for those with no subsyndromal-SAD and 9.3 (3.4) for those with subsyndromal-SAD, and 10.2 (2.7), 10.8 (1.9) and 9.4 (4.2) for those with WAS negative, positive, or neutral, respectively.

3.2. Trial outcome

At the end of the 3-week treatment, morning melatonin concentrations were significantly higher in group A compared with group B due to the exogenous melatonin administration (Table 2). There was no significant difference in any of the outcome measures between groups A and B as a whole (Table 3). Two subjects in each group reported headache as an adverse event.

3.3. Subgroup analysis

When subjects were posthoc classified with a priori criteria derived from the SPAQ and the M-EQ (see Table 1), significant differences in the baseline and outcome measures between these groups emerged.

At baseline, there was a significant difference in the GSS ($t=-3.6, d.f.=11.4, P=0.004$) by circadian type: behavioural patterns of the morning type were related to a better quality of sleep and a history of milder season-bound symptoms. However, there were no significant correlations between the GSS and weather-associated symptoms ($r=-0.17, P=0.2$) or M-EQ score ($r=-0.25$, $P=0.04$), and on the M-EQ ($r=-0.39, P=0.007$). In addition, scores on the M-EQ were associated with those on the GLSC ($r=0.35, P=0.02$), and on the VAS ($r=0.49, P=0.001$). The baseline values on these scales did not differ between the trial groups A and B. At baseline, the mean GLSC (S.D.) was 10.7(2.0) for those with no subsyndromal-SAD and 9.3 (3.4) for those with subsyndromal-SAD, and 10.2 (2.7), 10.8 (1.9) and 9.4 (4.2) for those with WAS negative, positive, or neutral, respectively.

Table 2
Mean (S.D.) melatonin concentrations (pg/ml) in saliva by trial group

<table>
<thead>
<tr>
<th>Sample</th>
<th>Time</th>
<th>Group A n=34</th>
<th>Group B n=19</th>
</tr>
</thead>
<tbody>
<tr>
<td>At baseline</td>
<td>06:00</td>
<td>50.0 (39.1)</td>
<td>57.3 (39.6)</td>
</tr>
<tr>
<td></td>
<td>06:30</td>
<td>44.3 (28.2)</td>
<td>55.1 (42.6)</td>
</tr>
<tr>
<td></td>
<td>07:00</td>
<td>32.7 (22.1)</td>
<td>45.3 (42.5)</td>
</tr>
<tr>
<td>At week 3</td>
<td>06:00</td>
<td>324.5 (293.5)</td>
<td>51.2 (49.3)</td>
</tr>
<tr>
<td></td>
<td>06:30</td>
<td>243.5 (201.8)</td>
<td>50.5 (47.1)</td>
</tr>
<tr>
<td></td>
<td>07:00</td>
<td>183.4 (133.8)</td>
<td>38.7 (42.7)</td>
</tr>
</tbody>
</table>

* Z = -5.0, P<0.001.
* Z = -4.8, P<0.001.
* Z = -4.8, P<0.001.

Table 3
Mean (S.D.) ratings of the outcome measures by trial group

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>At baseline</th>
<th>At week 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A n=33</td>
<td>Group B n=20</td>
</tr>
<tr>
<td>GLSC</td>
<td>10.4 (2.5)</td>
<td>10.4 (2.4)</td>
</tr>
<tr>
<td>VAS</td>
<td>5.3 (1.7)</td>
<td>5.8 (1.3)</td>
</tr>
<tr>
<td>ATYP</td>
<td>2.6 (3.4)</td>
<td>2.1 (2.9)</td>
</tr>
<tr>
<td>RAND Physical functioning</td>
<td>95.3 (7.9)</td>
<td>97.9 (4.1)</td>
</tr>
<tr>
<td>RAND Physical problems</td>
<td>90.9 (21.5)</td>
<td>90.0 (22.1)</td>
</tr>
<tr>
<td>RAND Emotional problems</td>
<td>83.8 (26.5)</td>
<td>81.7 (29.6)</td>
</tr>
<tr>
<td>RAND Vitality</td>
<td>60.3 (21.3)</td>
<td>65.0 (18.2)</td>
</tr>
<tr>
<td>RAND General mental health</td>
<td>74.0 (16.1)</td>
<td>75.4 (16.1)</td>
</tr>
<tr>
<td>RAND Social functioning</td>
<td>87.9 (17.0)</td>
<td>88.8 (12.8)</td>
</tr>
<tr>
<td>RAND Pain</td>
<td>88.9 (14.1)</td>
<td>87.4 (14.4)</td>
</tr>
<tr>
<td>RAND General health perceptions</td>
<td>75.5 (15.4)</td>
<td>80.5 (10.4)</td>
</tr>
</tbody>
</table>

Abbreviations: GLSC, the 15-item Groningen List of Sleep Complaints; VAS, a 10-cm Visual Analogue Scale; ATYP, the 8-item addendum of the Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorders Version Self-Rating Format, Revised; RAND, the RAND 36-item Health Survey 1.0.
### Table 4
Baseline mean (S.D.) melatonin concentrations (pg/ml) in saliva by subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Baseline melatonin in saliva</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At 06:00</td>
</tr>
<tr>
<td>SPAQ</td>
<td></td>
</tr>
<tr>
<td>Without subsyndromal SAD (n=39)</td>
<td>52.3 (42.6)</td>
</tr>
<tr>
<td>With subsyndromal SAD (n=13)</td>
<td>55.6 (33.2)</td>
</tr>
<tr>
<td>WAS</td>
<td></td>
</tr>
<tr>
<td>Neutral type (n=6)</td>
<td>63.0 (24.5)</td>
</tr>
<tr>
<td>Positive type (n=24)</td>
<td>60.8 (44.4) *</td>
</tr>
<tr>
<td>Negative type (n=21)</td>
<td>31.9 (16.7) *</td>
</tr>
<tr>
<td>M-EQ</td>
<td></td>
</tr>
<tr>
<td>Morning type (n=10)</td>
<td>34.5 (19.6)</td>
</tr>
<tr>
<td>Neither type (n=35)</td>
<td>53.2 (43.9)</td>
</tr>
<tr>
<td>Evening type (n=5)</td>
<td>72.0 (17.2)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
\* P=0.02.
\* P=0.03.
\* P=0.01.

Among those with subsyndromal SAD, the overall mean GLSC score was significantly improved in group A compared to group B (t=2.6, d.f.=10, P=0.03; see Fig. 1). This effect was seen for days 19–22 (t=2.7, d.f.=10, P=0.02), but not for days 23–24 when the melatonin treatment had ceased (t=1.4, d.f.=10, P=0.2). The group×subsyndromal SAD interaction was significant (t=2.2, d.f.=43, P=0.03). In addition, the RAND scale of vitality was enhanced (t=2.6, d.f.=10, P=0.02; see Fig. 2), and the group×subsyndromal SAD interaction was significant (t=2.8, d.f.=47, P=0.007).

Among those with WAS, positive type, the changes in...
Fig. 2. Mean changes in measures of mood (a) and quality of life (b) by trial group in the subsyndromal seasonal affective disorder subgroup. (a) Atypical symptom score ranges from 0 to 26, higher score indicating more depressive symptoms. (b) Index values, range from 0 to 100, higher score indicating better quality of life on the corresponding scale.

the ATYP \(t=2.4, \text{d.f.}=22, P=0.03\), and on the RAND subscales of role limitations due to physical health \(t=-2.4, \text{d.f.}=22, P=0.03\), group×WAS interaction \(t=-3.0, \text{d.f.}=41, P=0.005\), general mental health \(t=-3.2, \text{d.f.}=21, P=0.004\), group×WAS interaction \(t=-2.8, \text{d.f.}=40, P=0.008\), and social functioning \(t=-2.7, \text{d.f.}=21, P=0.01\), group×WAS interaction \(t=-3.5, \text{d.f.}=40, P=0.001\) differed significantly in group A compared to group B at the 3-week follow-up (Fig. 3). There were no significant differences in the sleep measures by trial group among

Fig. 3. Mean changes in the measures of mood and quality of life in the weather-associated syndrome, positive type, subgroup. (a) Scoring as in Fig. 2.
those with WAS, positive type, nor in any of the outcome measures by trial group among subjects with WAS, negative type.

4. Discussion

Our main finding was that melatonin had contradictory effects on sleep and well-being in subjects with subsyndromal SAD and weather-sensitivity, so that there was no difference in the outcome measures between the trial groups in the entire mixed subject population. We also showed that melatonin administration was well tolerated.

In the subjects with subsyndromal SAD melatonin administration significantly improved the quality of sleep and vitality, in agreement with previous findings of some beneficial effects of melatonin treatment in SAD (Wirz-Justice et al., 1990; Lewy et al., 1998). During winter, subjects with subsyndromal SAD generally complain of mild, reverse vegetative symptoms, which include diminished vigour and sleep disturbances. Melatonin has anxiolytic effects, possibly mediated by the central GABAergic system (Golombek et al., 1996), but our main finding was improvement in sleep. We observed that melatonin administration improved vitality and quality of sleep in subjects with subsyndromal SAD at trial end, although the effect was not maintained after cessation of the treatment. However, this finding must be interpreted cautiously because of the relatively small numbers of subjects with subsyndromal SAD.

Our data show for the first time that melatonin is not beneficial in WAS. Moreover, in the positive type of WAS, administration of melatonin actually attenuated the improvement of atypical symptoms and physical parameters of quality of life compared to placebo. Among those on whom changes in weather conditions have a positive effect, baseline melatonin levels were relatively high. In this group, positive changes in atypical depressive symptoms, general mental health and social functioning were seen in the subjects receiving placebo, but not melatonin. It seems that exogenous melatonin attenuates the positive changes possibly associated with weather conditions, but to our knowledge there are no previous studies addressing this hypothesis.

Some of the variation in responses to melatonin may be due to the baseline characteristics of the subject groups. In analysing baseline ratings, we found that behavioural patterns of the morning type were related to a better quality of sleep and a history of milder season-bound symptoms. Atypical depressive symptoms at baseline were linked to a history of more severe season-bound symptoms, and to behavioural patterns of the evening type. In addition, they were, as expected, negatively associated with the quality of sleep at baseline. Baseline melatonin concentration was correlated with circadian type. These data are consistent with a phase delay in the evening-types and a phase advance in the morning-types. However, there were only three measurements before and after the trial, which is not frequent enough to give a clear picture of the circadian phase.

Some SAD patients show greater sensitivity to weather conditions, which may reflect their greater mood variability in general (Molin et al., 1996; Partonen et al., 2000; Reid et al., 2000). Lingjaerde and Reichborn-Kjennerud (1993) found a correlation between the GSS and Weather score on the SPAQ in their study of winter depressives. No such association was found in this study of a more heterogeneous population. In fact, the WAS and seasonality types were distributed quite evenly, with a slight, but not significant emphasis on subsyndromal SAD plus negative effect of weather. The WAS type also seems to be independent of the self-perceived circadian type, and the differences in melatonin levels between the WAS subtypes were not related to either seasonality or circadian type. These findings merit further research to establish whether WAS type is really an independent trait, and how climatic changes possibly mediate mood.

4.1. Limitations of the study

A shortcoming is that our assessment was based on self-ratings only and carried out as a fieldwork in household settings. Another shortcoming is the sample size in our subgroups, which limits the interpretation of these results. The Groningen List of Sleep Complaints is not a validated instrument, and we do not know to which extent changes in the score correlate with clinical improvement in sleep.

5. Conclusions

Our results suggest that the beneficial effects of melatonin are specific to disorders connected to the photoperiod rather than to the weather-related aspects of season. These findings accord with the general concept that the effects of melatonin on seasonal changes in sleep, mood and behaviour are mainly derived from its role as the signal of darkness, as indeed found for seasonal reproduction and hibernation in a number of animal species (Berger and Phillips, 1995). This hypothesis warrants further investigation using more restricted inclusion criteria.

In conclusion, melatonin may have a significant effect on quality of sleep, sleepiness after wake-up, mood and health-related quality of life in healthy individuals with subsyndromal SAD. It may be contraindicated in subjects with WAS, positive type. Additional studies employing the long-term administration of melatonin in varying dosages are needed to substantiate the benefits of melatonin for subjects with seasonal changes in mood and behaviour.
Acknowledgements

The authors are indebted to all the volunteer subjects who took part in the study. Melatonin (Circadin®) and placebo tablets were manufactured and provided for this study by Neurim Pharmaceuticals Ltd. (Tel-Aviv, Israel). The authors thank Dr. Ybe Meesters, Ph.D., for providing the Groningen List of Sleep Complaints for use in this study, Dr. Esa Pulkkinen, MB, for technical assistance, Jari Haukka, Ph.D., for help with the statistical analysis, and Professor Nava Zisapel, Ph.D., for comments and intellectual support.

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