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Trastorno afectivo estacional: Un trastorno asociado con los ritmos endógenos.  
(Seasonal affective disorder: A disorder associated with endogenous rhythms.)  
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## Resumen

El trastorno afectivo estacional (SAD) es una forma de depresión recurrente o trastorno bipolar que se caracteriza por el inicio anual regular de episodios de depresión mayor durante el otoño y/o invierno y remisión o episodios maníacos/hipomaniacos durante la primavera y el verano. El SAD explica alrededor del 10% de todos los síntomas depresivos y afecta a entre un 2-5% de la población general en climas templados.

Durante las últimas dos décadas, una multitud de estudios han investigado los mecanismos patofisiológicos de esta enfermedad. Al respecto, las medidas actigráficas se han establecido como una importante herramienta de investigación. Existe una evidencia substancial sobre que el SAD se acompaña de por alteraciones cronobiológicas específicas, niveles de actividad bruscos, ritmos circadianos retrasados, y modelos de sueño alterados. Los métodos cronoterapéuticos como la terapia lumínica o la privación terapéutica del sueño son tratamientos altamente efectivos y no sólo capaces de invertir los síntomas psicológicos de la depresión sino también las irregularidades del ciclo sueño-vigilia, que se asocia con el SAD. Este artículo revisa las características cronobiológicas del SAD y proporciona ejemplos de casos para su ilustración.

### RESETTING THE INTERNAL CLOCK IN DEPRESSION: A NEW THERAPEUTIC APPROACH

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## Seasonal affective disorder: a disorder associated with endogenous rhythms

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Seasonal affective disorder (SAD, fall/winter depression) is a form of recurrent depressive or bipolar disorder that is characterized by the regular annual onset of major depressive episodes during fall and/or winter and remission or manic/hypomanic episodes during spring and summer. SAD accounts for about 10% of all depressive

syndromes and affects between 2% and 5% of the general population in temperate climates. During the last two decades, a multitude of studies have investigated the pathophysiological mechanism of this illness. In this regard, actigraphic measurements have been established as an important tool for research. There is substantial evidence that SAD is accompanied by specific chronobiological disturbances, such as blunted activity levels, delayed circadian rhythms, and disrupted sleep patterns. Chronotherapeutic methods such as bright light therapy or therapeutic sleep deprivation are highly effective treatments and are not only able to reverse the psychological symptoms of depression, but also the irregularities of the sleep-wake cycle, which are associated with SAD. This article reviews the chronobiological features of SAD and provides examples of case histories for illustration.

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Keywords: seasonal affective disorder; actigraphy; bright light therapy; chronobiological disturbance; therapeutic sleep deprivation

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#### TROUBLES AFFECTIFS SAISONNIERS :

##### UNE MALADIE ASSOCIÉE AUX RYTHMES ENDOGÈNES

Les troubles affectifs saisonniers (TAS), ou dépression automnale/hivernale, sont une forme de troubles dépressifs ou bipolaires récurrents caractérisée par la survenue annuelle régulière d'épisodes dépressifs majeurs pendant l'automne et/ou l'hiver, et leur rémission ou la survenue d'épisodes maniaques/hypomaniaques au printemps et en été. Les TAS représentent environ 10 % de tous les syndromes dépressifs et touchent entre 2 et 5 % de la population générale sous climats tempérés. Le mécanisme physiopathologique de ce trouble a fait l'objet d'un grand nombre d'études ces 20 dernières années.

À cet égard, l'actimétrie, ou mesure de l'activité motrice et de repos, s'est révélée un outil de recherche important. Les données confirment que les TAS s'accompagnent de perturbations chronobiologiques spécifiques à type de courbes d'activité aplaties, rythmes circadiens retardés et tracés de sommeil perturbés.

Les méthodes chronothérapeutiques comme la luminothérapie ou la privation thérapeutique de sommeil sont des traitements très efficaces qui permettent non seulement d'inverser les symptômes dépressifs mais également d'agir sur les irrégularités du cycle veille-sommeil associées au TAS. Cet article passe en revue les caractéristiques chronobiologiques des TAS en les illustrant par des cas-cliniques.

Fall/winter depression is the most common type of seasonal affective disorder (SAD) in the northern hemisphere; summer depression is rare,<sup>1</sup> and will not be discussed in this article. Many humans experience seasonal changes in mood, drive, appetite, and sleep throughout the year without any major problems in daily functioning.<sup>2,3</sup> If these variations occur regularly during fall and/or winter and are of sufficient intensity to qualify for a depressive episode (International Statistical Classification of Diseases, 10th revision [ICD-10]<sup>4</sup>) or a major depressive episode (Diagnostic and Statistical Manual of Mental Disorders, 4th revision [DSM-IV]<sup>5</sup>), they can be regarded as symptoms of SAD.

Seasonal depressive episodes must substantially outnumber the nonseasonal episodes over the patient's lifetime. Depression in fall or winter is typically followed by a remission during the subsequent spring and summer period. However, the disorder can also have a bipolar course of illness with hypomanic episodes (bipolar II) or more seldom manic episodes (bipolar I) during spring/summer. The prevalence of SAD in the general population is between 2% and 4% in temperate climates (for a review of epidemiological studies, see reference 6).

Studies from North America have shown that the prevalence of SAD increases with northerly latitude.

7 However, in some Scandinavian countries, the prevalence rates have been found to be unexpectedly low,<sup>8</sup> which could be explained by a population selection toward increased tolerance of winter darkness.

9 SAD is more common in female patients: the ratio of women to men is about 3.5:1 to 9:1 in most samples, which is higher than the 2:1 ratio found in nonseasonal depression.<sup>10</sup> In most patients, the onset of the disorder is in the late twenties or early thirties. The core symptoms of SAD are daytime fatigue, depressive mood, and low energy. The majority of the patients fulfill the criteria of the atypical feature specifier of DSM-IV. These patients frequently suffer from hypersomnia, heaviness in limbs, increased appetite, and carbohydrate craving. According to a recent study,<sup>11</sup> irritability and aggression, often in the form of anger attacks (sudden spells of inappropriate anger accompanied by vegetative hyperarousal similar to panic attacks), play an important role in the clinical picture of SAD. About half of female SAD patients suffer from premenstrual dysphoric disorder (PMDD).<sup>12</sup> Most SAD patients are treated as outpatients, as the severity of the disorder ranges mostly from mild to moderate.

However, severe courses with suicidality are possible and may require hospitalization.

Pathophysiology and chronobiological disturbances in SAD A multitude of studies have tried to elucidate the underlying pathophysiology of SAD. The research paradigm of tryptophan or catecholamine depletion has been especially helpful to study the effects of temporary monoaminergic dysfunction in SAD patients.

Monoaminergic neurotransmitter systems, especially serotonin,<sup>13,14</sup> but also noradrenaline<sup>15</sup> and possibly dopamine,<sup>16</sup> are involved in the pathogenesis of SAD. Serotonin receptor challenge studies and neuroimaging studies have been able to show subsensitivity of various serotonin receptors<sup>17</sup> and reduced serotonin transporter availability.<sup>18</sup> There is emerging evidence that genetic markers influence the predisposition of humans to SAD. Studies have examined the familiarity and heritability of SAD.<sup>19</sup> Genetic association studies have examined the role of several candidate genes such as serotonin transporter promoter repeat length polymorphism (5-HTTLPR),<sup>20</sup> guanine nucleotide-binding proteins, <sup>21</sup> and genetic variations in clock genes. <sup>22</sup>

The above studies are able to explain the depressive symptomatology of SAD patients in general.

However, they provide no theoretical explanation for the seasonal occurrence of the disorder. Furthermore, as many patients with SAD present with apparent chronobiological abnormalities (such as changes in sleep length and phase) and show a clinical pattern different from nonseasonal depression (ie, atypical symptoms), researchers have been searching for explanations. One of the first hypotheses concerning the pathogenesis of depression was that reduced ambient light during fall and winter led to SAD symptoms in predisposed subjects. Apart from social cues, environmental light is one of the most important zeitgebers in humans and is reliably

able to alter the length and the phase of the sleepwake cycle.<sup>23</sup> Melatonin, an indolamine hormone produced by the pineal gland, has been extensively studied in SAD. <sup>24</sup>

The duration of nocturnal secretion mediates the photoperiod signal, as melatonin production is inhibited by light. SAD patients display a delay of dim light melatonin onset<sup>25</sup> and show a supersensitive melatonin suppression to light.<sup>26</sup>

Furthermore, increased serum concentrations<sup>27</sup> and elevated daytime levels of melatonin<sup>28,29</sup> have been found. Abnormalities of melatonin metabolism may be involved in circadian disturbances as the suprachiasmatic nucleus is the main area of melatonin receptors.<sup>30</sup> The suprachiasmatic nucleus is the master circadian pacemaker in the human brain and influences all other biological clocks of the human body.<sup>31</sup> Therefore, it is not surprising that irregularities of the hormonal and endocrine system have been found in SAD: prolactin, growth hormone, and thyrotropin have been found to be diminished as a result of lower nocturnal secretion.<sup>32</sup>

Furthermore, the minimum of the body temperature curve is phase-delayed in SAD compared with healthy controls.<sup>33</sup>

Bright light therapy (BLT) can be used as an external zeitgeber for the internal clock. Several dozen studies have established BLT as a highly effective and well-tolerated treatment for SAD.<sup>34,35</sup> BLT involves exposure to full spectrum visible light of 10 000 lux at a distance of about 50 cm. The effect of BLT is mediated exclusively by the eyes<sup>36</sup> and induces a “reset” of the circadian pacemaker: the suprachiasmatic nucleus receives direct nerve collaterals from the eye by the retinohypothalamic tract.<sup>37</sup> Patients have to perform BLT for 30 to 60 minutes per day for effective treatment. It has been shown that the effect is highest when treatment is performed shortly after waking up in the morning (ie, 8 hours after dim light melatonin onset).<sup>38</sup>

Another chronotherapeutic method is therapeutic sleep deprivation. This treatment was first described in 1966 by Schulte.<sup>39</sup> When performing total sleep deprivation, the patient is asked to stay awake for up to 40 hours, starting from the morning before the night of the sleep deprivation until the evening after that night. Partial sleep deprivation<sup>40</sup> was introduced when it became apparent that it is the second half of the night’s sleep that is responsible for the depressogenic effect: The patient sleeps the first half of the night, and stays awake for the rest of the night and the following day.

Activity monitoring with actigraphy has been used in the past to investigate the chronobiological disturbances associated with psychiatric disorders such as mood disorders,<sup>41,42</sup> Alzheimer’s disease,<sup>43</sup> and attention deficit hyperactivity disorder.<sup>44</sup> Locomotor activity and the rest-activity cycle can be used as estimates for the circadian rhythm because they represent the most important psychobiological manifestations of the circadian oscillators. Wrist actigraphy is a method for objectively measuring motor activity with high-resolution time series.

#### SELECTED ABBREVIATIONS AND ACRONYMS

**5-HTTLPT** serotonin transporter promoter repeat length polymorphism

**BLT** bright light therapy

**DSM-IV** *Diagnostic and Statistical Manual of Mental Disorders, 4th revision*

**GSS** Global Seasonality Score

**HAM-D** Hamilton Depression Rating Scale

**ICD-10** *International Statistical Classification of Diseases, 10th revision*

**PMDD** premenstrual dysphoric disorder

**SAD** seasonal affective disorder

**SIGH-SAD** Structured Interview Guide for the Hamilton rating Scale–Seasonal Affective Disorder version

**SPAQ** Seasonal Pattern Assessment Questionnaire

Technological advances have made the production of miniaturized ambulatory monitoring devices possible.<sup>45</sup> Actigraphy can be used in a reliable and cost-effective manner in both research and clinical practice. The wrist activity monitor is a small microprocessor controlled device, approximately the size of a wristwatch (Figure 1). In contrast to electrophysiological techniques, actigraphy is noninvasive and unobtrusive with minimal impedance to the subject's lifestyle and allows ambulatory measurements in the patient's natural environment.<sup>46,47</sup>

**Table I. Circadian abnormalities found in seasonal affective disorder compared with healthy humans. Values are derived from reference 49.**

- \_ Reduction in total activity levels by 33%
- \_ Reduction in daytime activity levels (ie, activity levels between sunrise and sunset) by 43%
- \_ Reduction in the relative amplitude of the sleep-wake rhythm (amplitude relative to mesor as a normalized value that allows intraindividual comparisons) by 6%
- \_ Phase delay of cosine peak (ie, the acrophase of the circadian rhythm) of 55 minutes
- \_ 5% lower sleep efficiency (ie, actual sleep time divided by total time in bed)

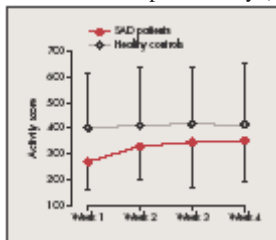


Figure 2.

Total activity (mean  $\pm$  SD) of 17 patients with seasonal affective disorder (SAD) and 17 healthy controls in weeks 1 to 4 during bright light therapy. Significant difference between patients and controls at week 1 ( $P=0.031$ ). Significant increase in activity in the patient group from week 2 onward ( $P=0.001$ ).

Adapted from reference 49: Winkler D, Pjrek E, Praschak-Rieder N, et al. Actigraphy in patients with seasonal affective disorder and healthy control subjects treated with light therapy. *Biol Psychiatry*.2005;58:331-336. Copyright © 2005, Elsevier.

In a controlled study including 25 patients suffering from SAD and 20 healthy adults, eicher et al<sup>48</sup> investigated rest-activity disturbances over 72 hours with actigraphy: they were able to demonstrate that patients had lower levels of intradaily stability and thus weakened entrainment of their circadian rhythms to the 24-hour day. Furthermore, patients were significantly phase-delayed compared with controls. However, in this study, there was no evidence for an attenuation of the amplitude of circadian rhythms. In a further study, Winkler et al<sup>49</sup> examined 17 SAD patients and matched healthy controls over 4 weeks. Patients and controls had to perform BLT (10 000 lux, half an hour in the morning) on a daily basis during the time of the measurements.

In the first week of treatment (Table I), patients showed significantly lower total activity (Figure 2), lower activity levels during the daytime, and diminished amplitude and relative amplitude (amplitude relative to mesor as a normalized value) of the sleep-wake cycle. Moreover, cosinor analysis revealed that SAD patients were significantly phase-delayed by about 55 minutes (Figure 3).

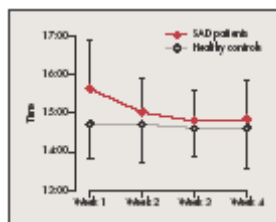


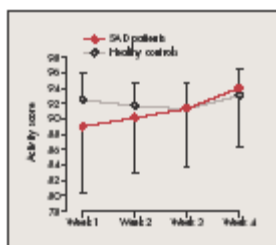
Figure 3. Time of cosine peak (acrophase of cosinor analysis; mean  $\pm$  SD) of the activity rest cycle of 17 patients with seasonal affective disorder (SAD) and 17 healthy controls in weeks 1 to 4 during bright light therapy. Significant delay of cosine peak in patients at week 1 ( $P=0.023$ ). Significant advance of the acrophase from week 3 onward ( $P<0.05$ ).

Reproduced from reference 49: Winkler D, Pjrek E, Praschak-Rieder N, et al. Actigraphy in patients with seasonal affective disorder and healthy control subjects treated with light therapy. *Biol Psychiatry*. 2005;58:331-336. Copyright © 2005, Elsevier.

In regard to sleep parameters, SAD patients had a significantly lower actual sleep time (ie, percentage of time asleep between sleep onset and end of sleep; Figure 4) and lower sleep efficiency (ie, actual sleep time divided through total time in bed). There were no significant differences between patients and healthy individuals regarding the intradaily stability (ie, the strength of coupling of the rhythm to external zeitgebers) and the ntradaily variability (indicating the fragmentation of the rhythm by measuring changes in hourly activity levels) in week 1. As hypothesized, treatment with BLT was able to reverse many of the chronobiological abnormalities observed in the patient sample (Table II): after two weeks of treatment, there was a significant increase in total (Figure 2) and daylight activity in the patient sample. The amplitude and the relative amplitude of the circadian rhythm likewise increased after 2 weeks of treatment. Furthermore, BLT phase-advanced subjects of the patient group with statistical significance from week 3 onward (Figure 3). Interestingly, BLT had an effect on patients' sleep: after 4 weeks of treatment, the actual sleep time (Figure 4) and the sleep efficiency had increased. BLT also seemed to exert a consolidating effect on the circadian rhythm both in SAD patients and normal subjects with increases in intradaily stability of about 9% at the end of the study.

Apparently, BLT is able to act as a powerful external zeitgeber even in healthy humans. Humans without apparent psychopathological deterioration possibly develop slightly diminished entrainment of their circadian rhythms during the fall/winter period.

Disturbances of the sleep-wake cycle, which can often be seen in patients with SAD, can easily be monitored with actigraphy. We would like to demonstrate the most prominent circadian abnormalities (blunted and delayed rhythms) by reporting on two patients who were diagnosed and treated at our hospital in Vienna. These cases have also been published elsewhere.<sup>50</sup> Both patients were given the Seasonal Pattern Assessment Questionnaire (SPAQ)<sup>51,52</sup> to derive the Global Seasonality Score (GSS), which is a measure of seasonal fluctuations of psychopathological symptoms. Furthermore, severity of depression was assessed by the Structured Interview Guide for the Hamilton Depression Rating Scale (29-items SAD-Version; SIGH-SAD)<sup>53</sup> at baseline, and after 2 and 4 weeks of antidepressant drug treatment. Patients wore activity monitors (Actiwatch Plus by Cambridge Neurotechnology Ltd, Cambridgeshire, UK; Figure 1) on their nondominant wrist and removed these devices only when showering or bathing.



**Figure 4.** Actual sleep time (ie, percentage of time asleep between sleep onset and end of sleep; mean ± SD) of 17 patients with seasonal affective disorder (SAD) and 17 healthy controls in weeks 1 to 4 during bright light therapy. Significant increase for patients between week 1 and week 4 ( $P=0.004$ ) and for controls between week 3 and 4 ( $P=0.023$ ). Note: no significant change between week 1 and 4 in healthy subjects.

Adapted from reference 49: Winkler D, Pjrek E, Praschak-Rieder N, et al. Actigraphy in patients with seasonal affective disorder and healthy control subjects treated with light therapy. *Biol Psychiatry*. 2005;58:331-336. Copyright © 2005, Elsevier.

- Increase in total and daytime activity after 2 weeks of bright light therapy
- Increase in the amplitude and relative amplitude of the circadian rhythm after 2 weeks
- Advance of delayed circadian rhythms after 3 weeks

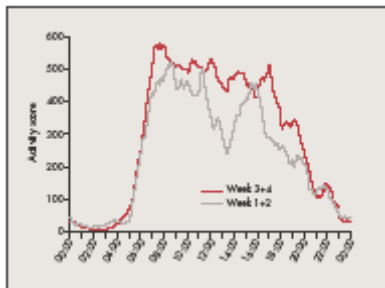
- Increase in actual sleep time (ie, percentage of time asleep between sleep onset and end of sleep) after 4 weeks
- Improvement in sleep efficiency after 4 weeks
- Increase in the intradaily stability quantifying the invariability between the days (ie, the strength of coupling of the rhythm to external zeitgebers) after 4 weeks. Note: this parameter also increases in healthy subjects employing bright light therapy during fall and winter

**Table II. Effects of bright light therapy on circadian disturbances in seasonal affective disorder. Values are derived from reference 49.**

## Patient 1

A 51-year-old female patient consulted our outpatient clinic for SAD in October. She had observed a regular decline in mood and drive in the fall and winter during the previous 5 years. The most prominent symptoms were daytime fatigue, loss of pleasure, and subjectively reduced energy. The patient obtained a GSS of 11 points on the SPAQ. SIGH-SAD rating yielded a score of 32 (16 points on the 21-item HAM-D subscale and 16 points on the 8-item atypical supplement). A diagnosis of SAD was made as the patient fulfilled the DSM-IV diagnostic criteria for recurrent major depression and those for the seasonal pattern specifier. The patient visited our clinic after 2 and 4 weeks of antidepressant treatment.

After 4 weeks, we were able to observe a reduction in SIGH-SAD scores to 21 points (17 points HAM-D-21; 4 points atypical supplement). Actigraphic data of the first 2 weeks were compared with those of the 3rd and 4th weeks of measurement (Figure 5). The actigraphic results were in good accordance with the clinical improvements:



**Figure 5. Activity profile (raw activity scores) of patient 1 during weeks 1+2 and weeks 3+4 of antidepressant treatment. Data are smoothed by applying a moving average of 15 minutes.**

*Modified from reference 50: Pjrek E, Winkler D, Konstandinidis A, Thierry N, Kasper S.*

Aktigraphie als Instrument zur Verlaufskontrolle bei saisonal abhängiger Depression—ein Bericht über zwei Fälle. *J Neurol Neurochir Psychiatr.* 2003;2:29-31. Copyright © Krause & Pachernegg GmbH

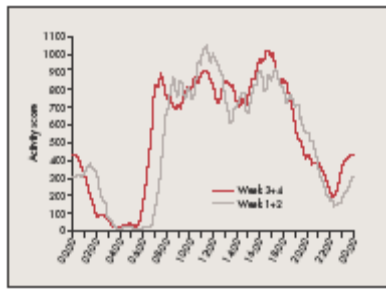
there was an increase in total activity of 23% corresponding to an increase in drive (SIGH-SAD item H2 at baseline: 2 points; week 2 and 4: 0 points).

## Patient 2

The second patient, a 41-year-old female, visited our outpatient clinic at the end of October for the first time. She suspected she was already suffering from winter depression. This was confirmed by a GSS of 13 points and a SIGH-SAD total score of 25 points (12 points HAM-D-21, 13 points atypical supplement).

The patient also said that she went to bed in the early morning hours and had difficulties waking up early. Furthermore, she said her mood was worse in the morning and she

experienced a noticeable deterioration of energy during the late afternoon and evening hours. Like the first patient, she had psychopathological ratings after 2 and 4 weeks of antidepressant treatment. The patient responded to treatment and obtained a SIGH-SAD total score of 12 points after 4 weeks (6 points HAM-D-21; 6 points on the atypical supplement). Comparison of the actigraphic data from week 1 and 2 with the data from week 3 and 4 showed an advance of the activity curve of about 1 hour (Figure 6). The patient reported that she no longer felt so tired and slow in the morning and was able to arrive punctually at work. Moreover, depressed mood (SIGH-SAD item H1 at baseline: 2; week 2: 0) and reduced energy (item H2 at baseline: 2; week 4: 1) also improved



**Figure 6.** Activity profile (raw activity scores) of patient 2 during weeks 1+2 and weeks 3+4 of antidepressant treatment. Data are smoothed by applying a moving average of 15 minutes.

Modified from reference 50: Pjrek E, Winkler D, Konstandinidis A, Thierry N, Kasper S. Aktigraphie als Instrument zur Verlaufskontrolle bei saisonal abhängiger Depression—ein Bericht über zwei Fälle. *J Neurol Neurochir Psychiatr.* 2003;2:29-31. Copyright © Krause & Pachernegg GmbH.

## Conclusion

As exemplified above, actigraphy is not only an important tool in chronobiological research, but also an efficient and noninvasive method to objectively study the clinical course of patients with SAD. It has been shown that actigraphic measurements have a high agreement with self-rating scales.<sup>54</sup> However, actigraphy can (depending on battery life and the size of the internal data storage of the devices) yield data over many months, whereas rating scales are vulnerable to memory bias<sup>55</sup> and rather produce a psychopathological cross-section of the current state of the patient. The graphical presentation of the activity levels during day and night may be used to demonstrate many of the clinical symptoms of SAD. Furthermore, the progress of treatment may be discussed with the patients, which may be helpful to increase adherence to treatment.

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[www.medizin-medien.info/mm/mm003/SADendogenous.pdf](http://www.medizin-medien.info/mm/mm003/SADendogenous.pdf)

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