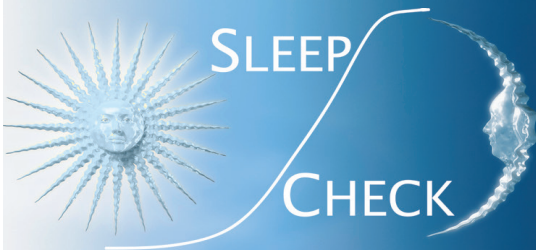


Sleep Check

In vitro diagnostic determination of
Circadian Rhythm Sleep Disorders

Partial
Melatonin
Profile for
DLMO



Sleep Check Concept Comprises:

Saliva Collection Tool Allowing
Comfortable Sample Collection at
Patient's Home

Assessment of the Biological
Circadian Sleep Rhythm by Defining
the Individual Melatonin Onset
(DLMO)

Melatonin Onset Allows you to
Define the Proper Application Time
for Therapeutic Intervention

Assessment of Melatonin Onset

DLMO - Melatonin Onset

Melatonin Onset is considered to be the most useful parameter of the 24 hour melatonin curve and is the recommended parameter to diagnose circadian rhythm sleep disorders.

Melatonin synthesis from the pineal gland is regulated by the circadian pacemaker, located in the suprachiasmatic nuclei, and by ocular light exposure. Melatonin has a circadian rhythm that peaks during the night in normally entrained individuals.

Daytime melatonin levels are very low and rise in the evening during decreasing light intensity. The onset point of melatonin secretion under dim light conditions is called DLMO (Dim Light Melatonin Onset). Melatonin onset is the preferred circadian marker because it is robust even in the presence of various external influences¹⁻².

The most comfortable way for the assessment of the individual DLMO is to follow the salivary melatonin concentration during the evening. Experience with a partial melatonin profile, composed of 5 saliva samples collected hourly showed a high success rate for the DLMO determination.

If the individual's circadian phase is normal, then his DLMO will be observed about 2 to 3 hours prior to habitual sleep. Normal DLMO time points are:

Adults 07:30 - 10:00 pm
Children 07:30 - 09:00 pm
(6-12 yrs.)

An abnormal timing of DLMO indicates a circadian rhythm sleep disorder and provides a clue for the optimal timing of treatment with exogenous melatonin or bright light³⁻⁵.

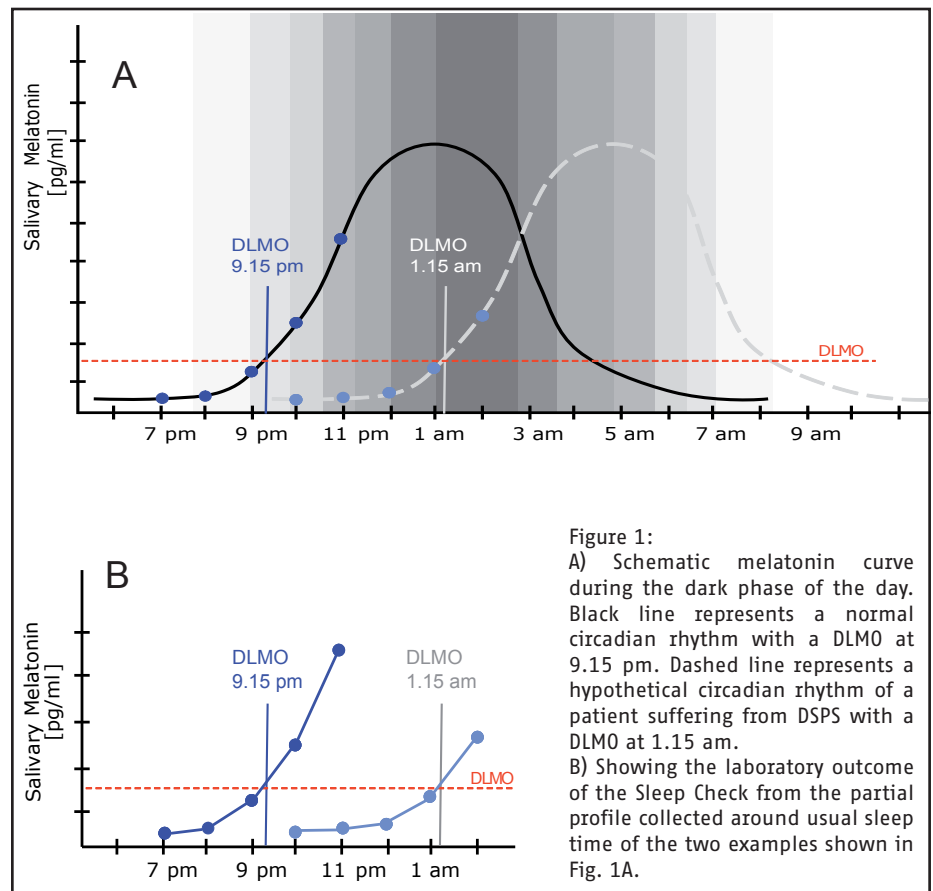


Figure 1:
A) Schematic melatonin curve during the dark phase of the day. Black line represents a normal circadian rhythm with a DLMO at 9.15 pm. Dashed line represents a hypothetical circadian rhythm of a patient suffering from DSPS with a DLMO at 1.15 am.
B) Showing the laboratory outcome of the Sleep Check from the partial profile collected around usual sleep time of the two examples shown in Fig. 1A.

Circadian Rhythm Sleep Disorders

Circadian rhythm sleep disorders are defined as a status of persistent or recurrent pattern of sleep disruption. This leads to excessive sleepiness or insomnia, due to a mis-matching between the sleep/wake schedule required by a person's environment and his circadian sleep-wake pattern. The sleep disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Delayed sleep phase syndrome (DSPS). The patient repeatedly has trouble getting to sleep and trouble awakening on time. People with this disorder are often misunderstood as irresponsible and lazy.

Other circadian rhythm disorders are Advanced sleep phase syndrome (ASPS), Jet lag syndrome, shift-work sleep disorder, irregular sleep-wake rhythm syndrome and 24-hour sleep-wake syndrome.

Additionally, there are diseases associated with sleep and circadian rhythm disorders like mood disorders,

seasonal affective disorders (SAD), chronic fatigue syndrome (CFS), chronic sleep onset insomnia in children with the so called attention deficit hyperkinesia disorder (ADHD) that manifest similar sleep disturbances⁶.

Treatment

Once a circadian rhythm disorder is diagnosed, exogenous Melatonin is one of the most effective treatments especially for DSPS patient⁷.

Melatonin intake advice: 5 hours before DLMO in DSPS patient and 10 hours after DLMO in ASPS patient.

Before applying Melatonin other treatments are recommended:

- Regular lifestyle characterized by strong "time cues" (zeitgeber), i.e.: meals, physical exercises, fixed bed-in and -out times.
- Light treatment: bright light, >3000 lux during 15 minutes (at night in ASPS patient and in the morning in DSPS patient).

Sleep Check Concept

BÜHLMANN has adapted the concept of Sleep Check from the out-patient concept of *Melatonin Poli*. Sleep Check is a saliva collection device that enables comfortable sample collection at home.

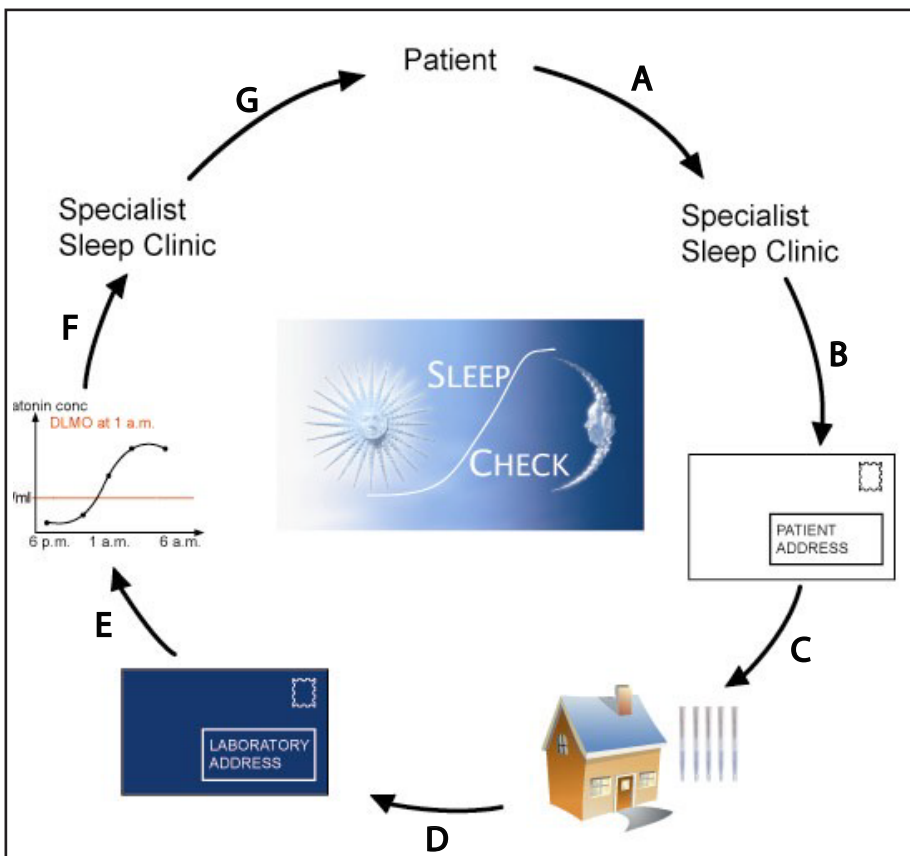
- A Patients suffering from sleep on- or offset problems contact the specialist.
- B After a preliminary diagnosis (with questionnaire) Sleep Check will be delivered by mail to the patient's home.
- C Sleep Check is composed of a manual with a detailed description of collection and precautions, a set of saliva collection device, a blue plastic envelope to mail the collected samples back and a patient information sheet.

With this package the patient can collect the samples comfortably at home. During one evening, 5 consecutive samples, collected hourly, around the usual sleep time have to be collected by the patient.

- D The included envelope enables the direct shipment of the samples to the laboratory.
- E The laboratory analyses samples with the ultra-sensitive *Direct Saliva Melatonin Radioimmuno Assay (RIA)* and determines DLMO.
- F The *in vitro* diagnostic result of the melatonin partial profile including DLMO will be transferred to the specialist.
- G Based on the time of DLMO an individual personalized therapy can be prescribed.

In vitro Diagnostic Determination of Melatonin

In addition to Sleep Check, BÜHLMANN offers a unique Test kit for the accurate determination of melatonin in saliva samples. The *Direct Saliva Melatonin RIA* (order code: RK-DSM2) supports the laboratory to use a methodology that is accurate, ultra-sensitive, reliable and well adapted for routine.



Outpatient Concept

Melatonin Poli is a Dutch outpatient clinic in Gelderse Valley Hospital (Netherlands). It is aimed to diagnose and treat patients with possible circadian rhythm sleep disorders. Specifically for children and adults who suffer from sleep problems for a long period. Dr. Smits and his group have been using this outpatient concept successfully for over 10 years.

Concept based on five pillars:

1. Patient contact via Internet
2. Preliminary diagnosis with the help of questionnaires
3. Investigation with the help of different tools (e.g. Sleep Check)
4. First visit and diagnosis of circadian rhythm sleep disorders
5. Treatment prescription with melatonin or bright light therapy

This outpatient concept offers the advantage of a fast, cost reducing and efficient diagnosis where at the first visit a secured diagnosis can be done.

The assessment of the melatonin onset is one critical pillar. The information resulting from the Sleep Check allows to the responsible sleep specialist not only to make a proven diagnosis of circadian rhythm sleep disorders. Moreover, the specialist can determine the correct and most efficient time of treatment with melatonin or bright light. And additionally, a first prediction of the treatment duration can be done.

Already at the second visit treatment result, satisfaction and improvement of quality of life can be discussed with the patient⁸⁾. A survey with 278 patients showed a satisfaction rate of 85% in children and young adults.

Figure 2: Principle of the Sleep Check concept see above

DLMO is acknowledged as robust and valid parameter to diagnose circadian phase disorders. Particularly, as DLMO is a very sensitive and robust system, a most accurate, and robust assay is needed for the determination of such low melatonin levels. The combination of the unique Direct Saliva Melatonin Radioimmunoassay (RIA) with SLEEP CHECK is a most valuable tool for both, your future patients and the laboratory.



References

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- ⁷⁾ Braam W *et al.* Dev Med Child Neurol 2009;51(5)
- ⁸⁾ Keijzer H *et al.* *Success rate of salivary DLMO measurement in patients with possible sleep wake rhythm disorders. in preparation*

Laboratories offering Sleep Check analysis:

Netherlands

Gelderse Vallei Hospital
Clinical Chemistry Laboratory
www.geldersevallei.nl

Switzerland

BÜHLMANN Laboratories AG
info@buhlmannlabs.ch
www.buhlmannlabs.ch

For further information please contact:
info@buhlmannlabs.ch

Specialized Sleep Centers:

Netherlands/Belgium:

Gelderse Vallei Hospital
info@medsys.nl
www.melatoninecheck.nl
www.slaapstoornissen.nl

Switzerland

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