

# **WHY DIM LIGHT MELATONIN ONSET (DLMO) SHOULD BE MEASURED BEFORE STARTING MELATONIN TREATMENT**

**H. Keijzer<sup>a,b</sup>, M. G. Smits<sup>a,b</sup> W Braam<sup>b,c</sup>, R. Didden<sup>b,d,e</sup>, A. Maas<sup>b,f</sup>, & L.M.G.  
Curfs<sup>b,h</sup>**

<sup>a</sup> Gelderse Vallei Hospital, Ede, The Netherlands

<sup>b</sup> Governor Kremers Center, University Maastricht, the Netherlands

<sup>c</sup> 's Heeren Loo Zuid-Veluwe, Wekerom, The Netherlands

<sup>d</sup> Behavioural Science Institute, Radboud University Nijmegen, Nijmegen, The Netherlands

<sup>e</sup> Trajectum, Zutphen, The Netherlands

<sup>f</sup> GROW School for Oncology and Developmental Biology, University Maastricht, Maastricht, The Netherlands

<sup>g</sup> Institute for Management Research, Radboud University Nijmegen, Nijmegen, The Netherlands

<sup>h</sup> Department of Clinical Genetics, Academic Hospital Maastricht/University Maastricht, Maastricht, The Netherlands

## **INTRODUCTION**

At 12 and 13 May 2011 the Castang foundation organized a workshop on sleep research needs for the problems of children with neurodevelopmental disorders in Vancouver. The Dutch multidisciplinary expert team for persons with intellectual disabilities who present with sleep disturbances was invited to discuss their ideas on future research. This article summarizes their vision on the value of Dim Light melatonin Onset measurements in patients with possible circadian sleep-wake disturbances.

Melatonin is a chronobiotic drug(1) which is increasingly prescribed for patients with insomnia. It is usually administered 1 or 2 hour before desired bed time, as recommended by several pharmacopoeias(2). However a meta-analysis showed that melatonin is not effective if administered in this way(3). On the contrary, if melatonin is administered at a time which is related to Dim Light Melatonin Onset (DLMO) it is remarkably successful in improving sleep(4;5). This suggests that the advices how to administer melatonin should be adapted at the present knowledge. The more because nowadays DLMO can be measured easily in home situations (6).

The present review summarizes the arguments supporting measuring DLMO before starting melatonin treatment. We focus on the relevance of DLMO for diagnosis and optimal treatment of circadian rhythm sleep-wake disorders. Furthermore we explored if DLMO can be predicted by sleep onset and to what extent DLMO predicts effectiveness of melatonin treatment. Finally we studied the reliability of DLMO measurement in clinical practice.

## METHODS

The databases PubMed and Embase were searched as well as the abstracts of sleep and chronobiologic societies that were published between January 1990 and May 2011 using the key words ‘human’, ‘melatonin’, ‘dim light melatonin onset’, ‘treatment’ and their combinations. We also asked leading chronobiologists to inform us about studies on DLMO in humans, and which were in press in international journals.

## RESULTS

The results of the literature search are summarized in table 1 and 2.

Reason	reference
<b>Diagnosis circadian rhythm sleep disorder</b>	
DLMO is the best characterisation of the 24-h melatonin rhythm, which is strongly associated with the circadian sleep-wake rhythm	(8-13)
Knowledge of DLMO increases the accuracy of the diagnosis of Delayed Sleep Phase Disorder with 32.5% .	(7)
Melatonin treatment before measuring DLMO may delay optimal treatment several months, as it may take several months after stopping melatonin treatment before a steady pre-treatment melatonin rhythm is reached again.	(14;15)
<b>Optimal treatment success.</b>	
Meta-analyses of studies where melatonin was administered at a time related to DLMO showed that sleep in insomnia patients improved considerably, while a meta-analysis of studies where melatonin was administered without knowing DLMO did not show improvement of sleep(3).	(3;16;17)
Exogenous melatonin, administered 5 hours before DLMO maximally phase advances melatonin rhythm and the sleep-wake rhythm which is associated with it. Exogenous melatonin, administered 10 hours after DLMO, delays these rhythms maximally. These effects are dose-dependent.	(18-20;20;21)
More delayed pre-treatment DLMO is associated with stronger advances of sleep onset after melatonin treatment.	(22;23) (20;21)
Knowing DLMO in children with chronic sleep onset insomnia and late DLMO is associated with a 92% treatment success rate.	ESRS congress Lisboa 2010
When patients who respond well on melatonin treatment delay the time of melatonin intake, treatment effect decreases. When they advance the time of melatonin intake treatment effect increases	Oral communication

Table 1. Reasons to measure Dim Light Melatonin Onset (DLMO) before starting melatonin treatment

<b>Prediction of DLMO</b>	<b>Reference</b>
Sleep onset measured with sleep log or polysomnography does not predict DLMO clinically reliable in patients with possible circadian sleep-wake rhythm disorder.	(24) (14)
<b>Clinical reliability of DLMO measurements</b>	
In home situations salivary DLMO can be measured reliably in 76.2% of patients with possible circadian sleep-wake rhythm disorders. In the remaining patients additional measurements reveal DLMO.	(14)
<b>Influences on DLMO</b>	
Beta-blockers, antidepressants and neuroleptcs influence the secretion of melatonin. Their influence on DLMO is unknown	(25-27)
Sleep-wake rhythm	(28-30)

Table 2. Predictive value of measuring Dim Light Melatonin Onset (DLMO), clinical reliability and methods to measure melatonin and exogenous influences on DLMO.

## DISCUSSION

Our literature search showed that DLMO is crucial for optimally diagnosing circadian rhythm sleep disorders and for optimally timing of melatonin treatment, an important pillar of treatment of circadian rhythm sleep disorders.

It is not yet known if knowing DLMO also helps the two other treatment pillars of circadian rhythm sleep disorders i.e. light treatment and strengthening time cues (*zeitgebers*). Light treatment delays or advances circadian and sleep-wake rhythm when administered at night and in the morning respectively. There are several reports showing that light treatment should be given during the increasing or decreasing phase of the melatonin curve, respectively. This suggests that knowing DLMO also might support effectiveness of light treatment.

The first pillar for circadian rhythm sleep wake disorders treatment is strengthening time cues. In patients with extreme DSPD or ASPD time cues might be shifted substantially. Knowing DLMO might help to shift time cues to times, which correspond with the patients' actual biological clock (i.e. melatonin rhythm). After that these time cues can be shifted in the desired direction, eventually supported by bright light or melatonin treatment.

Several comments can be given on the conclusions of our review. The 24-hour melatonin rhythm, of which DLMO is the best characterization, correlates well with sleep-wake rhythm in healthy persons and in patients with well diagnosed circadian rhythm sleep disorders studied in sleep labs. However, it is not known if and to what extent DLMO correlates with sleep-wake rhythm in insomnia patients studied at home.

Knowing DLMO increased accuracy of DSPD diagnosis considerably. However this conclusion is based on outcomes of only one study(7).

According to several studies, measuring DLMO a few weeks after stopping melatonin treatment might influence DLMO. However, more accurate studies are necessary to support this finding and to connect clinical consequences to it.

The meta-analyses showing that melatonin treatment is effective if DLMO is known, were conducted on studies where DLMO was calculated, but in several studies melatonin treatment was given at a fixed time, which was not related to DLMO. Furthermore DLMO was not known in all patients who participated. Nevertheless the treatment effect was quite different from that reported in the meta-analysis of the studies where DLMO was not known

Several clinical studies, performed by independent research groups, support the finding that exogenous melatonin advances sleep most when administered 5 hours before DLMO. The best way to assess to what extent DLMO indeed helps to establish best timing of melatonin treatment is to perform a randomized study in patients with severe DSPS, comparing the effectiveness of melatonin treatment given at a fixed time (i.e. one hour before desired bedtime) to melatonin administered 5 hours before DLMO.

The finding that a delayed pre-treatment DLMO is associated with stronger advances in sleep onset after melatonin treatment has important clinical implications. That is, when a patient with a delayed sleep-wake rhythm and an evident delayed DLMO without other co-morbidity does not respond to adequate treatment, hidden co-morbidity should be looked for. In these patients we often find previously undiagnosed psychiatric co-morbidity, such as adult ADHD or autism.

The remarkably high effectiveness of melatonin treatment in children with sleep onset insomnia and late DLMO should be confirmed in future studies, and in studies with adults. The present review shows that the guidelines of the American Sleep Report should be adapted as to the value of DLMO in diagnosing and treating patients with circadian rhythm sleep disorders. Worldwide Facilitation of DLMO measurements (e.g. [www.melatoninecheck.nl](http://www.melatoninecheck.nl)) will help these patients.

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