

The added value of dim light melatonin onset in diagnosing idiopathic delayed sleep phase disorder

O valor adicional do início da secreção de melatonina no diagnóstico da síndrome de atraso de fase idiopática

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ABSTRACT

Delayed sleep phase disorder (DSPD) is characterized by delayed sleep-wake rhythm and is associated with a delayed melatonin secretion. The diagnosis of DSPD is based on clinical history, supported by actigraphy monitoring and sleep diary. Many sleep disorders present with similar symptoms to DSPD. Consequently, it is frequently misdiagnosed. The time of onset of endogenous melatonin secretion (dim light melatonin onset – DLMO) can be reliably measured in saliva. Therefore, we investigated the potential added value of the DLMO test in diagnosing idiopathic DSPD. A literature search was performed to find relevant articles (search period: all articles published in preselected databases till March 18, 2010). Title and abstract were screened using predetermined inclusion and exclusion criteria. The relevance and validity of the selected articles were critically appraised. The literature search yielded 2,779 articles of which 4 were selected for critical appraisal. One study was considered relevant. This study evaluated the added value of DLMO in combination with polysomnography and sleep diary, but actigraphy was not used. The positive and negative predictive values of the test were both 87.5% and the added value of DLMO above sleep diaries combined with polysomnography was 32.5% in this study. Only one relevant study was found on the added value of DLMO in diagnosing DSPD. Further research on the added value of DLMO to clinical history and actigraphy monitoring is necessary.

Keywords: circadian rhythm; sleep stages; syndrome; sleep disorders, circadian rhythm; melatonin/secretion; polysomnography; sleep/physiology; sleep initiation and maintenance disorders; syndrome/diagnosis.

RESUMO

A síndrome de atraso de fase do sono (SAFS) é caracterizada por atraso do ritmo vigília-sono, associando-se com retardo na secreção de melatonina. O diagnóstico SAFS é baseado na história clínica, tendo como suporte a actigrafia e o diário de sono. Muitos distúrbios de sono apresentam-se com sintomas similares à SAFS. Consequentemente, esse distúrbio é frequentemente diagnosticado de modo errôneo. O tempo de início de secreção da melatonina (TISM) pode ser mensurado com segurança por meio da saliva. Assim, investigamos o potencial valor adicional do teste do TISM para diagnosticar a SAFS idiopática. Uma

pesquisa de literatura foi conduzida em busca de artigos relevantes (período da busca: todos os artigos publicados até 18 de março de 2010 foram pré-selecionados). Título e resumo foram avaliados por meio de critérios de inclusão e exclusão pré-determinados. A relevância e validade dos artigos selecionados foram criticamente avaliadas. A busca retornou 2.779 artigos, dos quais 4 foram selecionados para análise crítica. Apenas um artigo se mostrou relevante. Este estudo avaliou o valor adicional do TISM em combinação com polissonografia e diário de sono, porém sem uso de actigrafia. Os valores preditivos positivo e negativo do teste foram ambos de 87,5% e o valor adicional do TISM além da polissonografia associada ao diário de sono foi de 32,5% neste estudo. Apenas um estudo relevante foi encontrado para o valor adicional do TISM no diagnóstico da SAFS. Mais estudos sobre o valor adicional do TISM à história clínica e actigrafia são necessários.

Palavras-chave: ritmo circadiano; fases do sono; síndrome; transtornos do sono do ritmo circadiano; melatonina/secreção; polissonografia; sono/fisiologia; distúrbios do início e da manutenção do sono; síndrome/diagnóstico.

INTRODUCTION

Delayed sleep phase disorder (DSPD) is a circadian rhythm sleep disorder characterized by a persistent pattern of late sleep onset (often after 2 a.m.) and late awakening times, with an inability to fall asleep and awaken at a desired earlier time. The circadian related sleep disruption leads to insomnia, excessive daytime sleepiness, or both. The sleep disturbance is associated with impaired social or occupational functioning^{1,2}. DSPD typically has an onset in childhood³ or adolescence². This syndrome was first described by Weitzman et al., using the term “delayed sleep phase insomnia”⁴. Afterwards, it was retitled by the International Classification of Sleep Disorders as “circadian rhythm sleep disorder – delayed sleep phase type” and “delayed sleep phase disorder”².

Patients suffer from lack of sleep during daytime, which might result in educational and occupational problems. By

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contrast, on weekends or during holidays, when patients are not obliged to get up on a socially preferred time and they can wake up “late”, they may not have complaints of sleep maintenance or daily-functioning⁵. The prevalence of DSPD varies between 7% in adolescents⁶ and 0.7% in middle aged adults⁷. It is estimated that 10% of insomnia patients visiting a sleep centre suffer from DSPD². Genetic factors, including polymorphisms of clock genes⁸, play an important role in the aetiology of DSPD. Probably, behaviour could also be an aetiological factor (e.g. young adults tend to keep later bedtimes leading to a phase delay in the mornings). Patients with DSPD seem to have a relatively weak ability to reset their circadian systems in response to normal environmental time cues, appearing in a late-to-bed-late-to-arise sleep schedule in weekends or holidays². In addition, one of the physiological hypotheses suggests the influence of melatonin, which could be used as a marker for the timing of human circadian rhythms. Melatonin (5-methoxy N-acetyltryptamine) is secreted primarily by the pineal gland. Its concentration increases rapidly around the onset of darkness to a peak in the middle of the night and afterwards declines near one’s habitual waking time⁹. Besides, light exposure during the night suppresses melatonin. Melatonin acts as a “chronobiotic”, in which exogenous melatonin can both advance or delay circadian timing⁹. In DSPD, patients’ onset of melatonin secretion is delayed, which is associated with delayed sleep times¹⁰.

The time of the onset of endogenous melatonin secretion in dim light, or the dim light melatonin onset (DLMO), is useful to measure the circadian phase. In patients with a delay in circadian phase, DLMO occurs later than in persons without a delay in circadian phase. The DLMO can be easily measured from saliva or serum and therefore seems to be useful for assessing phase delays in patients suspected of DSPD¹⁰.

Diagnostic criteria for DSPD formulated by the The International Classification of Sleep Disorders (ICSD) show mainly subjective criteria:

- a) there is a delay in the phase of the major sleep period in relation to the desired sleep time and wake-up time, as evidenced by a chronic or recurrent complaint of inability to fall asleep at a desired conventional clock time together with the inability to awaken at a desired and socially acceptable time;
- b) when allowed to choose their preferred schedule, patients will exhibit normal sleep quality and duration for age and maintain a delayed, but stable, phase of entrainment to the 24-hour sleep-wake pattern;
- c) sleep log or actigraphy monitoring (including sleep diary) for at least seven days demonstrates a stable delay in the timing of the habitual sleep period;
- d) the disturbance is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

The International Classification of Sleep Disorders 2 (ICSD 2) further mentions in a note that “In addition, a delay in the timing of other circadian rhythms, such as the nadir of the core body temperature rhythm or DLMO, is useful for confirmation of the delayed phase”. According to the ICSD 2, polysomnography is not mandatory to diagnose DSPD. In clinical practice, polysomnography is only performed on a clinical suspicion of other sleep disorders (i.e. sleep apnoea syndrome or narcolepsia).

Many sleep disorders present with similar symptoms as DSPD. For instance, chronic sleep onset insomnia, one of the main characteristics of DSPD, may be caused by bad sleep hygiene and difficulty to wake up in the morning; another main characteristic of DSPD may be due to a mood or anxiety disorder. Treatment of these disorders differs considerably from that of DSPS. An objective measure which can discriminate DSPS from other sleep disorders will prevent misdiagnoses if only self-reports are used for diagnosis^{11,12}.

We hypothesised that DLMO is such an objective measure. Therefore, we performed a literature study to investigate the potential added value of DLMO in diagnosing DSPD in patients suspected for this circadian rhythm sleep disorder. In order to prevent interfering of other co-morbidities (i.e. attention-deficit/hyperactivity disorder (ADHD)^{13,14} and chronic whiplash syndrome¹⁵), we restricted this study to idiopathic DSPD.

RESEARCH METHODS

Definitions

DLMO from saliva is measured at scheduled time points until the patient falls asleep. Melatonin onset could be established at the moment when melatonin level in saliva increases above a designated threshold (i.e. 4 pg/mL) and remains elevated through following sampling^{10,16}. There is no consensus on the absolute threshold of DLMO. Therefore, every protocol should be read precisely.

Search strategy

A systematic literature search of Pubmed, EMBASE and CINAHL was performed on March 18, 2010. No period limitation was set. Consequently, our search included all articles published in these databases till this date. In order to find relevant original articles, various synonyms within the determinant (e.g. DLMO tests) and the outcome (e.g. DSPD) were combined (Table 1). The determinant was defined by the DLMO test and synonyms of melatonin. To minimise reporting and retrieving bias, the domain (i.e. patients suspected for DSPD) was excluded in the search syntax. Determinant and outcome were searched in title and abstract field. For the search in EMBASE, “Medline” was

Table 1. Search syntax*.

Search syntax	Date: March 18, 2010
((Melatonin OR Melatonine OR Melatonins OR Circadin OR Circadine OR Melovine OR Regulin OR "N acetyl 5 methoxytryptamine") AND (Dim OR Bleak OR Blur OR Blurred OR Darken OR Dimmed) AND (Light OR Brightness OR Brilliance OR Illuminate OR Illumination OR Illumine OR Luminance OR Luminousness OR Lightness) AND (Onset OR inception OR oncoming OR outbreak OR start)) OR (DLMO) OR (DLMOs) OR (Melatonin OR Melatonine OR Melatonins OR Circadin OR Circadine OR Melovine OR Regulin OR "N acetyl 5 methoxytryptamine")) AND (((((Delayed AND (sleep OR rest OR repose) AND phase) OR (Circadian AND (rhythm OR cycle OR periodicity)) OR (Circadian AND (sleep OR rest OR repose)) OR (sleep OR rest OR repose) OR ((sleep OR rest OR repose) AND (wake OR awake OR rouse)) OR ((sleep OR rest OR repose) AND (delay OR hold OR impede OR lag AND retard OR setback))) AND (syndrome OR syndrom OR disorder OR condition OR derange OR derangement OR disarrange OR disarrangement OR disease OR disorder OR disorganisation OR disrupt OR distract OR disturb OR disturbance OR illness OR ill OR indisposition OR malady OR malfunction OR type OR case OR form OR insomnia OR sleeplessness OR wakefulness))) OR (((sleep OR rest OR repose) AND (((deprivation OR bereavement AND lack OR loss OR need)) OR ((short OR abrupt OR brief OR deficient OR diminutive OR inadequate OR insufficient OR lacking OR scant OR scarce) AND (duration OR length OR period OR span)))) OR (((insomnia OR restlessness OR sleeplessness OR wakefulness) AND (onset OR start OR outset OR inception))))))	

*Search syntax was adjusted as required to PubMed, Embase or CINAHL.

excluded, to avoid double search in PubMed/MEDLINE. After filtering doubles, title and abstract were screened using predetermined inclusion and exclusion criteria, shown in the flowchart (Figure 1). Inclusion criteria were determinant and outcome mentioned in title and/or abstract, study population: patients with clinical suspicion for DSPD (with or without healthy controls) and melatonin measured from saliva samples. Although melatonin can be both measured from saliva and serum samples, in clinical practice, saliva samples are more easily and more often obtained. Therefore, studies which report serum melatonin only are excluded. Exclusion criteria were non-human studies, non-original studies (to avoid double data), non-diagnostic studies, studies written in languages other than English, Dutch or German and studies on subgroups of DSPD patients, with comorbidity like ADHD.

Full texts of the available articles were studied, using also predetermined inclusion- and exclusion criteria (Figure 1). The references of the articles were studied to identify missing relevant studies not identified by this search strategy.

Critical appraisal

The relevance, size of study population, study design, validity and statistics were critically appraised. Studies were considered as relevant if they investigated the DLMO test in humans suspected for DSPD. With respect to the study design, although studies with a cross-sectional design have limitations, it is possible to compare a new tests with a reference standard in this study design and thus showing the added value of the new test^{17,18}. The optimal design for assessing the accuracy of a diagnostic test is considered to be a prospective blind comparison of the test and the reference test in a consecutive series of patients from a relevant clinical population¹⁹.

The validity of the study contained blinding, standardisation (using protocols), stratification (making patient subgroups), the number of missing data and their transparency.

With respect to the statistical analyses, we would like to calculate the absolute difference between pre- and post-test probability. This indicated the added value of the DLMO test, otherwise defined as the diagnostic benefit of the test. A large difference between pre- and post-test probability suggests a large benefit of the test. In ideal circumstances, the added value showed the difference between patients' history (pre-test probability) and the objective test DLMO (post-test probability), because of the fact that every clinician starts with gaining patients medical history. However, the added value could also be investigated between other diagnostic instruments, i.e. when adding DLMO test to polysomnography or wrist actigraphy.

RESEARCH RESULTS

The literature search (Figure 1) yielded 2,779 articles. After filtering doubles and screening on title and abstract, 21 articles were extracted for full-text analysis. Of the 19 full-text articles available, 6 were relevant, considering the purpose of this study. Unfortunately, two of them investigated DSPD with ADHD as co-morbidity^{13,14} and were excluded from further analyses. The remaining four were selected for critical appraisal (Table 2).

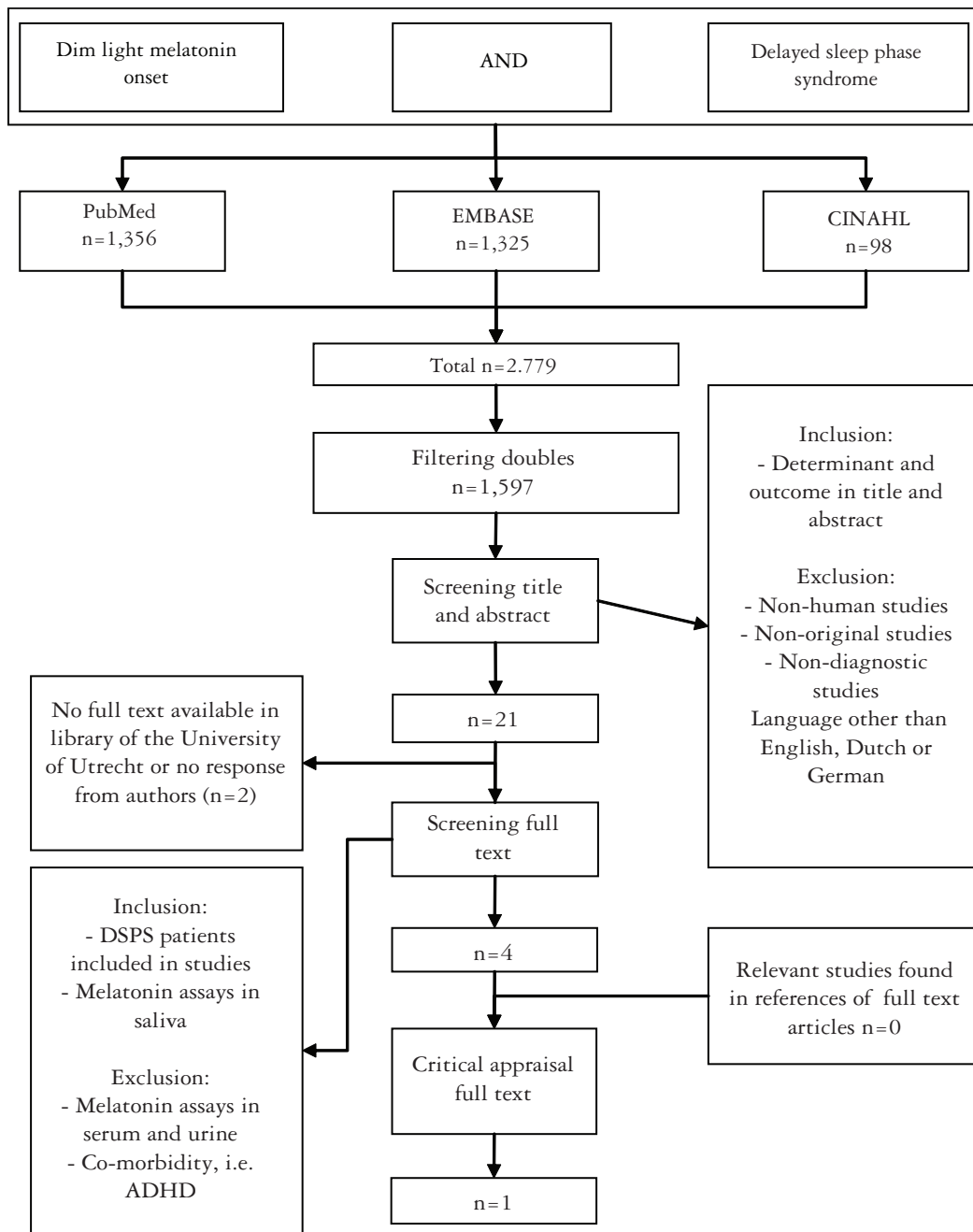
Nagtegaal et al.¹⁶ defined the equivalent salivary DLMO concentration in comparison to the DLMO concentration in blood. They studied the endogenous melatonin production in three patients with DSPD diagnosed on the basis of ICSD criteria. The value for DLMO in saliva was proposed to be 4 pg/mL and in serum 10 pg/mL. Measuring DLMO in saliva was considered as a valid and practical alternative for blood samples.

Wyatt et al. conducted a study to seek out alternative sources of objective data to confirm delayed circadian phase in patients diagnosed with DSPD and to determine the stability, or the lack thereof, of circadian phase in this population²⁰. Eight patients with DSPD were compared

with eight matched controls. Participants wore a wrist actigraph one week prior to the first DLMO assessments, and underwent three DLMO assessments. During these assessments, salivary samples were collected every 30 minutes, beginning 5 hours and 30 minutes prior to and terminating 30 minutes after the preceding mean bedtime. DLMO occurred significantly later in patients with DSPD than in controls ($p=0.006$). Wyatt et al. recommended collection

of saliva samples to assess DLMO as the simplest “gold standard” for verifying circadian phase in patients with suspected DSPD.

Chang et al.²¹ conducted a retrospective case-control study to determine the phase relationship between sleep-wake times and physiological markers of circadian phase (core body temperature and melatonin) in clinic patients with DSPD. Data from sleep diaries, wrist actigraphy, core



ADHD: attention-deficit/hyperactivity disorder.

Figure 1. Flowchart.

Table 2. Critical appraisal.

Article	Relevance			Population	Study design ^e	Validity					Statistics		Level of evidence ^m
	Domain ^a	Determinant ^b	Outcome ^c			Blinding ^f	Standardisation ^g	Stratification ^h	Missing data (n) ⁱ	Transparency of missing data ^j	Possibility to determine absolute difference ^k	Possibility to determine 95% confidence interval ^l	
Rahman et al. ²²	●	●	●	56 vs 0	CS	●	●	○	0	●	●	7/9	
Wyatt et al. ²⁰	●	●	●	8 vs 8	CC	●	●	○	0	●	○	5/9	
Chang et al. ²¹	●	●	●	66 vs 56	CC	●	●	○	105	○	○	4/9	
Nagtegaal et al. ¹⁶	●	●	●	3 vs 0	PS	○	●	n/a	0	●	○	4/9	

^aDomain: ● adults suspected for DSPD, ○ no suspicion; ^bDeterminant: ● DLMO, ○ no DLMO;

^cOutcome: ● DSPD, ○ no DSPD; ^dPopulation: population size in numbers; ^eStudy design – CS: cross sectional, CC: case-control, PS: patient series;

^fBlinding (determinant and outcome): ● yes, ○ no; ^gStandardisation: ● yes, ● moderate, ○ no; ^hStratification: ● yes, ○ no, n/a: not applicable; ⁱMissing data in numbers; ^jTransparency of missing data: ● yes, ○ no; ^kPossibility to determine absolute difference: ● yes, ○ no; ^lPossibility to determine 95% confidence interval: ● yes, ○ no; ^mLevel of evidence: ● 1 point, ● ½ point ○ 0 points; Missing data and transparency counts for one point.

body temperature and melatonin were measured in 66 patients diagnosed with DSPD and 56 healthy controls. Finally, saliva samples were collected in 17 DSPD patients and 31 controls every 30 minutes, beginning 4 hour prior to habitual bedtime until sleep time. In 8 DSPD patients and 31 control participants, blood samples were also required under dim light conditions. A significant phase delay of mean DLMO was seen in the DSPD group ($p < 0.001$). The DLMO was not significantly different between salivary and blood samples. No difference in phase relationship and circadian phase were found between patients and controls, suggesting that when allowed to sleep at their own habitual schedules, patients with DSPD have both normal sleep parameters and circadian phase angle. These results were consistent with Wyatt et al.²⁰

Finally, Rahman et al.²² determined the diagnostic efficacy of DLMO in diagnosing DSPD in a clinical setting by conducting a cross-sectional study on 56 participants symptomatic of DSPD. The two-night sleep study comprised self-report questionnaires, a saliva sample collection for melatonin assay and a polysomnography. On the first night, saliva samples were collected every hour from 1900 hour until 0300 hour, after which the patients retired to sleep. On the second night, an imposed sleep period was created to demonstrate the delay in timing of habitual sleep period and to thereby confirm DSPD. All patients retired to bed at a fixed time (2300 hour) and were awoken the next morning at a fixed time (0700 hour), without collecting sa-

liva samples on the second night. The potency of DLMO to diagnose DSPD was compared to the reference standard (polysomnography). DLMO was significantly delayed in DSPD patients. Based on the presented data, it was possible to calculate the positive and negative predictive value of the test together with pre- and post-test probability (Table 3). Clinical sensitivity and specificity of the test were 90.3 and 84.0%, respectively. The absolute added value of DLMO to polysomnography in diagnosing DSPD in young adults in this study was 32.5%.

Three out of four studies reported a significant phase delay of salivary melatonin secretion onset in DSPD patients compared to controls²⁰⁻²². However, three out of four studies did not correspond to our study purpose completely^{16,20,21}. In these studies, melatonin rhythms and sleep schedule differences in DSPD patients were analysed without investigating a potential added value of the DLMO test to other diagnostic instruments^{20,21} or only a comparison of melatonin concentrations in saliva and serum was made¹⁶.

Therefore, the study of Rahman et al.²² was the only one investigating the potential added value of the timing of DLMO. This study suggested an added value of 32.5% of DLMO test to polysomnography.

DISCUSSION

The strength of our study is its structured review strategy and critical appraisal. However, several limitations should be mentioned. First, only one appropriate publication was

Table 3. Results of Rahman et al.²².

	Polysomnography positive	Polysomnography negative
DLMO positive	a (true positive)=28 patients	b (false positive)=4 patients
DLMO negative	c (false negative)=3 patients	d (true negative)=21 patients
Accuracy measure of the dim light melatonin onset test (DLMO)		Confidence interval of 95% (%)
Positive predictive value ^a (%)	87.5	79-96
Negative predictive value ^b (%)	87.5	79-96
Pre-test probability ^c (%)	55.0	42-68
Post-test probability ^d (%)	87.5	79-96
Added value ^e (%)	32.5	

^aPositive predictive value: $a/(a+b)$; ^bNegative predictive value: $d/(c+d)$; ^cPre-test probability: prevalence = $a+c/(a+b+c+d)$; ^dPost-test probability: positive predictive value = $a/(a+b)$; ^eAdded value of DLMO test: post-test probability – pre-test probability.

available. This could be explained by the fact that the presented subject is hardly examined or that negative outcomes were not published. Furthermore, this remaining study²² calculated the added value of DLMO to polysomnography as a reference test. In clinical practice, polysomnography is hardly used to diagnose DSPD, and is also not recommended by the ICSD 2. Also, the lack of outcome blinding and the small number of patients in this article could lead to information bias.

Moreover, DLMO describes the moment of melatonin increase, but it is still unclear how far DLMO is delayed in DSPD patients compared to controls. Finally, in the literature, there is no cut-off point determined above which an added value is sufficient. It is possible to analyze test characteristics of a diagnostic test in a cross-sectional design, after which a multivariate regression analyses should be performed to evaluate other risk factors, such as age, gender and comorbidity. Cost-effectiveness and clinical outcome in terms of co-morbidity should also be investigated^{17,18}.

CONCLUSION

Nevertheless, our study suggests a clinically relevant added value of DLMO above sleep diary and polysomnography in diagnosing DSPD. More studies, including cross-sectional studies comparing DLMO to clinical history, sleep diary and actigraphy results (the current clinical practice and recommendation of the ICSD 2) in a larger study population, with multivariate regression and cost-effectiveness analyses, will strengthen its clinical application.

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