The evolving role of quantitative actigraphy in clinical sleep medicine

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Title: The Evolving Role of Quantitative Actigraphy in Clinical Sleep Medicine

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Summary

Actigraphy has a consolidated role in Insomnia and Circadian Rhythm Sleep-Wake Disorders (CRSWD) and recent studies have highlighted the use of actigraphy for narcolepsy and REM sleep behaviour disorder (RBD). This review aims at summarizing the results of studies published over the last decade regarding the use of actigraphy. Thirthy-five studies proved eligible, and results were analysed separately for insomnia, narcolepsy and RBD. Actigraphy showed to consistently differentiate insomnia patients from healthy controls. Furthermore, the application of advanced analytical techniques has been shown to provide both unique insights into the physiology of insomnia and sleep misperception and to improve the specificity of actigraphy in detecting wakefulness within sleep periods. Regarding narcolepsy, several studies showed that actigraphy can detect peculiar sleep/wake disruption and the effects of pharmacological treatments. Finally, although the number of studies in RBD patients is still limited, the available evidence indicates a reduced amplitude of the activity pattern, sleep-wake rhythm dysregulation and daytime sleepiness. Therefore, the potential use of these markers as predictors of phenoconversion should be further explored. In conclusion, quantitative actigraphy presents a renewed interest when considering the possibility of using actigraphy in clinical sleep medicine to diagnose, monitor, and follow sleep disorders other than CRSWD.

Keywords

Actigraphy, Insomnia, Narcolepsy, REM sleep behaviour disorder, Rest-Activity Rhythm, Motor Activity, Psychopharmacology

Abbreviations

AC – Acute insomnia

AASM – American Association of Sleep Medicine

CBT-I — Cognitive behavioural therapy for insomnia

EDS – Excessive daytime sleepiness

FLM — Functional linear modelling

HC – Healthy controls

ICSD-3 — International Classification of Sleep Disorders 3rd Edition

ID – Insomnia disorder

IH - Idiopathic hypersomnia

IS - Interdaily stability

IV- Intradaily variability

iRBD – Isolated REM sleep behaviour disorder

I<O - Activity in-bed versus out-of-bed

L5 – Least active 5 hours

M10 – Most active 10 hours

NapD — Nap duration

NT1 – Narcolepsy type 1

NAWK – Number of awakenings

OSA – Obstructive Sleep Apnoea

PI – Primary insomnia

PSG –Polysomnography

PTSD – Post-traumatic stress disorder

PSQI – Pittsburgh Sleep Quality Index

RA – Relative amplitude

REM – Rapid eye movement

RLS – Restless leg syndrome

SE — Sleep efficiency

SOL – Sleep onset latency

SMA — Sleep motor activity

TIB — Time in bed

TST —Total sleep time

TWT — Total wake time

WASO — Wake after sleep onset

FI — Fragmentation index

CSWRD — Circadian sleep-wake rhythm disorders

Introduction

Actigraphy is a non-invasive method that allows to evaluate sleep quality and duration through movement assessment. The estimation of parameters reflecting sleep quality (sleep efficiency, sleep latency, wakefulness after sleep onset, number of awakenings, and sleep motor activity) and duration (total sleep time) derives from the application of scoring algorithms to raw motor activity data. Actigraphy has been long used to study nocturnal sleep and circadian rest/activity rhythm in both healthy subjects and patients with sleep disorders [1,2]. Actigraphy presents the key advantage of providing objective information on subjects' sleep schedules in their natural environment for several consecutive nights, thus allowing an ecological quantification of habitual sleep duration and overall sleep quality [1–4].

The current International Classification of Sleep Disorders – 3rd Edition (ICSD-3) recognizes a diagnostic role of actigraphy in circadian sleep-wake rhythm disorders (CSWRD) and in idiopathic hypersomnia (IH). CSWRD can be reliably identified with actigraphy due to its excellent ability in documenting irregularities or misalignment of sleep-wake rhythms. Furthermore, the actigraphic documentation of more than 660 min of total sleep time across 24 hours is a diagnostic criterion for IH [1,2,4–8]. Consistently, several studies have highlighted novel applications of actigraphy in clinical sleep medicine in the recent past [9–17]. Actigraphy can be used for the differential diagnosis of insomnia disorder, in the diagnostic work-up of patients with central disorders of hypersomnolence, and, possibly, in the screening of rapid eye movement (REM) sleep parasomnias (in particular isolated REM sleep behaviour disorder - iRBD) [2–4,6,18–21].

Considering the growing body of scientific literature on actigraphy in various sleep disorders and its increasing use in the clinical practice of sleep medicine centres, this review aimed at updating the current knowledge on the clinical use of actigraphy in sleep medicine by providing a critical overview of studies published over the last ten years. For a systematic revision of previous studies, the reader can refer to the review by Sadeh in [1].

This review considered specifically studies that used quantitative actigraphy in insomnia disorder, narcolepsy, and RBD since growing evidence has highlighted a possible role of this technique in the diagnostic work-up and/or in the follow-up [9–17]. Other parasomnias and central disorders of hypersomnolence have not been considered due to the extreme rarity of studies. CRSWDs were not considered as a general consensus has already been reached on the role of actigraphy in these disorders, and literature on quantitative actigraphy has been recently reviewed by an expert task force commissioned by the American Academy of Sleep Medicine [2]. Similarly, a consensus has been reached on the role of actigraphy in IH and only one study reported quantitative actigraphy in this disorder. Thus IH was not considered in this review [9,22].

Finally, bearing in mind the clinical point of view of this review, clinical case boxes showing the typical actigraphic profile for each sleep disorder under investigation (i.e., insomnia, narcolepsy and iRBD, Figure 1 to 5) were included, as well an actigraphic profile of healthy control (Figure 6). These clinical boxes are provided to help the readers interpret a patient's actogram by identifying the main actigraphic features of these sleep disorders.

Methods

A systematic search of electronic databases for articles published in peer-reviewed journals over the last decade was performed, starting on 1st January 2010 and ending on 1st January 2020. Literature search was performed in accordance with the PRISMA® (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Supplementary materials). Studies that compared the sleep/wake profile of patients with insomnia, narcolepsy and iRBD to that of controls and/or other patients with sleep or psychiatric disorders were exclusively considered. Studies regarding the assessment of treatment effects through actigraphy in patients with insomnia were also considered.

The following databases have been used to search for relevant keywords: PubMed, Web of Science and Scopus. Regarding the search terms for actigraphy, the following keywords were used: *actigraph, actimetry, accelerometer, and motor activity.* Regarding the specific sleep disorders under investigation, the following terms for insomnia were used: *insomnia, insomnia disorder, chronic insomnia, misperception, psychophysiological insomnia, and primary insomnia.* As for narcolepsy, the following keywords were used: *narcolepsy, narcolepsy type 1, narcolepsy with cataplexy, and narcolepsy cataplexy.* With reference to iRBD, the search terms used were *rapid eye movement sleep behaviour disorder, idiopathic REM sleep behaviour disorder, isolated REM sleep behaviour disorder, RBD, and iRBD.* Finally, on the subject of insomnia interventions, the following keywords were used: *CBT-I, cognitive behavioural therapy, behavioural therapy, treatment, psychoeducation, sleep restriction, mindfulness, alternative therapy, drugs, natural treatment,* and *natural supplements*. These methods aim at providing a comprehensive overview of the actigraphic measure most used as a primary or secondary outcome measure in pharmacological and non-pharmacological studies on insomnia.

Excluded from consideration were non-English articles, book chapters, monographs, thesis dissertations, abstracts, and non-peer-reviewed material. The literature search yielded 594 studies (532 for Insomnia, 47 for Narcolepsy and 15 for iRBD) among which 35 fulfilled the criteria for full-text review (24 for Insomnia, 7 for Narcolepsy and 4 for iRBD). Regarding Insomnia three studies were excluded as they reported on a replicated sample. For Narcolepsy two studies were excluded: one reported only on physical activity levels without reporting sleep or circadian rhythm measures,

and one did not include a control group. Similarly, with reference to iRBD, one study was excluded as it did not include a control group. The flow diagram of study selection is reported in Figure 1. Detailed information for each study is reported in Table 1. A description of the actigraphic measures considered across studies is reported in Table 2. Detailed information for studies on cognitive and behavioural interventions and on alternative therapies for insomnia using actigraphy are shown in Table 3 and Table 4, respectively. Clinical boxes showing the typical actigraphic profile of insomnia, narcolepsy and iRBD patients, as well as a healthy control are described in Figures 1 to 6. Finally, a basic description of actigraphy and of the sleep and circadian measures it quantifies is reported in the "Actigraphy" box.

Actigraphy Box

Actigraphy is a methodology based on small watch-like portable devices that collect movement information for extended periods. An actigraph typically consists of a triaxial accelerometer that quantifies movement exceeding a predetermined amount of *g*, a photodiode that quantifies light exposure, a case temperature sensor to identify periods of device removal and an "event-marker" button that the subjects can press to mark a range of events (e.g., the period in and out of bed, diurnal naps, drug intake). Actigraphs are usually worn around the non-dominant wrist and are particularly useful for ecological monitoring of sleep-wake patterns and rest-activity cycles. Measurements of sleep quality and duration are estimated by applying validated scoring algorithms to movement data. The ability to monitor subjects in their natural environment is the key advantage of actigraphy over PSG, however since actigraphy does not measure sleep stages as defined by EEG or EOG, and EMG channels, is both unable to identify sleep stages and is less reliable in identifying sleep disorders needing a complete EEG-EOG-EMG monitoring.

Actigraphy variables can be divided into three broad macro-categories: measures of sleep timing, measures of sleep quality/continuity and circadian rhythm measures.

Sleep Timing

Actigraphy provides the following objective measures of the timing and duration of the major nocturnal rest period: bedtime, get-up time, the midpoint of sleep and time in bed. These measures do not derive from the application of scoring algorithms to movement data and therefore can be calculated independently of the specific type of actigraph used. However, for the correct identification of the main nocturnal rest period, it is mandatory that the subjects adequately complete the sleep diary and/or the event-marker procedure.

Sleep Quality/Continuity

Actigraphic measures of sleep quality and continuity are obtained by applying scoring algorithms to activity data. The algorithms are device dependent, and, within the same device, their performance is influenced by specific actigraph setting parameters (i.e., sleep-wake activity threshold).

Actigraphic measures of sleep quality/continuity include total sleep time, sleep efficiency, sleep onset latency, wakefulness after sleep onset, number of awakenings, duration of the longest continuous sleep episode and sleep motor activity. Sleep motor activity is not affected by the scoring algorithm but is expressed in arbitrary, device-specific, units.

Circadian rhythm measures
Actigraphy allows quantifying different features of the circadian rest-activity rhythm. Circadian measures are labelled parametric when they result from the adjustment of a cosine function to the rest-activity rhythm. The COSINOR is typically a parametric method: it applies a mathematical model that fits the data to a cosine curve, and this allows the extraction of information such as acrophase, MESOR, period and amplitude. Circadian measures unrelated to the above approach are labelled non-parametric and provide information on rhythm fragmentation (IV), day-to-day similarity of activity patterns (IS), relative amplitude of rest-activity rhythm (RA), least active hours (L5) and most active hours (M10) of the day.

Results

1. Insomnia

Twenty-four studies analysed actigraphic-estimated sleep measures, circadian measures, motor activity profile and night-time motor activity features of patients with insomnia. Collectively these studies analysed 1105 insomnia patients when compared with 1066 healthy controls (HC), 14 subjects with bipolar disorder and 45 subjects with post-traumatic stress disorder (PTSD) and concomitant sleep problems.

1.1.Comparison studies

Several studies used actigraphy to differentiate patients with insomnia from good sleepers. Rajna and colleagues showed that actigraphic measures of sleep onset latency (SOL), sleep efficiency (SE) and fragmentation index (FI) allow to effectively differentiate patients with primary insomnia (PI) from HC but not to differentiate the latter from 'bad sleepers' [23]. The study from Levenson et al. used a quantitative approach to delineate the optimal thresholds for actigraphic and sleep diary measures in differentiating older adults with insomnia from good sleepers [24]. The authors showed that sleep diary measures discriminate insomniacs from good sleepers more effectively than actigraphic measures as reflected by a wider area under the curve. [24]. Holloway and colleagues evaluated whether an analysis of nocturnal motor activity complexity (assessed through detrended fluctuation analysis) was able to differentiate patients with acute insomnia (AC) from HC. Patients with AC show higher complexity of nocturnal motor activity organization than HC, likely due to a higher frequency of night-time arousals which is a hallmark of insomnia pathology [11].

Fossion and colleagues analysed the time-series of motor activity data of young adults with AC and HC reporting a slight delay of circadian phase and increased day-to-day variability of motor activity acrophase and amplitude when compared to controls [10]. Only two studies reported that quantitative actigraphic measures were unable to differentiate insomnia disorder (ID) patients from controls [25,26]. The study from Bottary and colleagues showed that SOL but not SE, TST or WASO was able to differentiate ID patients from controls [25]. However, in this study, only nights with SE >

50% and/or with SE at a minimum of 20% of the subjectively reported SE (sleep diary) were included in the analysis. Conversely, the study from Devine and colleagues showed that TST is reduced in a small sample of male ID patients when compared to controls but did not find differences in SOL, SE and WASO [26].

In this regard, it is important to highlight that the study by Natale and colleagues showed that the quantitative actigraphic criteria capable of differentiating insomniacs from normal sleepers are strongly linked to the specific type of actigraphic device adopted, suggesting the need for shared technical solutions for actigraphy [27].

Several studies used actigraphy to confirm and extend the information collected through a sleep diary. Jang and colleagues have used actigraphy in conjunction with sleep diaries to analyse naps in patients with ID and HC [28]. ID patients showed higher nap frequency than HC, and additionally, the napping frequency was associated with poorer subjective sleep quality (assessed through the Pittsburgh Sleep Quality Index, PSQI) [28]. Winckelman and colleagues used actigraphy to confirm diary information [29]. The authors reported no objective differences between controls and insomnia patients in actigraphic measures of sleep duration (TST) and quality (SE, WASO and NWAK) [29]. Similar results are conveyed in the study by Seo and colleagues, which reported no differences in actigraphic and sleep diaries measures between ID and HC [30]. Drummond and colleagues, in a neuroimaging study aimed at examining the neural correlates of working memory in patients with primary insomnia and HC, used actigraphy, sleep diary, and polysomnography (PSG) to assess sleep duration and quality [31]. All actigraphy variables considered (i.e., TIB, TST, SOL, WASO, SE) showed significant differences between PI patients and controls with patients exhibiting lower TIB, TST and SE and longer SOL than controls [31]. However, despite all variables being in the clinical range, actigraphic sleep measures were not as impaired as diary-measured sleep in PI patients [31].

Sleep misperception is frequent in individuals with insomnia and a handful of studies used actigraphy to gain insight into this phenomenon. Te Lindert and colleagues used actigraphy to evaluate sleep-state misperception in a large cohort of ID patients and HC [13]. The authors applied latent class analysis and revealed three subtypes that markedly differed in misperception features. Kay and colleagues used actigraphy and a sleep diary to evaluate night-to-night variability in older adults with insomnia and HC [32]. The authors reported a higher night-to-night variability in sleep discrepancy (i.e., the discrepancy between SOL and WASO assessed with a sleep diary and actigraphy) in older adults with insomnia when compared to controls. Veeramachaneni and colleagues examined the association between subjective and objective measures of intraindividual variability in sleep and perceived stress among young adults with and without insomnia [33]. Intraindividual variability characterizes night-to-night, within-person fluctuations in sleep and has been suggested as an

important marker of physical and mental health. The authors showed that greater intraindividual variability in actigraphically measured TST was independently associated with greater perceived stress, while insomnia status was not associated with any of the objective sleep parameters [33].

Overall, one of the key issues of actigraphy is the low specificity in detecting wakefulness within sleep periods. Along these lines, a recent study established markers for nocturnal awakenings in AC derived only from wrist actigraphy. The authors adopted a machine-learning approach by training the models using data from 24 healthy sleepers and 21 subjects with AC and developed a two-level model for AC which showed good accuracy (84%), sensitivity (76%), and specificity (92%) [34]. Te Lindert and colleagues performed a study to define the optimal actigraphic setting configuration to improve the accuracy of actigraphic estimates of sleep onset and wakefulness in patients with ID [12]. The authors showed that sleep-wake discrimination and sleep onset estimation are overall worse in patients with ID than in HC. However, an algorithm that considers a minimum of 5 minutes of immobility period duration, with a sensitivity threshold of 40 (arbitrary unit) for sleep onset estimation, obtained optimal results in ID patients and a minimal loss of accuracy in HC [12]. Marino et al. compared the performance of actigraphy in identifying sleep and wake compared to PSG. With the aim of identifying both sleep and wake, sensitivity and accuracy were high, whereas specificity was low in actigraphy relative to PSG [4]. Troxel and colleagues examined whether social support could represent a protective factor for sleep quality in older adults with insomnia and age- and sex-matched controls. The authors showed that higher levels of social support were associated with shorter actigraphic-assessed WASO in both individuals with insomnia and controls, highlighting the importance of evaluating WASO in older insomnia patients [35]. Floam and colleagues investigated the extent to which sleep characteristics, assessed through actigraphy and sleep diary, could predict inflammatory, hypothalamic–pituitary–adrenal and autonomic systems markers [36]. The authors showed that in patients with insomnia disorder, cortisol is upregulated and significantly associated with actigraphy- and diary-estimated WASO [36]. This result is consistent with those of earlier studies which showed that insomnia patients are more likely to overestimate WASO and underestimate TST and SE in their sleep diaries when compared to actigraphic measures [1]. the actigraphic measure of nocturnal awakening frequency (NAWK) was reported only in three out of twenty-four studies on insomnia and was shown to differentiate patients from controls in only one study [26,27,29]. Kang and colleagues compared a commercial actigraph device (Fitbit Flex device) with PSG. TST and SE were overestimated in actigraphy in both insomnia and HC but the frequency of acceptable agreement between actigraphy and PSG was significantly lower for the insomniac than for good-sleepers (39.4% vs 82.4% respectively) [37]. Similarly, Carter and colleagues compared actigraphy and PSG in patients with chronic insomnia and HC to evaluate the association between

insomnia and hypertension [38]. In-laboratory PSG assessments of sleep duration and quality were not different between groups. In contrast, 2-week at-home actigraphy revealed that participants with insomnia had lower TST, SE, and higher WASO than controls [38].

Cosgrave et colleagues developed a model that included an interaction between PSQI and actigraphically-estimated TST to predict the risk for psychotic experiences. The authors showed that if sleep quality is perceived as poor but objectively of substantial length (above 7.5 h), the risk of psychotic-like experiences is negligible while with decreasing hours of objective sleep, this risk increases progressively [39]. St-Amand and colleagues reported that individuals with bipolar disorder showed no differences in sleep quality and duration when compared to HC but differed from individuals with insomnia on most subjective parameters measured with a sleep diary [40]. However, differences on actigraphic data were less marked between bipolar patients and individuals with insomnia, with patients with insomnia showing lower SE than bipolar patients [40]. Finally, Straus and colleagues used both actigraphy and subjective measures to characterize sleep in veterans with PTSD and reported worse sleep efficiency in PTSD patients than in PI patients [41]. These three articles were included in this review since there was also a comparison between insomnia patients and HC. However, the use of actigraphy on mental health disorders was not the goal of this clinical review. Nevertheless, the following recent review can be considered to further explore this topic [42].

1.2. Actigraphic assessment of drug-intervention

Twenty-nine studies explored the role of actigraphy in documenting treatment effects in patients with insomnia. Nineteen studies used actigraphy to assess the effects of cognitive and behavioural intervention (CBT-I, sleep restriction, mindfulness, psychoeducational/sleep programs) (Table 3), while ten studies focused on alternative therapies for insomnia (pharmacological interventions, cognitive training, transcranial magnetic stimulation, acupuncture, and naturals products) (Table 4). Collectively these studies analysed 2.243 patients. It is beyond the scope of this review to cover all comparison studies in this area, but we want to illustrate a panoramic concerning two main points: the use of actigraphy as a primary or secondary outcome measure, and the main actigraphic measures considered for the assessment of intervention effects. Both insomnia interventions (i.e., cognitive, and behavioural interventions and alternative therapies) used actigraphy as a primary or secondary outcome equally. Specifically, eight articles used actigraphy as the primary outcome [43–50], while ten studies used actigraphic measures as a secondary outcome [51–60]. Only one study used the SE variable as a primary outcome while most of the actigraphy variables were used as a secondary outcome (SOL, WASO, TST) [61]. Concerning alternative therapies, of ten studies, five used actigraphy as a secondary outcome [62–67].

With respect to actigraphy measures, regardless of the type of therapy, almost all of the studies (27/32) used actigraphy to measure TST [43–45,47–61,63–70], followed by SE (25/32) [43,46–59,61,63–68,70,71], WASO (20/32) [43,45,47–56,58,61–65,67,68,70] and SOL (18/32) [43,45,57,58,61,63,64,67,68,70,71,47,49–54,56]. In contrast, only five studies focused on actigraphy measures on NAWK [48,53,62,64], while total wake time (TWT) (consisting of SOL + WASO) was reported in three studies [43,44,59]. Overall, despite the poor performance in detecting motionless wakefulness, actigraphy is widely used to detect the effects of treatments in patients with insomnia as it represents a more reliable approach when compared to questionnaires and sleep logs and it is a more ecological approach when compared to PSG.

1.3. Summary

Taken together, these results suggest that actigraphy is a reliable method for assessing the three intrinsic features of insomnia namely, difficulty falling asleep, reduced SE and an increase in time spent awake at night. Some studies have not reported significant differences in SE and WASO between insomnia patients and HC, which is probably due both to how these variables were calculated (Bottary and colleagues considered only nights with SE > 50% and/or with SE at a minimum of 20% of the subjectively reported SE [25]) and to specific characteristics of the sample under examination (Devine and colleagues analysed a small sample composed exclusively of male patients [26]). Therefore, actigraphy would appear to be a useful tool to differentiate patients from HC with a good degree of accuracy. Furthermore, machine learning techniques have shown promising results in improving the ability of actigraphy to accurately detect WASO and identify misperception index with a good degree of certainty [34]. One of the main open questions remains the discrepancy, highlighted in some studies, between sleep diary and actigraphy in quantifying TST, SOL, and WASO. If one considers studies evaluating the effect of pharmacological or non-pharmacological interventions, actigraphy can represent a useful tool to monitor treatment effects, particularly when TST represents the primary outcome. Finally, the few studies that reported on nocturnal awakening frequency (NAWK) provided conflicting results precluding thus the possibility to draw a definitive conclusion about the usefulness of this measure in identifying patients with insomnia.

2. Narcolepsy

Seven studies have analysed actigraphic sleep measures and circadian motor activity profiles of narcolepsy type 1 (NT1) patients. Collectively these studies analysed a total of 309 NT1 patients compared to 64 HC, 24 IH and 13 PI patients.

2.1 Comparison studies

Three studies compared NT1 patients to HC and patients suffering from IH or PI. Filardi and colleagues compared adult drug-naïve NT1 patients to age- and sex-matched controls and IH patients [9]. The authors considered both night-time and daytime actigraphic-estimated sleep measures as well as diurnal motor activity intensity.

NT1 patients display a severe nocturnal sleep disruption, exhibiting reduced TST and SE, increased WASO, NWAK and sleep motor activity when compared to controls and IH patients, with the latter showing no significant differences when compared to controls apart from an increase in NWAK frequency. Concerning diurnal actigraphic measures, both NT1 and IH display increasing occurrence of diurnal sleep episodes and overall reduced motor activity when compared to controls although with a different degree of diurnal impairment between NT1 and IH (NT1 exhibit more frequent naps with the longest mean duration and lower motor activity than IH). Finally, the authors developed a discriminant function that, by combining actigraphic night-time (sleep motor activity and NWAK frequency) and daytime measures (mean nap duration), showed good accuracy in identifying NT1 cases (87% correctly classified) and could therefore prove to be useful in the diagnostic workup.

Leger and colleagues compared adult NT1 patients under stable pharmacological treatment to controls and treated primary insomnia patients [72]. Similarly to the study of Filardi and colleagues, the authors computed night-time and daytime measures as well as nonparametric actigraphic measures [9]. Treated NT1 show poorer nocturnal sleep quality and increased duration of naps when compared to controls while no difference emerged with treated primary insomnia patients. However, differently from the study by Filardi and colleagues, the authors showed that the fragmentation index is more reliable in identifying NT1 with respect to HC and PI patients.

In a subsequent study, Filardi and colleagues compared circadian motor activity profile and actigraphic-estimated sleep measures of NT1 children and adolescents versus HC children [73]. The authors considered both night-time and daytime actigraphic measures as well as measures of sleep timing. The features of circadian motor activity patterns were investigated through functional data analysis applied to the raw time series of motor activity [74].

Similarly, to adult patients, NT1 children and adolescents display a remarkable nocturnal sleep fragmentation coupled with numerous naps during daytime when compared to control children. Moreover, NT1 children show an altered motor activity profile compared to controls: despite exhibiting a comparable timing of sleep phase NT1, children show increased representation of motor events throughout night-time and blunted motor activity levels in the afternoon in correspondence to the postprandial period.

2.2 Within NT1 comparisons

Four studies investigated the sleep/wake profile of NT1 patients with respect to clinical features and physical activity engagement.

Alakuijala and colleagues analysed actigraphic profile of H1N1-vaccine-related narcolepsy patients compared to sporadic narcolepsy patients [75]. The authors have considered night-time sleep measures, applied cosinor analysis (a parametric method that applies a mathematical model based on the least squares method to fit a sine wave to time series data) to calculate the acrophase of rest-activity rhythm and computed the nonparametric variables L5 onset (the least active 5-hour onset time), M10 onset (the most active 10-hour onset time), and interdaily stability (IS). H1N1-vaccine-related and sporadic narcolepsy patients exhibit reduced sleep quality. No differences emerged in actigraphic-estimated sleep measures and nonparametric variables although sporadic narcolepsy patients reveal a slightly delayed rest-activity rhythm (delayed cosine peak).

In a subsequent study, Alakuijala and colleagues compared actigraphic profiles of NT1 patients with different hypocretin levels (namely hypocretin-1 below and above 30 pg/mL) [14]. NT1 patients with extremely low hypocretin-1 levels present significantly more fragmented sleep than patients with hypocretin-1 levels higher than 30 pg/mL. Although both groups reveal low sleep quality, no group differences emerged in actigraphic night-time measures (TST and SE%), or in circadian measures of rest-activity rhythm (cosine peak and interdaily stability - IS).

Filardi and colleagues assessed the actigraphic profile of NT1 patients with respect to their engagement in physical/sports activity [76]. NT1 children and adolescents were classified as engaged in a regular physical activity schedule if they performed any type of sport/exercise twice a week for at least 60 min. The authors considered night-time and daytime actigraphic-estimated sleep measures and diurnal motor activity intensity. NT1 patients performing regular physical activity showed higher sleep quality (higher SE, lower WASO and sleep motor activity - SMA) and longer sleep duration than physically inactive patients. Moreover, physically active patients took fewer naps, spent less time asleep throughout daytime and exhibited higher high-density lipoprotein and lower triglycerides levels than patients not performing physical/sports activities.

2.3 Actigraphic assessment of drug intervention

Only one study investigated whether actigraphy could be used to evaluate the effects of pharmacological treatment in NT1. Filardi and colleagues assessed changes in sleep/wake profile associated with treatment with Sodium Oxybate in NT1 children and adolescents [77]. Drug-naïve NT1 children were monitored during the regular school week at the time of diagnosis and after one year of stable pharmacological treatment. The authors have considered both night-time and daytime

sleep measures and carried out a nap analysis. Actigraphy documented an improvement in nocturnal sleep duration, quality (increased sleep efficiency) and continuity (duration of longest uninterrupted sleep episode) coupled with a reduction of diurnal total sleep time after one year of stable Sodium Oxybate treatment. Noticeably, Sodium Oxybate treatment was associated with an overall reduction in nap frequency (particularly marked for evening naps) and a reduction in afternoon nap duration.

2.4. Summary

NT1 patients show an actigraphic profile characterized by both nocturnal sleep and diurnal wake impairment. All studies analysing NT1 patients showed a marked impairment of sleep quality (increased WASO and awakening frequency, reduced duration of longest uninterrupted sleep episode) and sleep duration (reduced TST); moreover, an overrepresentation of motor events during sleep was evident. Concurrently all studies showed frequent and prolonged diurnal naps as well as fragmented daytime vigilance. A reduced level of diurnal motor activity was also documented particularly during early afternoon hours. No differences emerged in actigraphic measures of sleep timing, as circadian sleep-wake rhythm appeared preserved in those patients. More recently, Filardi et al. have shown that treatment with Sodium Oxybate improves actigraphic nocturnal measures of sleep quality and duration, and reduces nap frequency and mean duration, without affecting diurnal motor activity levels.

3. REM sleep behaviour disorder

Only four studies evaluated the actigraphic profile of patients with iRBD; however, all studies presented different research aims and study procedures. The study by Feng and colleagues report on two separate investigations (a case-control and a prospective study), thus results are reported and discussed separately [15].

3.1. Comparison studies

Stefani and colleagues compared patients with iRBD to HC and two groups of sleep disorder patients (i.e., restless leg syndrome – RLS – and untreated obstructive sleep apnoea – OSA) [78]. The authors considered exclusively measures related to nocturnal motor activity intensity, the duration of the major nocturnal rest period (i.e., TIB) and brief (i.e. < 1min.) awakening frequency. The actograms of all subjects were visually classified by experts in sleep medicine, blind to clinical diagnosis, as “no RBD”, “possible RBD” or “probable RBD” [78]. iRBD patients presented increased night-time motor activity when compared to controls, but no differences when compared to the other groups of patients affected by RLS or OSA. Considering nocturnal sleep duration and brief awakening frequency, no

differences were evident among all four groups of subjects (iRBD vs OSA vs RLS vs HC). Notably, the visual analysis of nocturnal motor activity performed by sleep medicine experts showed high sensitivity and specificity in identifying iRBD patients, thus highlighting the possibility of using actigraphy to screen RBD.

Liguori and colleagues compared iRBD patients to HC and documented a sleep-wake rhythm dysregulation in iRBD patients. Patients showed particularly impairment of nocturnal sleep quality, reduced diurnal motor activity levels, and a slight alteration of circadian rest-activity rhythm [16]., iRBD patients specifically showed lower SE, longer TIB and SOL than HC. Furthermore, patients with iRBD presented a reduction in motor activity during daytime hours (M10) and an increase in motor activity during night-time hours (L5) [16].

Similarly to the previous study, an analysis of the circadian sleep-wake rhythm was performed by Filardi and colleagues in a study comparing iRBD patients to RLS, untreated OSA patients and HC [17]. In this study, the authors have considered night-time and daytime sleep parameters and non-parametric circadian measures (IS, interdaily stability; IV, intradaily variability; RA, Relative amplitude; and the dichotomy index I<O). iRBD patients exhibited lower SE, higher WASO, and higher frequency of prolonged motor activity bouts during the night compared to RLS patients and HC, while no difference emerged with OSA patients [17]. Moreover, iRBD patients had a higher frequency of diurnal naps compared to RLS, OSA and HC; conversely, mean nap duration was similar among groups. No differences were observed in the non-parametric measures commonly used to characterize rest-activity rhythm (IS, IV and RA) but, similarly to the study by Liguori and colleagues [16], a non-parametric 24-h measure (I<O) reflecting both diurnal motor hypoactivity and nocturnal motor hyperactivity was able to successfully distinguish iRBD patients from RLS patients, OSA subjects and HC.

Finally, Feng and colleagues performed an actigraphy-based study comparing iRBD patients to patients with RBD and clinically diagnosed α-synucleinopathies, and non-RBD controls (i.e., patients with obstructive sleep apnoea syndrome and periodic limb movement disorder) [15]. The authors considered night-time and daytime sleep parameters and non-parametric circadian measures (IS, IV, L5, and M10). In addition, differences in circadian motor activity patterns were investigated through functional linear modelling (FLM). No differences emerged between iRBD patients and non-RBD controls in nocturnal sleep quality (SE, WASO, wake bouts and fragmentation index), sleep duration (TIB), and in measures reflecting the circadian sleep-wake rhythm (bedtime and wake-up time, L5 onset, M10 onset, and rhythm acrophase). When comparing diurnal naps, patients with RBD and clinically diagnosed α-synucleinopathies presented the highest frequency of naps with respect to both iRBD patients and “non-RBD controls”. The same trend of differences was observed regarding nap

duration, diurnal activity levels and M10, with RBD patients concomitant with α-synucleinopathy being more likely to show a more severe alteration than the other two groups. Time-series analysis of motor activity (FLM) documented a trend of diurnal motor activity reduction (from 11:00 am to 5:00 pm) more evident in RBD patients with α-synucleinopathy but low too in iRBD patients with respect to non-RBD controls.

3.2. Within iRBD comparison

In a prospective case-control study, Feng and colleagues compared differences in baseline rest-activity patterns between patients who converted to full-blown α-synucleinopathy ("convertors") and those who remained α-synucleinopathy free ("non-convertors") at two years of clinical follow-up. Night-time, daytime, and non-parametric measures (IS, IV, L5, and M10) were considered and features of motor activity patterns were analysed through FLM. Convertors exhibited a higher frequency of diurnal naps, with longer mean duration, lower diurnal activity levels, and M10 reduction when compared to non-convertors. No differences were observed in nocturnal sleep quality and duration between convertors and non-convertors. Finally, FLM analysis revealed lower levels of diurnal motor activity (from 8:00 to 24:00) in convertors when compared to non-convertors.

3.3. Summary

Research on actigraphy in iRBD is still in its infancy and the paucity of available studies limits the possibility of drawing definite conclusions and directions. Nonetheless, increased daytime nap frequency, sleep-wake cycle dysregulation, and diurnal motor hypoactivity have been consistently documented across the available studies and could be reasonably tested as biomarkers for phenoconversion, especially considering the results from Feng and colleagues. Therefore, the clinical potential of actigraphic recording in patients with iRBD can be exclusively hypothesized and needs to be further tested, although these preliminary results suggest the importance of this assessment in the diagnostic setting of patients with iRBD.

4. Clinical Boxes

Representative actogram of 4 patients and a healthy control (52 years old; Figure 6). One patient with PI, two patients with NT1 (adult and children), and one patient with iRBD. To avoid possible variations in sleep timing related to the weekend, only data relative to weekdays were plotted. Red bars indicate the most prominent features of actigraphic profiles.

4.1 Insomnia Disorder

Activity data of a 49-year-old female patient with Primary Insomnia was recorded during the regular working week (Figure 2). This woman complained of insomnia starting 5 years prior to observation, characterized by difficulties in initiating sleep as well as of nocturnal awakenings in the past two years and of extreme difficulty in returning to sleep. This happened almost but not every night, and there were a few recovery nights of acceptable sleep, both in duration and quality. The decision to perform actigraphy was based on night variability, as conveyed in the sleep diary. The clinical interview suggested the absence of possible snoring/sleep apnoea and Restless Legs Syndrome or periodic leg movements during the night. Consequently, polysomnography was not indicated and the sole possible objective measure of sleep throughout different nights was actigraphy at home. The figure shows an estimated long sleep latency with some awakenings during the sleep period on 4 out of 5 nights and one night with a normal length sleep period without elevated motor activity during the night. In the day periods, one can see some decrease in motor activity around 2 pm in 3 days, suggesting relaxation or tentative to sleep in the afternoon, without reaching characteristics of sleep estimation.

4.2. Narcolepsy Type 1

Left Panel (Figure 3): Activity data of a 5-year-old male patient with Narcolepsy Type 1 was recorded during the regular school week. The nocturnal profile is characterized by an overrepresentation of motor events during sleep and severe sleep fragmentation with a marked inability to maintain prolonged periods (i.e., > 60 min) of uninterrupted sleep. Diurnal profile is characterized by long-lasting diurnal naps time-locked to the early afternoon hours in correspondence to postprandial dip. Circadian rest-activity rhythm is stable, and no major reduction of diurnal motor activity intensity is detectable

Right Panel (Figure 4): Activity data of a 45-year-old female patient with Narcolepsy Type 1 was recorded during the regular working week. The nocturnal profile overlaps with the one displayed by the paediatric patient (i.e., increased motor activity, marked sleep disruption and reduced duration of uninterrupted sleep periods). Contrariwise, diurnal period is characterized

by shorter but more frequent diurnal naps scattered throughout daytime hours, most likely due to the need to adapt the napping behaviour to work activities.

4.3 Isolated REM sleep behaviour disorder

Activity data of a 72-year-old male patient with isolated REM sleep behaviour disorder (iRBD; Figure 5). The nocturnal profile documents a cluster of motor activity possibly related to cyclic RBD episodes (according to the ultradian rhythm). However, nocturnal awakenings and sleep fragmentation also appeared related to less stable and continuous sleep. The diurnal profile documented motor activity fragmentation possibly owing to daytime drowsiness, apathy, or fatigue. In addition, lower motor activity related to sleep inertia or physical activity reduction is also evident a few hours ensuing awakening. Considering the sleep-wake cycle parameters, both the increased motor activity during the night (not related to the RBD symptomatology) and the reduced motor activity during the day can reflect the lower relative amplitude of the circadian sleep-wake rhythm already documented in iRBD patients.

Discussion

This review provides an update on the use of actigraphy in sleep medicine clinical practice and research by summarizing the results of studies published after 2010 [1] that analysed both sleep and sleep-wake rhythm in patients affected by insomnia, NT1, or iRBD. Most of the reviewed studies focused on patients with insomnia, similarly to the previously published review by Sadeh. Notably, there is a significant growth in the number of studies on narcolepsy (2 vs 7), and iRBD emerged as a new potential field of application for this sleep assessment technique. Overall, the reviewed studies displayed a marked difference in experimental design, actigraphy models, and actigraphic measures. Furthermore, within the context of quantitative actigraphy, the actigraphic variables reported are widely different among studies, which limits, to some extent, the comparability of results. Insomnia has been the most extensively studied sleep disorder in terms of actigraphic profile. Its effectiveness is highest in SOL and SE detection. Compared to the previous review, the application of machine learning approaches has shown the possibility to significantly ameliorate the detection of wakefulness

within the sleep period in insomnia with potentially major implications for both insomnia recognition and for the assessment of treatment effect. However, it remains difficult to compare results from different algorithms and devices. The specificity in recognising sleep and wakefulness compared with PSG is still not optimal, but it has improved and, as suggested by Sadeh [1], it is compensated by the increased number of recordings in a naturalistic environment. Very few studies have assessed circadian rhythms in insomnia through classical parametric and/or non-parametric measures.

At the same time, several studies have applied more advanced analytical and/or data-adaptive techniques to analyse the full-time series of activity data, providing novel insight into insomnia physiology. The study by Holloway and colleagues showed that by analysing the full actigraphy data through the fractal analysis technique, it is possible to ecologically identify impaired sleep dynamics, the physiological hallmark of insomnia, as well as night-to-night fluctuations in the complexity of nocturnal motor activity organization [11].

Similarly, singular spectrum analysis applied to actigraphy data has provided novel information on the circadian and ultradian components of insomnia suggesting that this approach could provide more advanced information on circadian activity alterations when compared to classic nonparametric actigraphic measures [10]. Alternatively, results on sleep misperception are less unequivocal and it is still difficult to conclude whether the discrepancy between the actigraphic estimation of TST (and WASO, SOL) and subjective perception (sleep log) is due to the limitations and inaccuracy of the current device or to the tendency of insomnia patient to underestimate or overestimate specific aspects of sleep alteration. Noteworthily, the only study specifically aimed at insomnia misperception showed that the application of latent classes to sleep measures derived from sleep diaries and actigraphy is able to efficiently characterize different phenotypes of insomnia misperception bringing us one step closer to use personalized medicine for this sleep disorder [13].

Concerning the use of actigraphy in insomnia therapies, the studies analysed considered the main sleep variables that characterize insomnia disorder (TST, SOL, WASO, SE) but did not show any differences in the primary or secondary use of the actigraphy based on the type of therapy and it is reasonable to speculate that actigraphy could be a major tool to use when evaluating changes in sleep measures, regardless of the type of therapy.

Actigraphy seems particularly useful in various situations namely when objective estimates of sleep parameters are necessary for some clinical evaluation in case of non-response to cognitive behavioural therapy, in specific drug treatment for insomnia, when the reliability of patient reporting data is doubtful, or even in the follow-up treatment of patients with insomnia. Nevertheless, it is important to highlight that the studies reviewed were highly heterogeneous including different

therapies, evaluation times, diagnostic methods and control samples which limits the possibility of identifying specific treatment-sensitive variables.

As suggested by the AASM Clinical Practice Guidelines [2], the core benefits of actigraphy include its convenience, it carries a fairly low patient burden as well as promotes good compliance while allowing for a longitudinal assessment and it is relatively cost-effective, in particular in respect to polysomnography. Moreover, especially in insomnia patients, naturalistic home-based sleep assessment gives a further advantage compared to polysomnography, which may be performed preferentially in the sleep lab and only for one or two nights and days and is susceptible to the "first night effect".

Concerning central disorders of hypersomnolence, several studies have consistently pointed out a peculiar nychthemeral alteration in NT1 patients. Patients with NT1, both adults and children, display a marked increase of motor events during sleep resulting in impairment in sleep quality (increased WASO and awakenings frequency) and continuity (decreased TST). In parallel, NT1 patients exhibit frequent diurnal naps of prolonged duration, especially in the hours corresponding to the postprandial period. These alterations of actigraphic profile resulted specific in NT1 patients when compared to both healthy controls and patients suffering from IH.

Whether NT1 patients present reduced daytime motor activity is more controversial. Studies that considered summary measures highlighted a slight, yet significant reduction of diurnal motor activity levels in adult NT1 patients compared to controls. However, studies that used more advanced analytical techniques on time series of motor activity showed that, in NT1 children, the reduction of motor activity is time-locked to the early afternoon while no difference was observed in the morning and evening hours. In contrast, a handful of studies have correlated actigraphic measures with demographic, clinical and biological data, disclosing significant associations between actigraphic measures of sleep quality and hypocretin-1 levels as well as between actigraphic nocturnal and diurnal measures and regular engagement in physical/sport activities. Collectively, these results seem to suggest that when actigraphy is used in combination with clinical or biological information it could represent a potential approach to stratify patients in the apparently highly homogeneous clinical picture of NT1. Finally, although shown solely in a single study, actigraphy has proven sensible enough in detecting the effects of treatment with Sodium Oxybate, thus representing an alternative and more ecological approach to assess treatment efficacy and patients' compliance.

That said, less is known about the clinical potential of using actigraphy in patients with iRBD. Indeed, few studies have investigated the usefulness of actigraphy for screening iRBD, which remains challenging and needs further confirmation. Similarly to the proposed use of actigraphy for monitoring the treatment effect in NT1 patients, from a clinical point of view, the use of actigraphy

can be suggested for evaluating the effects of drugs counteracting iRBD symptoms in patients with no bed partner or less-violent manifestations (low- or non-traumatic and thus possibly not reported by patients). More promising data have been proposed about the monitoring of the sleep-wake cycle of iRBD patients with respect to the possibility of marking phenoconversion. This potential of actigraphic recording concords with the evidence that excessive daytime sleepiness and daytime napping can be considered non-motor symptoms which increases the risk of phenoconversion in patients with iRBD [79]. In agreement with this proposed evidence, the single study by Feng and co-authors documented a higher risk of conversion in iRBD patients showing at the baseline assessment a higher frequency of diurnal naps, with a longer mean duration, lower diurnal activity levels, and M10 values when compared to patients who did not convert at follow-up [15]. Moreover, actigraphy can permit monitoring diurnal motor activity for extended time periods, and considering the findings by Feng et al, who demonstrated that lower levels of diurnal motor activity at baseline were evident in patients phenoconverted to α-synucleinopathies at follow-up, it seems of particular importance to assess not only nocturnal sleep but also daytime habits of iRBD patients. The aforementioned results may present a significant clinical implication as they suggest the practicality of monitoring iRBD patients through actigraphy during the disease-course, in order to identify changes in circadian rhythm that could be considered a marker of phenoconversion. The actigraphic monitoring during follow-up may thus help identify the phenoconversion of patients and may permit the timely starting of disease-modifying treatments, in the light of future pharmacological and non-pharmacological trials. It is widely established that RBD diagnosis requires video-polysomnography, although the recent debate about the opportunity to screen RBD with more ecological and cost-effective instruments opened the potential use of actigraphy for this purpose. Since the clinical potential to screen patients for RBD by actigraphy is not already demonstrated, another suggested use of actigraphy is to monitor the RBD symptoms following the diagnosis, particularly in patients with no bed partner, to check the effectiveness of the therapeutic strategy prescribed and possibly modify treatments according to actigraphic recognition of minor RBD episodes. Consistently, actigraphy can also support the clinical evaluation of RBD patients by investigating the sleep-wake cycle, daytime napping, and sleep inertia. Nonetheless, whether these alterations could be considered biomarkers for the evaluation of phenoconversion or monitoring the effect of treatment on RBD episodes should be investigated in future studies. [79]

Several limitations should be considered when interpreting the findings of this review. As already mentioned, a wide variation in the design of the included studies was evident (e.g., population, sleep parameters, type of actigraphic recording, and treatment duration) and limits the comparability of results. Notably, some studies only compared outcomes in patients against HC, and not with baseline

or placebo, which indicates that the effects of the treatment were indistinguishable from the effects of the disease. In addition, most of the studies on NT1 and iRBD included a relatively small sample size, suggesting a moderate-to-high risk of bias. A possible explanation for the limited number of studies investigating the potential use of actigraphy in RBD or narcolepsy can also be related to the absence of standardized protocols for using the instrument in these sleep disorders. It is viable to consider how useful it could be to suggest nomenclature, definitions, and illustrative examples of the use of actigraphy in these sleep disorders, promoted by study groups or by establishing international agreements, in order to increase the use of actigraphy in sleep medicine settings.

Conclusions

Overall, evidence on the usefulness of actigraphy for the clinical evaluation of patients with insomnia, EDS; or RBD is accumulating, and the scientific literature has expanded since the Sadeh review [1], particularly on what concern EDS and RBD. [1]. While producing evidence about the clinical potential of using actigraphy in these sleep disorders continues to be a challenge, it seems that some sleep disorders, and possibly EDS, may be monitored by actigraphy, in particular regarding treatment effects, and may be linked to the improvement of daytime vigilance and nocturnal sleep. However, research on RBD is in an embryonic stage and needs further investigation, although clinicians may consider this instrument when monitoring treatment effects, particularly for patients without bed partners. Based on sleep studies and clinical data, insomnia may be suited to actigraphic monitoring. In addition, the applications of a more advanced analytical framework have been shown to provide unique insight into insomnia physiology documenting both increased night-time complexity and alteration in circadian and ultradian rhythmicity.

Practical points

1. Actigraphy remains a cost-effective instrument to monitor sleep in insomnia, and the accuracy in recognizing TST, WASO and SOL has been improved in comparison with PSG.
2. Actigraphy is useful when objective estimates of sleep parameters are necessary for evaluating treatment responses: in case of non-response to cognitive behavioural therapy or specific drug treatment for insomnia, or when the reliability of patient reporting data is doubtful, actigraphy may be helpful from a clinical point of view.
3. Actigraphy can represent a useful instrument to monitor patients with iRBD, particularly in the absence of a bed partner. Moreover, the possibility to monitor daytime activity and napping in iRBD patients became more important considering the need of stratifying the risk for phenoconversion in those patients.
4. Actigraphy offers unique potentialities in NT1 since it can detect a peculiar 24-hour sleep-wake rhythm disruption and allows monitoring the effects of pharmacological treatments immediately after drug prescription.

Research agenda

1. Improve the research on the homogenization of the different devices in terms of sampling frequency and software analysis, using some common software parameters for scoring estimated sleep and wake during the night.
2. Consider large studies on patients with different sleep characteristics (short sleep duration or normal sleep duration) in naturalistic habits, comparing the effect of both CBT-I and drug therapy.
3. Consider large studies on healthy people of different age range to achieve a better understanding of normal sleep behaviour from an actigraphic perspective.
4. Improve the role of actigraphy in RBD diagnosis and management with further studies using more sophisticated software analysis, in order to perform long-term daytime and night-time monitoring of patients.
5. Evaluate the performance of multi-sensor (activity, heart rate, temperature) wearable devices in the detection of unique sleep patterns associated with specific sleep disorders.

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* The most important references are denoted by an asterisk

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Figure captions

Figure 1. Flow diagram of study selection.

Figure 2. Actogram of a patient with insomnia

Figure 3. Actogram of a paediatric patient with narcolepsy.

Figure 4. Actogram of an adult patient with narcolepsy.

Figure 5. Actogram of a patient with Isolated REM sleep behaviour disorder

Figure 6. Actogram of a healthy control

Table captions

Table 1. Summary of studies included within the review.

Table 2. Description of Actigraphic measures considered by the studies included within the review

Table 3. Use of actigraphy in Behavioral Therapies (CBT-I, sleep restriction, mindfulness, psychoeducational/sleep programs)

Table 4. Use of actigraphy in alternative therapies (pharmacological interventions, cognitive training, transcranial magnetic stimulation, acupuncture, and naturals products)

Table 2. Description of Actigraphic measure considered by the studies included within the review

Variable	Definition	Alternative Name	Abbreviation
Quantitative actigraphic measures - Nighttime			
Bedtime	Clock time, in hours and minutes, when subject goes to bed and turns off the light	Light-off Time	BT
Wake up time/Get up time	Clock time, in hours and minutes, when subject gets out of bed in the morning	Sleep end	WT/GUT
Time in Bed	Time, in minutes, from Bedtime to Wake up time	Sleep Period/Nocturnal rest period	TIB/SP/NRP
Midpoint of Sleep	Clock time, in hours and minutes, that split in half the time in bed	Central Phase Measure	MS/CPM
Sleep Onset Latency	Interval, in minutes, between Bedtime and sleep onset	Sleep Latency	SOL/SL
Total Sleep Time	Sum of all epochs scored as sleep between sleep onset and Wake up time	Sleep duration	TST
Sleep Efficiency	Total Sleep time divided by time in bed multiplied by 100		SE%
Wake after sleep onset	Sum, in minutes, of all epochs scored as wake between sleep onset and wake up time	Wake Time	WASO
Sleep Bouts	Number of all epochs scored as sleep between sleep onset and wake up time	Sleep episodes	SB
Wake bouts	Number of all epochs scored as wake between sleep onset and wake-up time	Wake bouts/Nocturnal awakenings	WB/Awk/NWAK

Prolonged wake bouts	Number of all wake bouts lasting more than a predetermined number of minutes (typically 5 min.)	Prolonged Wake bouts/Prolonged awakening	PWB/Awk>5/NA >5
Longest sleep	Mean duration of the longest continuous episode scored as sleep between sleep onset and wake up time	Longest Sleep Bouts	LSLEEP
Terminal wakefulness	Time, in minutes, between final awakening and wake up time	Early morning awakening	TWAK/EMA
Sleep motor activity	Sum of all activity counts during TIB divided by its duration	Mean activity score	SMA/MA
Fragmentation Index	Number of epochs with movement divided by TST duration plus number of consecutive epochs of immobility divided by the total number of immobility epochs multiplied by 100	Sleep Fragmentation Index	FI/SFI
Quantitative actigraphic measures - Daytime			
Diurnal motor activity	Sum of all activity counts between wake up time and bedtime divided by its duration	Mean motor activity	DMA/MA
Nap	Number of sleep episodes between wake-up time and bedtime	Daytime sleep episodes	Nap
Nap duration	Mean duration, in minutes, of the daytime sleep episode	Longest Nap	NapD/ LNap
Diurnal total sleep time	Sum, in minutes, of all epochs scored as sleep wake up time and bedtime	Diurnal Sleep	DTST
24-hour total sleep time	Sum, in minutes, of all epochs scored as sleep across the 24-hours	Nyctemeral total sleep time	24hrTST

Nonparametric actigraphic measures		
Interdaily stability	Ratio of activity level variance within each 24-hour pattern to the overall activity level variance	IS
Interdaily variability	Ratio of the mean squares of the difference between consecutive hours and the mean squares around the overall mean	IV
M10	Average amplitudes of the most active 10 hour period	M10
L5	Average amplitudes of the least active 5 h period	L5
Relative Amplitude	Ratio of the most active 10-hour period minus the least active 5 h period to the most active 10-hour period plus the least active 5 h period	RA
Dichotomy index	Percentage of motor activity counts measured during TIB which is lower than the median of diurnal motor activity	I<O

Table 3. Use of actigraphy in Behavioural Therapies (CBT-I, sleep restriction, mindfulness, psychoeducational/sleep programs)

Reference	Sample	Diagnosis according to	Treatment	Outcome	Timing	Measure Considered	Sensible actigraphy variables to treatment among the group (pre-post)
Bathgate et al., 2017 [43]	60 Primary sleep maintenance insomnia	DSM-IV	35 pts CBT-I in insomnia with objective short sleep vs 25 pts CBT-I in insomnia with objective normal sleep	Primary	2-week baseline, 8-week treatment, and 2 follow-up periods (3and 6 months post-treatment)	SE, SOL, TWT, TST	For insomnia subjects with objective normal sleep: TST, TWT
Buysse et al., 2011 [51]	79 Chronic insomnia	DSM IV-TR, ICSD 2	39 pts BBT-I vs 40 information control	Secondary	Pre-treatment and 4 weeks after the start of the intervention	SOL, WASO, TST, SE	For BBT-I group: WASO, SOL, SE, TST
Chan et al., 2017 [52]	62 Insomnia disorder	Sleep diary	32 pts BBT-I vs 30 pts self-monitoring and attention control	Secondary	from baseline to post-treatment and at 3-month follow-up (10 weeks continuously)	TIB, SOL, WASO, TST, SE, sleep variability variables: varSOLa, varWASOa, varTSTa, and varSEa.	For BBT-I group: variability in SOL, WASO, TST, and SE
Dzierzewski et al., 2019 [44]	159 Insomnia disorder	Fulfilment of diagnostic criteria for insomnia disorder	106 pts CBT-I vs 53 control	Primary	baseline, post-treatment, 6-month and 12-month follow-up	Sleep and wake discrepancy: TWT, TST	Sleep and wake discrepancy: TWT, TST
Epstein et al., 2012 [45]	179 Chronic primary insomnia	Sleep diary	44 pts stimulus control therapy, 44 pts sleep restriction and 41 pts MBI vs 50 pts waiting list	Primary	14 days baseline, post-treatment, and follow-up	SOL, WASO, TST, TIB, SE	No treatment-sensitive for actigraphy variables

Falloon et al., 2015 [61]	97 Primary insomnia	Sleep diary, questionnaire	46 pts MBI (Sleep Restriction therapy, instructions, and sleep hygiene advice) vs 51 pts only sleep hygiene advice	Primary for SE	1-week before treatment (baseline) and 6 months after treatment	SOL, WASO, TST, SE	No treatment-sensitive for actigraphy variables
Galbiati et al., 2021 [53]	53 Insomnia disorder	ICSD-2, ICSD-3	38 pts CBT-I in insomnia with short sleep duration vs 15 pts CBT-I in insomnia with normal sleep duration	Secondary	1-week baseline	SE, SL, WASO, NAWK, TST, TIB	Actigraphy was used for identifying insomnia patients with and without short sleep duration
Harris et al., 2012 [54]	79 Chronic sleep-onset insomnia	Sleep diary, questionnaire, PSG	19 pts ISR, 20 pts SCT, 20 ISR+SCT vs 20 sleep hygiene control condition	Secondary	2-week baseline, throughout treatment, and during follow-up assessments.	SOL, TST, WASO, SE	No treatment-sensitive for actigraphy variables
Janku et al., 2020 [49]	36 Insomnia disorder	ICSD-3	16 pts CBT-I in overestimating TST group vs 20 pts CBT-I in underestimating TST group	Primary	1-week pre-treatment, during all intervention periods and post-treatment	SOL, TST, WASO, SE, Misperception index	Total sample: SOL, TST, WASO. Underestimating group: SOL, TST, WASO, SOL discrepancy, TST discrepancy. Overestimating group: SE, WASO, SOL discrepancy, WASO discrepancy,

							TST discrepancy.
Lovato et al., 2014 [55]	118 Sleep maintenance insomnia	Interview, sleep diary, actigraphy, questionnaire, PSG	63 pts CBT-I vs 28 pts waiting list	Secondary	1-week pre-treatment, during treatment, post-treatment, and at 3months follow-up.	WASO, TST, SE	WASO
Lovato et al., 2016 [56]	91 Chronic insomnia	Interview	30 pts CBT-I with short total sleep time, 33 pts CBT-I with long total sleep time vs 28 pts waiting list	Secondary	1-week pre-treatment, during treatment, post-treatment, and at 3-months follow up	SOL, WASO, TST, SE	For CBT-I with a short total sleep time group: TST
Martin et al., 2017 [48]	42 Insomnia disorder	Interview, sleep diary, questionnaire	21 pts sleep Intervention Program vs 21 pts only information	Primary	baseline, post-treatment and 4-months follow-up (3 days/nights)	SE, TST, NAWK, WASO	For sleep intervention program group: SE, NAWK, WASO
Maurer et al., 2020 [57]	56 Chronic insomnia	DSM-5	27 pts sleep restriction therapy vs 29 pts time in bed regularization	Secondary	14 days baseline, during treatment, and 2 weeks post-treatment	SOL, WASO, TST, SE	NA
McCrae et al., 2018 [58]	52 Insomnia disorder	Sleep diary	32 pts BBT-I vs 30 pts SMC	Secondary	baseline, post-treatment, and 3 months follow-up	SOL, WASO, TST, SE	For BBT-I and SMC groups: WASO
Nishikawa et al., 2021 [47]	52 Primary insomnia	DSM IV-TR	Pre CBT-I vs post-CBT-I	Primary	1-week pre-treatment and 1-week post-treatment	TIB, TST, SOL, WASO, SE and sleep discrepancies for all variables	TIB, sleep discrepancies for WASO and SE
Ong et al., 2014 [59]	54 Chronic insomnia	Diagnostic criteria for insomnia	19 pts MBSR and 19 pts MBTI vs 16 pts self-monitoring condition	Secondary	1-week pre, 1 week post treatment and 6 months follow up	TWT, TST, SE	For MBSR and MBTI groups: TWT

Schiller et al., 2018 [46]	51 Insomnia disorder	ISI	25 pts CBT-I vs 26 control	Primary	10 days before and after 3 months of treatment	SE, TST	No treatment-sensitive for actigraphy variables
Sato et al., 2010 [50]	20 Psychophysiological insomnia	ICSD-2	Pre CBT-I vs post-CBT-I	Primary	Pre and post-CBT periods	SONT, SOFT, SOL, TST, NOA, WASO, SE, MT	SOL, WASO, SE, MT
Quintiliani et al., 2017 [60]	38 Chronic insomnia	ICSD-3	19 pts psychoeducational intervention vs 19 control	Secondary	14 days	TST, Misperception index	Misperception index

Abbreviations MBI, multicomponent behaviour intervention, BBT-I, Brief Behavioural Therapy for insomnia; ISR, intensive sleep retraining, SCT stimulus control therapy; MBSR, mindfulness-based stress reduction, MBTI mindfulness-based therapy for insomnia; SMC, self-monitoring control; SONT, sleep onset time; SOFT, sleep-offset time; NOA, number of awakening episodes lasting more than 5 min; MT, moving time during sleeping; TWT, total wake time; TST discrepancy, (Diary – Actigraphy); TWT discrepancy, (Diary – Actigraphy); PTS, patients;

Table 4. Use of actigraphy in alternative therapies (pharmacological interventions, cognitive training, transcranial magnetic stimulation, acupuncture and naturals products)

Reference	Sample	Diagnosis according to	Treatment	Outcome	Timing	Measures Considered	Sensible variables to treatment
Bergdahl et al., 2017 [71]	58 Insomnia disorder	DSM-5	28 pts auricular acupuncture (AA) vs 30 pts CBT-I	Primary	Baseline, post-treatment and 6-month follow-up.	BT, fell asleep, wake up and rising, TIB, SE, SOL, actual sleep time, actual wake time	For CBT-I group: BT, wake up, rising, TIB, SE, SOL, actual sleep time, actual wake time. For AA group: wake up, TIB, SOL, actual sleep time
Chung et al., 2017 [66]	224 Insomnia disorder	DSM-5	96 pts acupuncture and 96 pts acupuncture wit auricular acupuncture vs 32 pts waiting list	Secondary	1-week baseline, 3-weeks after treatment	TST, SE	No treatment-sensitive for actigraphy variables
Dekker et al., 2020 [67]	175 Insomnia disorder	ICSD-3, DSM-5	Randomization: half of 175 received 4 weeks of ICBTI in weeks 1–4, the other half in weeks 6–9. In both groups, participants were then additionally randomized to receive scheduled CT, or a placebo in weeks 1–4.	Secondary	Pre-treatment, post-treatment and follow-up assessment in 10-weeks period	SOL, WASO, TST, SE	For ICBTI group: TST
Gross et al., 2011 [70]	30 Chronic insomnia	DSM-IV-TR	20 MBSR vs 10 pts drug (Zopiclone)	Primary	2-weeks before the start intervention and the last 2-weeks before ending intervention	SOL, WASO, TST, SE	For MBSR group: SOL For drug group: TST, SE

Ha et al., 2019 [65]	80 Mild insomnia	N/A	40 pts natural product (Polygonatum sibiricum rhizome extract) vs 40 placebo	Secondary	1-week pre-treatment, and during the last week of the administration	TST, SE, WASO	TST
Haimov et al., 2013 [64]	51 Insomnia disorder	ICSD-2	34 pts computerized cognitive training vs 17 control group	Primary	1-week before and after training	SOL, SE, WASO, TST, NAWK	SOL, SE, WASO, NAWK
Langade et al., 2021 [68]	80 Insomnia disorder	DSM-IV	40 pts natural product (ashwagandha root extract) vs 40 placebo	Primary	1-week at baseline, week 4 and week 8	SOL, TST, WASO, SE, TIB	SOL, TST, WASO, SE, TIB
Vgontzas et al., 2020 [69]	15 Chronic insomnia	Interview	8 pts CBT-I vs 7 pts drug (Trazodone)	Primary	2-week period at each time point (pre-treatment, post-treatment, and follow-up)	TST	For drug group: TST
Yin et al., 2017 [62]	72 Primary insomnia	DSM-IV	36 pts acupuncture vs 36 pts shame acupuncture	Secondary	2-weeks and 4-weeks after treatment and 2-weeks and 4-weeks follow up	SE, TST, SA	2-week post-treatment: TST 4-week post-treatment: SE, SA, TST
Zhang et al., 2018 [63]	78 Chronic insomnia	N/A	40 pts acupuncture with rTMS vs 38 control group	Secondary	3 days baseline, end of 4-weeks of treatment and after 2-weeks as follow-up.	TST, SOL, WASO, SE, NAWK	No treatment-sensitive for actigraphy variables

Abbreviations: AA, auricular acupuncture; CT, chronobiological treatment; ICBTI, internet cognitive behavioural therapy for insomnia; MBSR, mindfulness-based stress reduction; SA, sleep awakenings; PTS, patients

Table 1. Summary of studies included within the review.

Reference	Sample	Mean age	Diagnosis according to	Treatment	Actigraph Type	Settings	Scoring approach
Alakuijala, 2015 [75]	69 H1N1-vaccine-related narcolepsy	14.61 ± 8.37	ICSD-2	Drug-naïve	Actiwatch	1-2 weeks of recording non-dominant wrist 1 min epochs medium sensitivity	Sleep diary
	57 sporadic narcolepsy	21.48 ± 9.47					
Alakuijala, 2016 [14]	26 NT1 (Hcrt-1 < 30 pg/mL)	18 (range 7.9–63.2)	ICSD-3	Drug-naïve	Actiwatch	1 week recording non-dominant wrist 1 min epochs medium sensitivity	Sleep diary
	10 NT1 (Hcrt-1 ≥ 30 pg/mL)	24.9 (range 17.1–39.1)					
Angelova, 2020 [34]	21 acute insomnia	25 ±6	N/A	N/A	Actiwatch	2 weeks recording (7 days analysed) non-dominant wrist 30-sec epochs	N/A
	24 healthy controls	28 ± 6					
Bottary, 2020 [25]	24 insomnia disorder	30.38 ± 13.60	DSM-5, ICSD-3	Drug-naïve	Actiwatch 2	2 weeks recording 30 sec epochs	Event marker
	24 healthy controls	30.79 ± 13.71					

Carter, 2018 [38]	12 insomnia disorder	37 ± 14	DSM 5	Treated	Actiwatch	2 weeks recording non-dominant wrist	N/A
	12 healthy controls	41 ± 15					
Cosgrave, 2018 [39]	21 insomnia disorder	23.9 ± 3.6	ISI, PSQI	Drug-naïve	MotionWatch 8	2 weeks recording non-dominant	Sleep diary
	22 healthy controls	22.8 ± 3.2				1-min epochs	
Devine, 2018 [26]	20 insomnia disorder	30 ± 2.5	DSM-5	N/A	Actiwatch	2 weeks recording non-dominant	N/A
	20 healthy controls	26 ± 1.4				30-sec epochs	
Drummond, 2013 [31]	25 primary insomnia	32.3 ± 7.2	Duke structured interview for sleep disorders	Drug-naïve	Actiwatch	7-10 days of recording	Sleep diary
	25 healthy controls	32.4 ± 7.1					
Feng, 2020 [15]	88 iRBD	69.8 ± 7.7	ICSD-3	Treated	Actiwatch	7 days 1 min epochs	N/A
	44 clinically diagnosed α-synucleinopathies	70.7 ± 8.8		Treated			
	44 “non-RBD” controls						

		70.1 ± 10.0					
Filardi, 2020 [17]	19 iRBD	71.68 ± 7.85	ICSD-3	3/19 Treated	Micro Motionlogger Watch	2 weeks recording (7 days analysed)	Environmental light + motor activity
	19 untreated OSA	50.53 ± 11.29				30 sec epochs	
				5/20 Treated			
	20 RLS	47.50 ± 14.19					
	16 Healthy controls	43.63 ± 15.66					
Filardi, 2014 [9]	39 NT1	34.21 ± 15.58	ICSD-3	Drug-naïve	Micro Motionlogger Watch	1 week recording non-dominant wrist	Event marker + sleep diary
	24 IH	31.96 ± 15.20		Drug-free		1 min epochs	
	30 Healthy controls	29.37 ± 9.47					
Filardi, 2016 [73]	22 NT1	12.09 ± 2.37	ICSD-3	Drug-naïve	Micro Motionlogger Watch	5 days of recording non-dominant wrist	Event marker + sleep diary
	21 healthy controls	10.95 ± 2.25				1 min epochs	

Filardi, 2018 [76]	30 NT1 physically active	12.16 ± 2.70	ICSD-3	Drug-naïve	Micro Motionlogger Watch	1 week recording non-dominant wrist 1 min epochs	Event marker + sleep diary
	20 NT1 physically inactive	13.23 ± 3.23		Drug-naïve			
Filardi, 2018 [77]	24 NT1 off and then on Sodium Oxybate	12.20 ± 2.95	ICSD-3	Drug-naïve then on Sodium Oxybate	Micro Motionlogger Watch	1 week recording non-dominant wrist 1-min epochs	Event marker + sleep diary
Floam, 2014 [36]	29 insomnia disorder	25.3 ± 1.6	DSM-5	Drug-naïve	Actiwatch-64	2 weeks recording non-dominant wrist 1-min epochs	Sleep diary
	19 healthy controls	25.4 ± 1.4					
Fossion, 2017 [10]	18 acute insomnia	25 ± 6	N/A	N/A	Actiwatch	2 weeks recording (7 days analysed) 1-min epochs	N/A
	23 healthy controls	28 ± 6					
Holloway, 2014 [11]	26 acute insomnia	32 ± 12	N/A	N/A	Actiwatch	1 week recording 1-min epochs	N/A
	21 healthy controls	40 ± 16					

Ho Jang, 2018 [28]	115 insomnia disorder	62.67 ± 12.21	ICSD-2	Drug-free	Actiwatch-2	1 week recording non-dominant wrist	Sleep diary
	80 healthy controls	53.62 ± 13.54				1-min epochs	
Kang, 2017 [37]	33 insomnia disorder	38.4 ± 11.2	DSM-5	Drug-naïve	Actiwatch-2	1 night recording non-dominant wrist	N/A
	17 healthy controls	32.1 ± 7.4				1-min epochs	
Kay, 2013 [32]	29 insomnia disorder	74.00 ± 5.50	N/A	N/A	Actiwatch-L	2 weeks recording non-dominant wrist	N/A
	74 healthy controls	72.47 ± 7.32				30-sec epochs	
Leger, 2018 [72]	13 NT1	39.38 ± 11.48	ICSD-3	Treated (12/13)	Actiwatch	1 week recording non-dominant wrist	Event marker + sleep diary
	13 PI	38.69 ± 10.72		Treated		low sensitivity	
	13 healthy controls	38 ± 10.77					
Levenson, 2013 [24]	79 insomnia disorder	71.7 ± 7.3	DSM-IV, ICSD-2	Drug-free	Actiwatch-64	1 week recording non-dominant wrist	Sleep diary
	40 healthy controls	71.8 ± 7.1				1-min epochs	

Liguori, 2020 [16]	27 iRBD	69.03 ± 4.9	ICSD-3	Drug-naïve	Actiwatch-2	2 weeks recording non-dominant wrist	Sleep diary
	19 healthy controls	69.1 ± 15.6				15-sec epochs	
Marino, 2013 [4]	2 Acoustics pilot	29.5 ± 0.7	DSM-IV	N/A	Actiwatch-64, Actiwatch	30-sec epochs	N/A
	10 Acoustics III	22.2 ± 2.1					
	9 Tiagabine	56.4 ± 3.4					
	16 Sleep Restriction	27.2 ± 4.9					
	17 Insomnia	40.5 ± 8.2					
	23 Nightwork	35.2 ± 9.2					
Natale, 2014 [27]	151 insomnia disorder	42.67 ± 14.81	ICSD 2	Drug-naïve	Actiwatch	1 week recording 1-min epochs	Event marker
	342 healthy controls	31.81 ± 17.22					

Rajna, 2014 [23]	17 primary insomnia	47.7	Hungarian protocol*	N/A	Actiwatch	1 week recording	Event marker
	17 “bad sleepers”	28.18					
	13 healthy controls	41.75					
Seo, 2018 [30]	23 insomnia disorder	28.96 ± 11.95	DSM-5	Drug-naïve	Actiwatch-2	2 weeks recording	Event marker
	23 healthy controls	29.65 ± 12.81					
St-Amand, 2013 [40]	14 bipolar disorder	44.6 ± 11.0	DSM-IV-TR, ICSD-R	Treated	Actiwatch-64	2 weeks recording non-dominant wrist	N/A
	13 insomnia disorder	42.8 ± 15.9		Drug-naïve			
	13 healthy controls	47.15 ± 10.4					
Straus, 2015 [41]	45 PTSD	35.00 ± 9.14	DSM-IV, ISI	Drug-free	Actiwatch-2	1 week recording	Event marker + sleep diary
	25 primary insomnia	32.28 ± 7.24		Drug-free			
	27 healthy controls	32.15 ± 7.54					

Stefani, 2018[78]	20 iRBD	72 (median)	ICSD-3	Treated (9/20)	Micro Motionlogger Watch	2 weeks recording 30-sec epochs	Environmental light + motor activity
	20 RLS	45 (median)		Treated (9/10)			
	10 RLS+OSA	57 (median)					
	20 OSA	53 (median)		Treated (6/20)			
	20 controls	37 (median)		Treated (7/20)			
te Lindert, 2020 [12]	58 Insomnia disorder	47.8 ± 14.0	DSM-5, ICSD-3	Drug-naïve	GENEActiv	2 consecutive nights of recording 30-sec epochs	Sleep diary
	56 healthy controls	43.2 ± 15.0					
te Lindert, 2020 [13]	181 insomnia disorder/misperception	50.5 ± 12.0	DSM-5, ICSD-3	N/A	GENEActiv	1 week recording 15-sec epochs	Sleep diary
	55 healthy controls	46.4 ± 15.1					

Troxel, 2010 [35]	79 insomnia disorder 40 healthy controls	≥ 60 y	DSM-IV, ICSD-2	Treated	Actiwatch-64	2 weeks recording non-dominant wrist 1-min epochs	Sleep diary
Veeramachaneni, 2019 [33]	68 insomnia disorder 81 healthy controls	20.2 ± 2.4 (whole sample)	Interview	N/A	Actiwatch	1 week recording non-dominant wrist 30-sec epochs	Event marker
Winkelman, 2010 [29]	21 primary insomnia 15 healthy controls	39.3 ± 8.7 38.8 ± 5.3	DSM-IV	Drug-naïve	Actiwatch-64	2 week recording non-dominant wrist 30-sec epochs	N/A

Abbreviations: ICSD-R — International classification of sleep disorders, revised; ICSD-2 — International classification of sleep disorders second edition; ICSD-3 — International classification of sleep disorders third edition; DSM-5 — Diagnostic and Statistical Manual of Mental Disorders fifth edition; ISI — Insomnia severity index; PSQI — Pittsburgh Sleep Quality Index; DSM-IV — Diagnostic and Statistical Manual of Mental Disorders fourth edition; DSM-IV-TR — Diagnostic and Statistical Manual of Mental Disorders fifth edition, text revision; IH — Idiopathic hypersomnia; iRBD — Isolated REM sleep behaviour disorder; OSA — Obstructive sleep apnoea; RLS — Restless leg syndrome; NT1 — Narcolepsy type 1; PTSD — Post-traumatic stress disorder.

* reference at https://kollegium.gyemszi.hu/site/index.php?action=pdf&tip=227&bek=632&rec=22