Title: Actigraphy Assessments of Circadian Sleep-Wake Cycles in the Vegetative and Minimally Conscious States

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ABSTRACT

Background

The Vegetative and Minimally Conscious States (VS; MCS) are characterized by absent or highly disordered signs of awareness alongside preserved sleep-wake cycles. According to international diagnostic guidelines, sleep-wake cycles are assessed by means of observations of variable periods of eye-opening and eye-closure. However, there is little empirical evidence for true circadian sleep-wake cycling in these patients, and there have been no large-scale investigations of the validity of this diagnostic criterion.

Methods

We measured the circadian sleep-wake rhythms of 55 VS and MCS patients by means of wrist actigraphy, an indirect method that is highly correlated with polysomnographic estimates of sleeping/waking.

Results

Contrary to the diagnostic guidelines, a significant proportion of patients did not exhibit statistically reliable sleep-wake cycles. The circadian rhythms of VS patients were significantly more impaired than those of MCS patients, as were the circadian rhythms of patients with non-traumatic injuries relative to those with traumatic injuries. The reliability of the circadian rhythms were significantly predicted by the patients’ levels of visual and motor functioning, consistent with the putative biological generators of these rhythms.

Conclusions

The high variability across diagnoses and aetiologies highlights the need for improved guidelines for the assessment of sleep-wake cycles in VS and MCS, and advocates the use of actigraphy as an inexpensive and non-invasive alternative.

Keywords: Vegetative State, Minimally Conscious State, Circadian Rhythms, Sleep, Actigraphy
BACKGROUND

The Vegetative State (VS) or Unresponsive Wakefulness Syndrome (UWS [1]) is thought to reflect the dissociation of the two primary components of consciousness – awareness and wakefulness[2, 3]. A common tool for the assessment of awareness is the Coma Recovery Scale Revised[4] (CRS-R) which includes subscales designed to assess a range of functions, including auditory, visual, motor, verbal, communication, and arousal. A brain-injured patient is considered to possess awareness if they produce non-reflexive responses to stimulation, such as tracking an object that is moving in front of the eyes, or following a verbal command. Patients in the VS do not produce non-reflexive behaviour, and are therefore considered to lack awareness[5, 6]. Patients in the Minimally Conscious State (MCS) exhibit some reproducible but inconsistent signs of awareness, although communication remains absent[6, 7].

Wakefulness, on the other hand, is thought to be preserved in both VS and MCS patients. According to the standards for VS and MCS outlined by the Multi-Society Task Force for Permanent Vegetative State[5] and the Royal College of Physicians[6], ‘wakefulness’ refers to the presence of typically cycling periods of eye-closure and eye-opening that give the appearance of sleep-wake cycles. While a great deal of behavioural and neuroimaging research has focused on the assumption of unawareness in these patients[4, 8-10], very little is known regarding the assumption of preserved sleep-wake rhythms.

A typical sleep-wake cycle follows a circadian rhythm, with a period of between 19- and 28-hours[11]. Electroencephalography (EEG), in combination with other physiological measures as part of polysomnography, is the gold-standard approach for the assessment of sleep-wake cycles[12]. However, the results of the limited EEG investigations of circadian sleep-wake cycling in VS and MCS patients are inconsistent with the assumption of preserved wakefulness. Landsness et al.[13] observed sleep-wake-like changes in the EEG of 6 MCS patients across one day, while the EEG of 5 VS patients remained unchanged between periods of eye-opening and eye-closure. Isono et al.[14] also reported an absence of EEG sleep-wake changes in 4 out of 12 VS patients. High variability has also been observed in other physiological circadian rhythms in VS and MCS including body temperature and hormone levels[15, 16], blood pressure and heart rate[16, 17], and sleep-related erections[18]. Circadian-like variations in arousal have also been reported in both VS and MCS patients, as indexed by fluctuating behavioural abilities across the day[19]. Bekinschtein et al.[20] observed well-formed circadian rhythms in the body temperatures of two VS patients with traumatic brain injuries (TBI), but absent rhythms in three VS patients who had sustained non-traumatic brain injuries (non-TBI), indicating the potential relationship between aetiology and circadian rhythms. It appears, therefore, that, contrary to the diagnostic guidelines describing these conditions, a great deal of variability exists both within and across VS and MCS patient groups with regard to the relative preservation of circadian rhythms.

An indirect and inexpensive approach to detecting circadian sleep-wake cycles from large numbers of patients is wrist actigraphy, in which a wrist-mounted
device is used to record the frequency and amplitude of motor activity[12]. This method is known to correlate well with polysomnographic measurements of sleep and wakefulness in healthy individuals, as well as non-ambulatory patients such as those with C5-C7 tetraplegia[21-23]. A number of algorithms have been developed in order to produce minute-to-minute estimations of sleeping/waking from short-term variations in actigraphy data in healthy individuals. Broadly, these algorithms judge an individual to be awake or asleep at a given sample point by weighting the amount of movement in a number of preceding sample points by a set of predefined constants. Such approaches have reported between 88-97% concordance with polysomnography in healthy individuals (see [21] for a full review). However, none of these approaches have been validated with VS or MCS patients by means of concurrent polysomnography and actigraphy recordings. Nevertheless, a circadian sleep-wake rhythm – i.e. more activity during waking hours and less activity during sleeping hours – can be readily identified from raw actigraphy recordings, and makes fewer assumptions than these unvalidated algorithms (e.g. [24, 25]). In the only article to report actigraphy-based assessments of sleep-wake rhythms in VS, Bekinschtein et al.[26] described a greater deterioration in the circadian rhythmicity evident in the actigraphy of one VS patient relative to an MCS patient. De Weer et al.[27] also reported day-night variation in the amount of movement (as measured by actigraphy) in two TBI MCS patients, but not in a non-TBI MCS patient. However, in neither of these studies was circadian rhythmicity examined statistically.

In order to investigate the relative preservation of circadian sleep-wake rhythmicity in patients in the VS and MCS, we recorded wrist actigraphy from 55 patients (18 VS, 37 MCS) across 4-days, and subjected the data to cosinor rhythmometry analyses (see Methods), a standard statistical approach for circadian rhythm identification. By definition, all of these patients are considered to possess circadian sleep-wake cycles[5-7]. In keeping with the studies described above, however, we expected to see variability in the extent to which circadian sleep-wake rhythms were preserved across patients as a function of aetiology (TBI vs. non-TBI) and diagnosis (VS vs. MCS). We also predicted significant relationships between the behavioural profiles of these patients – as indexed by their CRS-R subscales – and the relative preservation of their circadian sleep-wake rhythms.
METHODS

Patients
Fifty-five patients were recruited from the University Hospital of Liège, Belgium. Actigraphy recordings were made for at least 4-days. All patients were VS or MCS. During their admission, all patients were manually turned in their beds 4-times per day. No patient had skin pressure sores that required more frequent manual turning. No patient required mechanical ventilation. All patients were admitted as part of the same research protocol, and completed the same tasks across each day e.g. behavioural tests, positron emission tomography (PET), and magnetic resonance imaging (MRI). Across their admission, all patients were assessed multiple times with the CRS-R[4]. The highest CRS-R score and diagnosis across this period are shown in Table 1, along with other demographic information. In total, 18 VS patients (mean age 38.0, SD 14.8; 7 TBI) and 37 MCS patients (mean age 35.7, SD 15.2; 24 TBI) contributed data to the study. There was no significant difference in the proportions of each aetiology contributing to the VS and MCS groups. Two two-way ANOVAs with factors of diagnosis (VS, MCS) and aetiology (TBI, non-TBI) conducted on age (in years) and months post-ictus revealed only a reliable main effect of aetiology on age (F(1,51) = 10.363, p<.01) reflecting the older average age of non-TBI patients. Informed consent was obtained from the patients’ surrogate decision makers. The Ethics Committee of the University and University Hospital of Liège provided ethical approval for the study.

Procedure
Actigraphy recordings were made with a Phillips Actiwatch Spectrum attached to the wrist with the highest range of movement (never the hemiplegic side) for a minimum of 4-days, sampled in 1-minute epochs. In order to normalise across patients, only the first 4-days of actigraphy data were included in the analyses for those patients who were admitted for longer than 4-days. The first two-hours of data were also excluded to avoid initial artifacts from attachment of the Actiwatch.

Circadian Rhythm Analyses
Cosinor rhyhmetry analyses[28] were performed on each patient’s dataset individually. This approach uses the least squares method to fit a sine wave with a period of 24-hours to the raw actigraphy data[11, 12, 28]. The rhythmicity of the fit can be described by three parameters: the amplitude, the acrophase, and the mesor. The amplitude of the fit refers to half the distance between the peak and the trough of the fitted wave – in effect describing the amount of movement produced during periods of activity. The acrophase describes the point in the cycle at which activity is maximal. Finally the mesor (an acronym for midline-estimating statistic of rhythm[28]) describes the rhythm-adjusted mean of the wave, or the value around which the fitted wave oscillates. For equidistant data samples (as employed here), the mesor is equivalent to the arithmetic mean of the fitted wave, or the average amount of activity produced across the recording period. The goodness-of-fit of the wave – i.e. the statistical reliability of the circadian rhythm – can also be determined by means of a zero-amplitude F-test[28].
In order to control for over-fitting of noise to the sine wave, this goodness-of-fit p-value was subsequently subjected to a permutation test. Specifically, a set of sine waves with periods ranging in 10-minute intervals from 6-hours to 48-hours were fit to the data (excluding rhythms between 19- and 28-hours since these are defined as circadian periods; see Introduction[11]). The p-values from these 200 zero-amplitude tests were then used to form a surrogate distribution to test the hypothesis that a 24-hour rhythm does not fit the data better than a non-circadian period. When the goodness-of-fit p-value associated with the 24-hour rhythm fell below the smallest 5% of surrogate p-values, the circadian rhythm was considered to be significant at p<.05.
RESULTS
46 out of the whole group of 55 patients (84%) exhibited significant 24-hour rhythms in their actigraphy data after permutation testing. This proportion is significantly lower than the diagnostic expectation that all patients retain significant circadian rhythms (Fisher's Exact Test, p<.01). When separated according to diagnosis, 15/18 VS patients (83%) and 31/37 MCS patients (84%) returned circadian rhythms that passed this statistical test. When separated according to aetiology, 24/31 TBI patients (77%) and 22/24 non-TBI patients (92%) exhibited circadian rhythms. There was no significant effect of diagnosis or aetiology on the proportions of patients exhibiting circadian rhythms (Fisher's Exact Tests, all p>.14). While age significantly differed across aetiologies, it did not significantly correlate with any of the four rhythmicity variables (mesor, amplitude, acrophase, or goodness-of-fit, as indexed by the log-transformed zero-amplitude F-ratio).

VS versus MCS patients
Four one-way ANOVAs with diagnosis (VS, MCS) as the factor of interest revealed main effects of mesor (F(1,54) = 4.441, p<.05), amplitude (F(1,54) = 6.819, p<.05), and goodness-of-fit (F(1,54) = 16.517, p<.001), but not acrophase. Together these reflect the greater average amount of movement across the 4-days (mesor), greater amount of movement during periods of activity (amplitude), and greater statistical reliability of the circadian rhythms (goodness-of-fit) of MCS patients relative to VS patients (see Figure 1).

Due to the high inter-correlations between these three significant rhythmicity variables (all absolute r>.33), all three variables were entered into a backward stepwise logistic regression in order to determine their relationships with diagnosis, over and above the effects of the other two variables. This regression retained only goodness-of-fit in the model as a significant predictor (Wald = 10.189, Beta (SE) = -2.043 (.640), p<.01) indicating significantly weaker circadian rhythms in VS patients relative to MCS patients, regardless of the amount of movement produced by these patients.

Traumatic versus Non-Traumatic Brain Injury
Four one-way ANOVAs with aetiology (TBI, non-TBI) as the factor of interest revealed main effects of amplitude (F(1,54) = 4.299, p<.05) and goodness-of-fit (F(1,54) = 4.226, p<.05), but not mesor or acrophase. These effects reflect the greater amount of movement during periods of activity (amplitude) and the greater statistical reliability of the circadian rhythms (goodness-of-fit) of TBI patients relative to non-TBI patients.

As with the analyses across diagnosis, due to the high inter-correlations between the two significant rhythmicity variables, both were entered into a backward stepwise logistic regression in order to determine their relationships with aetiology, over and above the effect of the other variable. This regression retained neither variable as a significant predictor, likely due to the weak effects of aetiology on these variables (contrast F-values above with those in the analyses across diagnosis).
Relationship Between Rhythmicity and Behavioural Profile

Four backward linear regressions were conducted on the four rhythmicity variables with the six subscales of the CRS-R as predictors. Diagnosis was also included as a predictor since the higher scores on each subscale are also more likely to be associated with MCS and the lower scores with VS. The motor subscale was found to significantly predict mesor \((F(1,54) = 7.792, p < .01, B(SE) = 6.174 (2.212), p < .01)\) and amplitude \((F(2,54) = 6.178, p < .01, B(SE) = 3.462 (1.453), p < .05)\). The visual subscale was found to significantly predict acrophase \((F(1,54) = 4.636, p < .05, B(SE) = -.108 (.050), p < .05)\), and both the visual and motor subscale together were found to predict goodness-of-fit \((F(2,54) = 16.487, p < .001, B\text{-visual(SE)} = .208 (.055), p < .001, B\text{-motor(SE)} = .225 (.071), p < .005)\).
DISCUSSION

On the basis of periodic eye-opening and eye-closure, patients in the VS and MCS are considered to have preserved circadian sleep-wake rhythms\[5, 6\]. However, by means of an indirect measure of sleep-wake rhythmicity – wrist actigraphy – we have shown that a significant proportion of these patients do not exhibit statistically reliable circadian sleep-wake rhythms. The observed variability across patients is consistent with previous smaller studies of circadian rhythmicity in VS and MCS (see Introduction), and is the first evidence from a large-scale study of sleep-wake cycling using the inexpensive and non-invasive method of wrist actigraphy.

While there was no significant difference in the proportion of patients exhibiting significant sleep-wake rhythms between VS and MCS patients, the goodness-of-fit of the circadian rhythms in the data of MCS patients were significantly higher than those of the VS patients (see Figure 1). This result indicates that the circadian sleep-wake cycles of MCS patients were significantly more statistically reliable than those of VS patients. Importantly, this remained true when taking into account the morphology of the rhythm (i.e. its mesor and amplitude), indicating that the effect of diagnosis on the statistical reliability of the circadian rhythms is not driven by simple differences in the amount that a patient moves, but rather reflects differences in the circadian rhythmicity with which this movement occurs.

A master biological clock in the hypothalamic suprachiasmatic nuclei (SCN) is considered to maintain the timing of circadian rhythms. The SCN in turn modulates the activity of the ascending reticular activating system (ARAS) – a circuit of subcortical nuclei responsible for promoting wakefulness (see [29] for a review). One region of the ARAS – the central thalamus – is known to be crucial for the regulation of arousal and has been linked to the disorders of consciousness exhibited by VS and MCS patients[30]. Indeed, the extent of atrophy in this region of the thalamus has been associated with the degree of disability exhibited by these patients[31]. More broadly, greater thalamic atrophy has been observed in VS patients relative to MCS patients using in vivo diffusion tensor imaging[32] (DTI). The weaker circadian sleep-wake rhythms observed in the VS patients in the current study are therefore entirely consistent with these differential patterns of damage to the thalamus.

Aetiology was also shown to have a small effect on the amount that patients moved during periods of activity (amplitude) and the statistical reliability of the circadian rhythm (goodness-of-fit). Similarly, Bekinschtein et al.[20] observed reliable circadian temperature rhythms in only TBI VS patients, but not in non-TBI patients, while De Weer et al.[27] detected sleep-wake activity changes in only TBI MCS patients. The primary neuropathology associated with TBI is diffuse axonal injury with relative preservation of the cortex, while non-TBI involves more widespread damage to the cortex and basal ganglia [33-39]. The greater impairment of circadian rhythms in non-TBI patients relative to TBI patients reported here is therefore consistent with the general patterns of neuropathology associated with the two aetiologies. Indeed, mouse models of
hypoxic brain injury have been shown to result in impaired sleep-wake cycling [40].

Significant relationships were also observed between the behavioural profiles of the patients – as indexed by their CRS-R sub-scales – and aspects of their circadian rhythmicities. A significant positive relationship was found between the motor subscale and the mesor and amplitude of the rhythm. The motor subscale of the CRS-R is scored from flaccid motor tone at its lowest, to object manipulation and automatic motor responses at its highest (before emergence from MCS). Since wrist movements were used to indirectly measure the circadian rhythms, it is unsurprising that greater amounts of movement exhibited by patients across the recording period (mesor, amplitude) are related to their overall abilities to produce motor output during behavioural assessments. This result suggests the need for caution in the use of actigraphy for assessing circadian sleep-wake rhythms since they rely on motor output for a rhythm to be detected. Nevertheless, our analyses have demonstrated that significant changes in the statistical reliability of the rhythms across diagnoses are not dependent on the amount of movement produced, suggesting that actigraphy can be used to assess the statistical reliability of circadian sleep-wake cycles, regardless of the degree of activity exhibited by the patients.

A combination of the visual and motor subscales significantly predicted the goodness-of-fit of the circadian rhythms. The visual subscale score describes behaviours from absent visual startle at its lowest, through fixation and pursuit, to object recognition at its highest. This relationship is of particular interest since the master clock for circadian rhythms, the SCN, is itself timed by light inputs from the retina during the day, as well as melatonin from the pineal gland at night[29]. The more purposeful eye-movements of those scoring highly on the visual subscale may allow for differing levels of light to reach the retina – perhaps through a greater ability to orient toward light or to maintain eye-opening for longer periods – and consequently result in a strengthening of the rhythm via the SCN. The predictive value of the visual subscale could therefore be considered to be consistent with our understanding of the biological generators of sleep-wake rhythmicity. This conclusion is necessarily speculative, however, since it is unclear whether high visual functioning is associated with a greater degree of orientation toward light or longer periods of eye-opening. Further investigation of this relationship will contribute to our understanding of the exogenous queues that drive circadian rhythms in VS/MCS patients.

A significant relationship was also found between the visual subscale of the CRS-R and the acrophase (time of maximal activity) of the rhythm, over and above the contribution of the other CRS-R subscales, or of the diagnosis of the patient. The relationship with acrophase reflects the tendency for patients with higher visual functioning to be most active later in the afternoon than patients with lower visual functioning (Visual Score >=1, Mean acrophase (SD) 18:20 (3-hrs); Visual Score = 0, Mean acrophase (SD) 17:20 (2-hrs)). Consistent with this observation, exposure to higher levels of light has been associated with later peaks of activity in institutionalized individuals[41, 42]. However, the activity peaks of healthy individuals occur earlier in the day than those observed in the patients here,
typically between ~13:30pm and ~16:00pm [24]. It has been observed that the levels of light experienced by institutionalized patients are considerably lower than those of non-institutionalized individuals[42, 43], and since the patients in the current study were residing on a hospital ward during the recording period, it is likely they were exposed to abnormally fluctuating levels of light compared with healthy individuals. Unfortunately, we were unable to record light levels alongside actigraphy, however future studies investigating their contribution to the timing of activity of VS and MCS patients will be invaluable.

Since we inferred the circadian rhythms of patients from wrist actigraphy, it is likely that the recordings contain some levels of exogenous activity, perhaps from nurses moving the patient from bed to chair. Since these patients were all admitted to the same ward of the University Hospital of Liège as part of the same research protocol, they all received equivalent levels of care and were involved in the same assessments throughout the day – e.g. behavioural tests, PET, and MRI. As a result, the potential exogenous noise in the data would then be equally distributed across all patients. Our conclusions regarding the effects of diagnosis, aetiology, and behavioural profile on sleep-wake cycles, therefore, would remain valid despite this potential confound. The use of simultaneous video-recordings would allow for the exclusion of activity that is generated exogenously and would further validate our findings.

Some prescribed medications may also have an effect on actigraphy-detected circadian rhythms. For example, treatment for spasticity (e.g. with Baclofen) is common in VS/MCS patients and may increase the amount of movement that will be detected with actigraphy, while psychoactive medications (e.g. Amantadine) may also serve to exogenously modulate a patient’s level of arousal. Caution in this regard is not limited to actigraphy, however, since psychoactive medications will also alter the resting EEG of a patient, thereby modulating the level of wakefulness that will be inferred from polysomnography. Due to differences in the wishes of families and physicians, a wide variety of medications are prescribed to VS and MCS patients (see Table 2 for details). As a result, it is not possible to statistically control for each of these drugs individually, nor for their many interactions. Nevertheless, there is no reason to believe that prescribed medications would systematically differ between VS and MCS groups due to the paucity of treatment recommendations for all patients with disorders of consciousness ([44]). Future controlled clinical trials are needed in order to provide insights into the effects of specific medications not only on circadian rhythmicity, but also on VS/MCS patient outcome in general.

A final caveat is that the apparent absence of reliable circadian rhythms in some of our patients may be a result of a lack of sensitivity of the actigraphy method, rather than the true absence of those rhythms. While wrist actigraphy has been validated for sleep assessment in patients with C5-C7 tetraplegia [23], these patients are nevertheless capable of small but purposeful wrist movements. Patients in the VS, however, are by definition unable to produce purposeful movements, although spontaneous movements are common. Similarly, due to the heterogeneity of brain injuries of these patients, it is not clear whether the presence of actigraphy-detected waking is necessarily indicative of concurrent
cerebral waking. Future validation of the relationship between polysomnography and actigraphy measures of sleeping and waking in VS and MCS patients is needed in order to fully characterize the nature of their circadian rhythms.
CONCLUSIONS
Our analyses indicate a greater impairment of circadian sleep-wake cycling in patients in the VS compared with those in the MCS, and in those with non-TBI compared with TBI. The significant differences observed between VS and MCS patients support the conclusion that these are diagnostically distinct entities. However they also suggest that despite periods of eye-closure and eye-opening, sleep-wake cycles are not necessarily present despite the clinical criteria for these conditions[5-7]. Wrist actigraphy is considerably less expensive and less invasive than other forms of sleep-wake monitoring, and may therefore provide a reliable means of determining the extent to which these cycles are preserved in individual patients. These recordings could also allow clinicians and researchers to identify the time of day in which a patient is most active, in order to schedule behavioural and/or neuroimaging assessments for a time that maximizes the likelihood of detecting an appropriate response (see [26]). Future validation of the relationship between actigraphy and polysomnography measures of sleeping/waking in VS and MCS patients will allow for a more complete understanding of the physiological nature of these circadian rhythms. Follow-up studies will also determine the prognostic utility of wrist actigraphy for VS and MCS patients.
Table 1. Demographics and circadian rhythm fits for all patients. The final column indicates whether the circadian rhythm fit was significant or not. VS: Vegetative State, MCS: Minimally Conscious State, TBI: Traumatic Brain Injury.

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<th>Age (Years)</th>
<th>Post-Ictus (Months)</th>
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<th>Aetiology</th>
<th>CRS-R</th>
<th>Mesor</th>
<th>Acrophase</th>
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<td>24</td>
<td>Trauma</td>
<td>3 x Baclofen 25mg  3 x Domperidone 10mg  2 x Clonazepam 2.5mg  1 x Promethazine 16mg</td>
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<tr>
<td>25</td>
<td>Trauma</td>
<td>1 x Amantadine 100mg  2 x Baclofen 10mg  1 x Esomeprazole 20mg  1 x Tizanidine 4mg</td>
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<td>26</td>
<td>Trauma</td>
<td>2 x Valproic Acid 7.5ml  1 x Lamotrigine 25mg  3 x Baclofen 10mg  2 x Esomeprazole 20mg  1 x Enoxaparin Sodium 20mg</td>
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<tr>
<td>27</td>
<td>Trauma</td>
<td>1 x Esomeprazole 40mg  3 x Clonazepam 2mg  3 x Paracetamol 1000mg  2 x Levetiracetam 500mg  3 x Benserazide 250mg</td>
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<tr>
<td>28</td>
<td>Trauma</td>
<td>1 x Acetylcysteine 600mg  1 x Esomeprazole 20mg  1 x Baclofen 25mg</td>
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| 28   | Trauma    | 1 x Atenolol 50mg  
1 x Enoxaparin Sodium 40mg  
1 x Glycopyrrolate 10mg |
| 29   | Trauma    | 1 x Amantadine 100mg  
1 x Paroxetine 20mg  
3 x Domperidone 10mg  
1 x Esomeprazole 20mg |
| 30   | Trauma    | 2 x Bisopropol 2.5mg  
1 x Esomeprazole 20mg  
1 x Amantadine 100mg  
3 x Metamizole 500mg  
3 x Meropenem 1000mg  
3 x Ciprofloxacin 400mg |
| 31   | Trauma    | 3 x Baclofen 25mg  
1 x Amantadine 100mg  
1 x Escitalopram 10mg  
1 x Enoxaparin Sodium 40mg |
| 32   | Trauma    | 1 x Omeprazole 20mg  
1 x Ranitidine 300mg  
3 x Valproic Acid 2ml  
1 x Sertraline 2.5mg  
2 x Baclofen 5ml |
| 33   | Trauma    | 2 x Bisopropol 2.5mg  
1 x Esomeprazole 20mg  
1 x Amantadine 100mg  
3 x Metamizole 500mg  
3 x Meropenem 1000mg  
3 x Ciprofloxacin 400mg |
| 34   | Trauma    | 3 x Baclofen 25mg  
1 x Amantadine 100mg  
1 x Escitalopram 10mg  
1 x Enoxaparin Sodium 40mg |
| 35   | Trauma    | 1 x Omeprazole 20mg  
1 x Ranitidine 300mg  
3 x Valproic Acid 2ml  
1 x Sertraline 2.5mg  
2 x Baclofen 5ml |
| 36   | Trauma    | 2 x Bisopropol 2.5mg  
1 x Esomeprazole 20mg  
1 x Amantadine 100mg  
3 x Metamizole 500mg  
3 x Meropenem 1000mg  
3 x Ciprofloxacin 400mg |
| 37   | Trauma    | 3 x Baclofen 25mg  
1 x Amantadine 100mg  
1 x Escitalopram 10mg  
1 x Enoxaparin Sodium 40mg |
| 38   | Anoxia    | 1 x Levetiracetam 3000mg  
1 x Phenobarbital 100mg  
1 x Esomeprazole 40mg  
1 x Simvastatin 40mg  
1 x Aspirin 100mg  
1 x Escitalopram 10mg |
| 39   | Anoxia    | 1 x Levetiracetam 3000mg  
1 x Phenobarbital 100mg  
1 x Esomeprazole 40mg  
1 x Simvastatin 40mg  
1 x Aspirin 100mg  
1 x Escitalopram 10mg |
| 40   | Anoxia    | 1 x Levetiracetam 3000mg  
1 x Phenobarbital 100mg  
1 x Esomeprazole 40mg  
1 x Simvastatin 40mg  
1 x Aspirin 100mg  
1 x Escitalopram 10mg |
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| 41   | Anoxia    | 1 x Amiodarone 200mg  
1 x Clopidogrel 75mg  
3 x Baclofen 25mg  
2 x Diltiazem 60mg  
1 x Trazodone 100mg  
1 x Lorazepam 2mg  
2 x Prazepam 10mg  
1 x Enoxaparin Sodium 40mg  
2 x Acetylcysteine 400mg  
3 x Dantrolene 25mg |
| 42   | Aneurysm  | 1 x Bisopropol 5mg  
3 x Baclofen 10mg  
1 x Levothyroxine 50mg  
1 x Prednisolone 5mg |
| 43   | Meningitis | 1 x Moxifloxacin 500mg  
1 x Levetiracetam 500mg  
2 x Ranitidine 150mg  
1 x Enoxaparin Sodium 40mg |
| 44   | Anoxia    | 2 x Levetiracetam 1000mg  
1 x Phenytoin 500mg  
6 x Valproic Acid 6.5ml  
1 x Lorazepam 1mg  
1 x Ranitidine 300mg  
2 x Enoxaparin Sodium 60mg |
| 45   | Anoxia    | 3 x Valproic Acid 600mg  
1 x Ranitidine 150mg |
| 46   | Cardio-respiratory Arrest | 2 x Acetylcysteine 200mg  
1 x Enoxaparin Sodium 60mg  
1 x Ranitidine 10ml |
| 47   | Anoxia    | 1 x Atenolol 25mg  
2 x Modafinil 100mg |
| 48   | Anoxia    | 3 x Baclofen 10mg  
1 x Diazepam 5mg  
1 x Prazepam 5mg  
2 x Omeprazole 20mg  
1 x Levocetirizine 10mg |
| 49   | Trauma    | 3 x Dantrolene 100mg  
3 x Carbamazepine 200mg  
3 x Baclofen 25mg  
1 x Omeprazole 20mg  
1 x Enoxaparin Sodium 40mg |
| 50   | Trauma    | 3 x Baclofen 25mg  
1 x Pantoprazole 20mg  
3 x Dantrolene 100mg  
1 x Enoxaparin Sodium 40mg |
| 51   | Trauma    | 3 x Baclofen 25mg  
1 x Trazodone 100mg  
1 x Enoxaparin Sodium 40mg  
2 x Levetiracetam 5ml |
| 52   | Trauma    | None |
| 53   | Trauma    | 4 x Paracetamol 500mg  
3 x Baclofen 10mg  
2 x Esomeprazole 20mg  
4 x Acetylcysteine 300mg |
| 54   | Trauma    | 2 x Oxcarbazepine 450mg  
1 x Levetiracetam 5ml  
1 x Baclofen 25mg  
1 x Tizanidine 4mg |
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<th>55</th>
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<td>2 x Ranitidine 150mg</td>
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<td></td>
<td>2 x Lamotrigine 25mg</td>
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<td>3 x Baclofen 25mg</td>
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<tr>
<td></td>
<td>1 x Enoxaparin Sodium 40mg</td>
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FIGURE LEGENDS
Figure 1. Actigraphy data from four representative patients. Each panel shows intensity of activity across each recording day. Red lines indicate the fit of the circadian rhythm. Note the periodic structure of the activity of the two patients with significant rhythms (left), compared with those without (right). Patients 19, 21, 52, and 45 are shown (clockwise from top-left). Log activity data smoothed across 5-minutes is plotted for clarity of visualization.

COMPETING INTERESTS
All authors declare no competing interests.

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AUTHOR CONTRIBUTIONS
DC designed and conducted the analyses and wrote the manuscript. AT, AD, MAB, OG, and AV collected all data and contributed to the final manuscript. JCN contributed to the analyses and the final manuscript. TAB, AMO, and SL provided conceptual input and contributed to the final manuscript.
REFERENCES


