



Registry and survey of circadian rhythm sleep-wake disorder patients

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ABSTRACT

Objective: Circadian Sleep Disorders Network has created a registry of circadian rhythm sleep-wake disorder (CRSWD) patients, and a survey of their experiences. The purpose of the registry is to provide volunteers willing to participate in research; the purpose of the survey is to fill some of the knowledge gaps on these disorders, including information on subjective patient experience and the efficacy and durability of treatments.

Researchers are invited to contact Circadian Sleep Disorders Network for permission to use the registry to find potential research participants, and to further analyze the survey data.

Patients: Over 1627 patients have participated; 1298 have completed the entire survey. Here we present results based on the 479 clinically diagnosed CRSWD patients.

Methods: The survey covers a variety of topics relating to CRSWDs, including diagnosis, comorbidities, treatments, and work/educational accommodations.

Conclusions: Results of this survey diverged from much of the literature. More than half the participants reported tiredness even when sleeping on their preferred schedule. While depression may cause sleep problems, our data suggests that sleep/circadian problems often precede depression.

There were more people suffering from sighted non-24-hour sleep-wake rhythm disorder than some of the literature would lead us to expect.

Current treatments did not appear to be helpful to a large percentage of our participants. Most of them did not find light therapy helpful and nearly all participants who tried phase-delay chronotherapy reported at best only short-term improvement. A sizable proportion of people who tried phase-delay chronotherapy subsequently developed non-24-hour sleep-wake rhythm disorder.

1. Introduction

Human sleep typically exhibits a rhythmic 24 h pattern following the day-night cycle driven by the underlying circadian rhythm [1]. Circadian rhythm sleep-wake disorders (CRSWD) are defined as alterations in the sleep-wake rhythm resulting from changes to the underlying clock or its ability to synchronize with the external environment [2]. These can include alterations in the phase of the rhythm, such as delayed sleep-wake phase disorder (DSWPD) where patients fall asleep and get up much later than average; and advanced sleep-wake phase disorder (ASWPD), which is characterized by early sleep-wake times. Alterations in the period of this rhythm constitute non-24-hour sleep-wake rhythm disorder (N24SWD). N24SWD patients, as the name implies, follow a sleep-wake cycle that is longer or (rarely) shorter than 24 h. They may, for example, fall asleep an hour later each day, until their sleep cycle makes a complete rotation around the clock. N24SWD can present in individuals who are both sighted and not sighted. Finally, in irregular

sleep-wake rhythm disorder (ISWRD), the rhythmic pattern is lost, so that patients sleep in multiple irregular intervals during a 24-h period.

CRSWDs are hypothesized to be partially due to disturbances in this biological clock [3]. While the sleep wake cycle is the most obvious output of the clock, in reality hundreds or more biological processes follow a circadian pattern [4]. Some of the more prominent rhythms known to be altered in circadian disorders are those of the core body temperature and of hormones including melatonin and cortisol [5–7]. Studies of the transcriptome during mis-timed sleep reveal effects on gene expression in multiple target organs [4].

Both circadian rhythms and sleep are essential to human health. Consequently, circadian rhythm sleep-wake disorders can have a devastating effect on the lives of those with these conditions [8,9]. In severe cases this has been termed sleep-wake schedule disability [10].

Some physicians at referral centers have published their experiences with CRSWD patients [11–13]. However, until now there has been no available source reflecting real-world patient experience of these

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disorders or a centralized registry of CRSWD patients.

In response to this, Circadian Sleep Disorders Network, an international patient non-profit organization, created a patient registry and survey of CRSWD patients. The project has two main purposes. First, the registry aims to provide a central source of potential volunteers for the research community, along with the information necessary to select desired sub-populations. This information has already been used to solicit participants in an on-going drug trial by Vanda Pharmaceuticals Inc [14]. Second, the survey collected data on a large population of CRSWD sufferers. This new information may suggest different directions for future research.

2. Materials and methods

2.1. Registry and survey

In 2016 Circadian Sleep Disorders Network created a registry of people who signed up on the Invitae®

website and self-identified as having a circadian rhythm sleep-wake disorder. The survey includes a questionnaire consisting of 122 questions about patients' experiences with their disorder, and it is currently still open to respondents.

The patient registry and survey was first advertised on the website of Circadian Sleep Disorders Network (<https://www.CircadianSleepDisorders.org>) in December 2016. The survey covers a variety of topics relating to CRSWDs including diagnosis, comorbidities, treatments, and work/educational accommodations.

2.2. Hosting

We sought commercial hosting for a registry and survey that would meet HIPAA (U.S. Health Insurance Portability and Accountability Act) and GDPR (E.U. General Data Protection Regulation) standards, and that would also permit us and others to view and analyze de-identified survey responses. The company we selected was bought by Invitae in 2017, who rebranded the survey support platform as a "Patient Insights Network (PIN)®" (<https://pindirectory.invitae.com/>).

2.3. Consent

All participants completed an online consent form prior to their participation, in which they were asked multiple consent questions including their preferences for sharing their de-identified information, whom the information can be shared with, if they would like to be contacted about new research, and if they want to share their contact information with patient advocacy groups. The choices participants made for the consent questions can be updated at any time.

Invitae assures that participants' information is de-identified: anyone accessing the survey responses does not know the identity of the respondents. Furthermore, participants can only be contacted by researchers if they have given prior consent to be contacted by Invitae for research. If a researcher asks Invitae to contact certain people based on their responses, Invitae will send a request to those people to contact the researcher.

There was no treatment or intervention or follow-up of any kind, and no direct contact with participants, so IRB approval is not required.

2.4. Recruitment

We solicited participants through our Circadian Sleep Disorders Network newsletter, our website (<https://www.CircadianSleepDisorders.org>), our Facebook page (<https://www.facebook.com/CircadianSleepDisordersNetwork>), and various Facebook groups formed around DSWPD or N24SWD. Patients were solicited world-wide, but since the survey is in English, most respondents (87 %) live in five English-speaking countries. Data for this study was collected between

December 1, 2016 and August 18, 2022. In total, 1627 people participated, of whom 1298 completed the entire survey.

2.5. Sighted only

Note that the survey platform was not conducive to navigation by blind people; all of our respondents to date are sighted, as confirmed by the responses to the question "Are you blind?" Characteristics we report for N24SWD are therefore only applicable to sighted N24SWD. Indeed, the etiology of sighted N24SWD is different from blind N24SWD, and there is no reason to expect patient experiences to be the same [15].

2.6. Survey questions

Survey questions were developed by members of the Board of Directors of Circadian Sleep Disorders Network in 2016. Each of them had their own experience with a CRSWD, and some familiarity with the research literature. In addition, several board members had been in active discussions with other people with CRSWDs via email and social media for 10 years or more. Based on this knowledge and experience, questions of interest that reflected the patient experience were developed. These were then tested on the board members for further refinement before being ported to the survey platform.

The survey contains 122 questions, which can be viewed, without signing up, at <https://www.circadiansleepdisorders.org/registry/survey.questions.php>. Most of these are multiple choice. Some allowed free-form text answers. In all cases the questions were answered by the respondents themselves, not their doctors.

Some questions are only relevant under certain conditions; these questions are not asked if the conditions are not present according to previous answers, using branching logic. One example is the presence of N24SWD; questions about how many hours the respondent advances each day would not be asked of people without N24SWD. Another is having different schedules on work days versus non-work days; separate questions about how many hours of sleep the person gets on work days would not be asked if their schedule is the same.

Since responses were multiple choice, participants had to round responses to some questions (e.g., sleep duration) to whole hours.

We estimate it would take about an hour to complete the entire survey.

2.7. Data format

De-identified respondents' data was downloaded from Invitae in the form of a large spreadsheet. Each row of the spreadsheet contained all the responses of one respondent during one survey session. For questions that allowed only a single response, the question was assigned one column of the spreadsheet. For questions that allowed multiple responses, each response option was assigned one column, so the responses to these questions spanned multiple columns.

Data was only available for download from the 1627 respondents with sufficient informed consent. Due to host compliance with GDPR privacy requirements, only responses to multiple-choice questions are currently available for download.

2.8. Removal of incomplete entries

Of the 1627 patients, 329 survey sessions did not progress through to the end. These were not included in this study, as partial results would have interfered with statistical analysis. We also included only the most recently completed surveys of participants who had completed the survey more than once, using a Visual Basic for Applications (VBA) script. That left 1298 completed surveys.

2.9. Limiting data to clinically diagnosed patients

Respondents were asked to select which circadian rhythm sleep-wake disorder they believe they have, as well as which have been formally diagnosed by a medical professional. In both cases the choices were DSPWD, ASWPD, irregular sleep-wake rhythm disorder (ISWRD), and N24SWD.

To avoid questions about whether self-diagnosed patients properly diagnosed themselves, we present results based only on the 479 respondents who were clinically diagnosed.

3. Results and discussion

Responses were analyzed using Excel formulas to count responses, compute averages, and perform other computations.

Many of our findings contradict common assumptions among researchers and clinicians; others lend support to or expand on hypotheses in the field.

3.1. Subtypes

Of the 479 respondents in this sample, 391 (82 %) had DSPWD, 101 (21 %) had N24SWD, 7 (1 %) had ASWPD, and 26 (5 %) had ISWRD. Some of these patients had multiple CRSWD diagnoses, possibly at different times.

Previous publications have suggested that sighted Non-24 is very rare [15]. For example, a telephone survey that found a prevalence of 0.13 % for DSPWD found no cases of N24SWD (sighted or blind) among the 1525 patients surveyed [16].

We are limited in the conclusions we can draw about the true prevalence of sighted Non-24 based on a self-selected survey population. For example, the large number of sighted N24SWD respondents may in part reflect the fact that N24SWD interferes so catastrophically with people's lives that they are more motivated to take the time to participate in a survey leading to sample bias. At the same time the relatively large number of respondents reporting this disorder does suggest that sighted Non-24 may be less rare than has been presumed.

Very few respondents reported ASWPD. This could reflect a true low prevalence of the disorder or it may be due to ASWPD being unlikely to interfere with hours for school or work, causing less need for peer support or medical diagnosis or treatment, and less likelihood that these patients would participate in the survey [17].

3.2. Difficulty in obtaining diagnosis

24 % of diagnosed patients took 10 years or more, from when they first sought help for their sleep disorders, to receive an accurate diagnosis. 77 % were misdiagnosed initially, many with multiple incorrect diagnoses over the years. Chief among these incorrect diagnoses: depression; insomnia; or no diagnosis at all (i.e., respondent selected option "Doctor said nothing is wrong").

Difficulty obtaining a diagnosis appears to be a serious issue for people with CRSWDs, and multiple misdiagnoses were a common problem. This indicates a need for greater attention to these disorders by the medical community.

3.3. Tiredness

One area of particular interest is the connection between abnormal sleep timing and other symptoms such as tiredness. It has been asserted that tiredness in CRSWDs only occurs when sleep is curtailed by attempting to sleep at a time not consistent with the patient's internal circadian rhythm [2].

When sleeping on what respondents believed was their body's preferred schedule, 45 % felt alert during the day, 55 % still felt tired, and 19 % felt very tired or worse. The words used here ("alert", "tired")

are the words in the response options selected by the users.

On average, respondents sleeping on their preferred schedule felt they needed 8.7 h of sleep, with 25 % of participants needing 10 or more hours of sleep to function adequately.

This set of findings suggests a complex interaction between circadian rhythms and tiredness, with several possible reasons, including: (i) an abnormality of circadian function leads to tiredness which is not mitigated by sleeping at the preferred time; (ii) "needing" more sleep leads to circadian disorders (for example, someone may sleep through the phase advance portion of the light PRC); (iii) one common factor (neurochemical, hormonal, homeostatic) leads both to overall tiredness and changes in circadian rhythms. (iv) tiredness may result from internal desynchronization of the sleep-wake rhythm relative to other circadian processes (such as the temperature cycle) or a loss of synchrony between different circadian processes, a phenomenon that has been termed dyschronism [18].

We also note that it can take several weeks for a patient to entrain to a new schedule, and they might report fatigue during this adjustment. The relevant survey question asks "When you sleep on your body's preferred schedule ..." with the intent of Inquiring about an established schedule, and we believe most respondents understood this. But that was not made explicit. However, it has been the personal experience of the authors and many of our contacts on social media, of having maintained a regular schedule of sleeping on our bodies' preferred schedules (at a fixed time for DSPWD or a uniformly delaying time for N24SWD) for long periods of time, yet still experiencing chronic tiredness. While acknowledging that our data may somewhat overestimate the numbers, it seems reasonable to conclude that the tiredness is a common experience.

3.4. Work impact

As expected, tiredness and other adverse impacts, such as late arrival at work or school, are even more severe when patients are forced to alter their sleep times for work or other obligations.

Of those who had to get up for work, school, or family reasons, the average sleep duration on workdays was 5.9 h. 61 % got 6 h or less sleep on workdays. This is significantly less than the recommended 8 h a night for adults [19].

63 % were late for work or school at least once a week, which one would expect to have a significant impact on job or school evaluations.

3.5. Comorbidities

58 % of participants also suffered from depression. It has long been recognized that depression can result in changes in circadian rhythms [20]. However, 57 % of our respondents reporting depression said that the depression started *after* the CRSWD had developed. This suggests that the arrow of causality is more often in the other direction, with circadian changes leading to depression [21,22]. This may be a biological effect [23]. It may also be a result of the psychological struggle against feeling tired all the time. A role for social factors is also apparent. It would not be surprising that conditions that greatly interfere with both work life and social life – often to the point of disability – could lead to depression [10]. This may be particularly true for CRSWD where the disorder is not well understood and the patient is often blamed for what is outside their control [24].

51 % of respondents with a CRSWD had also been diagnosed with another sleep disorder, most commonly bruxism, sleep apnea, or restless leg syndrome. Restless leg syndrome is reported to have circadian aspects, which may contribute to its comorbidity with CRSWDs [25]. The presence of other sleep disorders could complicate diagnosis and may contribute to the diagnostic delay previously noted.

46 % of respondents felt they were unusually sensitive to bright light. This is of interest in relation to studies that have suggested sensitivity to the phase-shifting effect of light as an etiological factor in DSPWD [26].

This is supported by the finding that 26 % of our participants reported migraines. Studies have connected photophobia and light-induced migraines to the same ipRGC cells that perform the crucial light sensing role in regulating circadian rhythms [27]. ipRGC cells project both to the hypothalamus via the retinohypothalamic tract, regulating circadian rhythms, but also via a monosynaptic projection to a subset of dura-sensitive cells in the posterior thalamus that are involved in migraine [27]. Thus, pathways exist by which stimulation of ipRGCs could contribute to both circadian disorders and migraine.

3.6. Treatments

3.6.1. Light

Of the 263 people (55 % of CRSWD patients) who tried light therapy, 30 % are still using it. Only 13 % of those who used light therapy said they achieved their desired sleep times. Only 26 % said it helped somewhat or more. Thus light treatment was not successful (as interpreted by the patient) in most patients.

There are some limitations in interpreting this result. It may be that our survey respondents included relatively more people who were unsuccessfully treated (by any modality); those who were successfully treated would no longer be involved in online support groups or web sites where the survey was advertised. We also do not know the details of how light therapy was prescribed or the degree of compliance. Nevertheless, these results would seem to suggest a substantial number of patients in whom light treatment is not efficacious.

It should be noted that while there are multiple clinical trials of light treatment reported in the literature, these have significant limitations, including small numbers of participants and the difficulty of devising a placebo form of light therapy [28,29]. Studies often lack long-term evaluation and emphasize physiological measurements rather than patients' subjective feelings and ability to function in the world [29]. Consequently, the American Academy of Sleep Medicine, in their practice guidelines, found that there was not sufficient evidence to recommend light treatment for either DSWPD or N24SWD [30]. It is also worth noting that studies may report light treatment as successful if it advances sleep by an hour or so [31]. This may not be considered a success by a DSWPD patient who falls asleep at 4 a.m., which was the most common sleep onset time in our survey. Finally, as mentioned, many respondents reported sensitivity to bright light. If light sensitivity is part of the cause of DSWPD or N24SWD, light therapy is less likely to be either tolerated or successful [26].

3.6.2. Light restriction

Of the 228 people (48 % of CRSWD patients) who tried light restriction (avoidance or reduction of evening light), 59 % are still using it. 32 % said it helped somewhat or more. In line with the observations on light sensitivity, evening light restriction fares a bit better than morning light exposure among our respondents, but the rate of success was still dismayingly low.

3.6.3. Melatonin

Of the 386 people (81 % of CRSWD patients) who tried melatonin, most used it within an hour of bedtime. Only 37 % are still using it. Only 12 % said they achieved their desired sleep times. Melatonin was by far the most commonly attempted treatment in our survey, but had a very poor success rate in terms of patient satisfaction.

Many of the same limitations mentioned regarding light therapy also apply here, including a possible bias toward surveying non-responders, but the results do suggest a large number of patients have tried melatonin without achieving their desired sleep times. Melatonin is also a particularly tricky substance to apply therapeutically as both the timing and dose-response curve may seem counter-intuitive. Over the counter melatonin is often sold in doses of 3–10 mg, but studies have indicated that the optimal dose for circadian disorders is 0.5 mg or less, with larger doses causing a "spillover" which can negate any benefit or even worsen

phase delays [32]. Most of our respondents took doses of 3–10 mg, with fewer taking lower doses. Unlike sleeping medications which are prescribed to be taken at bedtime, melatonin has a maximal phase advancing effect when taken 2–4 h before dim-light melatonin onset (DLMO) [33]. Typically, this would be 4–6 h before bedtime, although the time between DLMO and sleep onset is highly variable [34]. Many patients may not be aware of the best time for melatonin use or may not be able to use it at that time due to acute undesired sedative effects. The most common time for our respondents to take melatonin was 1 h before bedtime with very few taking it 4–6 h before bedtime. In addition, measurement of DLMO is not available to most patients and assuming DLMO occurs 2 h before sleep onset may not always be accurate. There are no standardized guidelines for the timing of melatonin administration in N24SWD where DLMO may change daily, or melatonin production may be entirely absent [6]. We did not ask about the brand of melatonin supplement, and we recognize the lack of regulation of over-the-counter supplements which could confound the results [35].

3.6.4. Phase-delay chronotherapy

The most disturbing results concern the use of phase-delay chronotherapy as a treatment for DSWPD. This treatment regimen involves the patient delaying their sleep more each night – 3 h a night was the original suggestion – until their sleep shifted to a more desirable wake time [36].

Of the 201 people (42 % of all CRSWD patients, 51 % of DSWPD patients) who tried phase-delay chronotherapy, only 1 % said it succeeded indefinitely. 95 % said it helped for a month or less or not at all.

Of the people who tried phase-delay chronotherapy, 11 % subsequently received a clinical diagnosis of N24SWPD, while 26 % believe their DSWPD became N24SWD after using it. Many of those never went back to the doctor who recommended the chronotherapy treatment, since it had such a disastrous result for them. We believe the 11 % doesn't fully capture the extent of the problem, while the 26 % may over-estimate it because some people may have self-diagnosed N24SWD incorrectly.

This risk of chronotherapy was first reported by Oren and Wehr in 1992 [8]. It is particularly concerning as N24SWD is usually regarded as the more severe disorder, being "extremely debilitating in that it is incompatible with most social and professional obligations" [8]. We do not know how many of our respondents were prescribed phase-delay chronotherapy and how many undertook it on their own, either reading about it or just doing what might seem a natural idea for someone whose sleep is severely delayed. The low success rate and the high risk suggest that even 30 years after the risk was first published it is not widely recognized, putting many patients in danger of progressing to N24SWD from attempting phase-delay chronotherapy.

3.7. Limitations

The survey is in English, and most respondents live in English-speaking countries.

The platform is not conducive to navigation by blind people; all of our respondents to date are sighted.

We recognize that, if treatment of the circadian rhythm disorder worked for a patient, they would be less likely to seek out support groups and spend time filling out our survey. Therefore, our sample may be biased towards people for whom the treatments did not work.

The survey is taken by patients, and one of its purposes is to identify patient perspectives on treatment efficacy. However, some respondents may be rushed, or may not fully understand the questions. Some may remember their experiences incorrectly.

3.8. Implications for future research

There is a wealth of data available in our survey, and multiple ways to analyze it further. For example, further studies could involve the

stratification of data into groups of people with DSWPD vs N24SWD diagnoses. We could examine the success rate of treatments as a function of the number of hours needed to shift (for DSWPD). Similarly, we could investigate the success rate of melatonin depending on the number of hours before bedtime it was taken. For patients who developed N24SWD as a result of using phase-delay chronotherapy, we could investigate whether other factors made that more likely.

Comparison of the results reported above for clinically diagnosed patients with the corresponding results for the self-diagnosed respondents might be interesting.

4. Conclusions

Patient responses to our survey cast light on aspects of CRSWDs that have not always been reflected in prior research. Additional analysis of these data, and future surveys, promise to provide further insight.

Researchers are invited to use the registry to find potential volunteers for study, and to further process the collected data. We welcome more formal research to further elucidate patient experience with these disorders.

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CRediT authorship contribution statement

Peter Mansbach: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Validation, Writing – original draft, Writing – review & editing. **James S.P. Fadden:** Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing. **Lynn McGovern:** Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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