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Disease Symptomatology and Response to Treatment in People with Idiopathic Hypersomnia: Initial Data from the Hypersomnia Foundation Registry

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Abstract

Objective/background: Knowledge of idiopathic hypersomnia symptomatology derives from clinical case series. Web-based registries provide complementary information by allowing larger sample sizes, with greater geographic and social diversity.

Patients/Methods: Data were obtained from the Hypersomnia Foundation's online registry. Common clinical features of idiopathic hypersomnia and other central disorders of hypersomnolence were queried, for the last thirty days and when symptoms were most severe. Symptoms were compared between idiopathic hypersomnia participants with and without long sleep durations and between participants with idiopathic hypersomnia and those with either form of narcolepsy. Frequency of medication use and residual symptoms on medication were evaluated.

Results: Five-hundred sixty-three registry respondents were included, with idiopathic hypersomnia (n = 468), narcolepsy type 2, (n = 44), and narcolepsy type 1 (n = 51). "Brain fog," poor memory, and sleep drunkenness were all present in most idiopathic hypersomnia respondents, with brain fog and sleep drunkenness more commonly endorsed by those with long sleep durations. Eighty-two percent of participants with idiopathic hypersomnia were currently treated with medication, most commonly traditional psychostimulants such as amphetamine salts. Among treated patients, symptoms improved while on medication, but substantial residual hypersomnia symptoms remained. Participants with narcolepsy type 1 were more likely than those with

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idiopathic hypersomnia to endorse intentional and unintentional daytime naps and automatic behaviors.

Conclusions: Symptoms of idiopathic hypersomnia extend well beyond excessive daytime sleepiness, and these symptoms frequently persist despite treatment. These findings highlight the importance of online registries in identifying gaps in the use and effectiveness of current treatments.

Keywords

registry; idiopathic hypersomnia; narcolepsy; long sleep; sleep drunkenness; treatment

1. Introduction

Idiopathic hypersomnia is a chronic disorder of presumed neurologic origin that manifests as severe daytime sleepiness, after exclusion of other known causes of daytime sleepiness, such as circadian rhythm disorders, sleep deprivation, or dysregulation of REM sleep state. It is traditionally characterized as rare, although a large, population-based study revealed that symptoms consistent with idiopathic hypersomnia are present in approximately 0.5% of the general population (1). The pathophysiology of idiopathic hypersomnia is currently unknown. Proposed mechanisms include abnormal potentiation of the GABA-A system (2), circadian system dysregulation (3–5), autonomic dysfunction (6, 7), and altered functional connectivity or regional brain activity (8–10).

Separate from questions about pathophysiology, much remains unknown about idiopathic hypersomnia at a phenomenological, symptomatic level. Current knowledge has been heavily informed by clinical case series of patients presenting to sleep clinics (11–15). These have the clear advantage of face-to-face evaluation and diagnosis. However, because each individual sleep center may see relatively few patients with idiopathic hypersomnia, published case series are generally composed of fewer than 100 patients. Furthermore, because of regional variation in referral, practice, and other factors, patients at a single center may not be representative of the larger population of individuals with idiopathic hypersomnia.

Web-based registries represent an expeditious way to collect novel phenotypic information from a diverse array of people with a given disease. Although most typically used to study relatively rare conditions (16), including, for example, conditions such as sarcoid (17) or neurofibromatosis (18), internet-derived registries have also seen use for more common medical conditions (e.g., chronic back pain, multiple sclerosis) (19, 20). The United States Agency for Healthcare Research and Policy defines a patient registry as “an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition or exposure, and that serves one or more predetermined scientific, clinical or policy purposes” (21). Another function of registries is to generate data on the impact and cost-effectiveness of treatments in the real world (16). Such information can identify potential shortcomings in the uptake of treatments or reveal gaps in patient care. Within the Sleep Medicine arena, for example, the internet-based survey conducted by the Unite Narcolepsy collaboration

highlighted the problematic diagnostic delay and frequent residual symptoms despite treatment present among people with narcolepsy (18).

Using a primarily United States-based patient registry for hypersomnia disorders, we sought to evaluate symptoms and phenomenology in a large group of participants with IH. In particular, our goals were to: 1) survey symptoms of IH in a large population, including whether symptoms differed based on habitual sleep durations; 2) survey current or prior use of different medication classes for IH; 3) determine reported persistence or resolution of symptoms while on medication for IH; and 4) perform preliminary comparison of symptomatology in those with IH versus those with narcolepsy without cataplexy (narcolepsy type 2, NT2).

2. Material and Methods

The Hypersomnia Foundation, a nonprofit organization for people with idiopathic hypersomnia and related disorders of excessive daytime sleepiness (hypersomniafoundation.org), launched an online patient registry in 2016. The registry questionnaire was developed by members of the Hypersomnia Foundation Board of Directors (including author CFM), members of the Foundation Medical Advisory Board (authors LMT, DTP), and other content experts (author DLB). The initial questionnaire was revised based on feedback from a focus group and results of pilot testing. The final questionnaire assessed multiple symptoms at two time points: 1) symptom severity at the current time (within the past 30 days); 2) symptom severity when symptoms were estimated by the participant to have been the worst they had ever been (see Supplemental Data for questionnaire). Symptoms assessed were those typically associated with idiopathic hypersomnia, including, for example, excessive daytime sleepiness, sleep inertia, and subjective cognitive dysfunction, but also those more typically associated with other central disorders of hypersomnolence, such as cataplexy, sleep paralysis (both associated with narcolepsy type 1), and hyperphagia (often associated with Kleine-Levin syndrome). Single questions assessed the frequency of each symptom. The registry is hosted in partnership with the Coordination of Rare Diseases (CoRDS) at Sanford Research (Sanford Research, Sioux Falls, South Dakota). Findings presented here represent data collection for the two-year period from June 2016 through May 2018.

Participants were recruited by the Hypersomnia Foundation through online advertisements, presentations at patient meetings, and fliers placed in physician offices. Potential participants were recruited if they had been diagnosed with idiopathic hypersomnia, narcolepsy, Kleine-Levin syndrome, hypersomnia due to a medical condition, or hypersomnia associated with psychiatric conditions. All participants provided informed consent and responded to questionnaires via the CoRDS online platform or by mail. This study was approved by the Institutional Review Boards of Sanford/CoRDS and Emory University.

2.1 IH diagnosis validation

Because the registry questionnaire uses self-reported hypersomnolence diagnosis, we undertook a series of steps to attempt to validate diagnoses. First, participants were asked to specify their diagnosis twice at different points during the data capture process. They were

first required to select their rare disease from a drop-down menu to enroll in the study. Then at a later point in the survey, they were asked in checklist format if they had received a current diagnosis of one or more hypersomnia disorders and whether a doctor had told them that a particular diagnosis was the cause of their symptoms. Participants who selected the same disorder on both queries were preliminarily considered to have that diagnosis. Participants who selected two different disorders in the two different questions were excluded, as were participants who reported a current diagnosis of more than one hypersomnolence disorder on the second item.

Second, once this central disorder of hypersomnolence diagnosis was assigned, we evaluated habitual sleep durations as a potentially important confounding factor. Because insufficient sleep syndrome can induce excessive daytime sleepiness and thereby mimic hypersomnia diagnoses, we excluded anyone with a preliminary diagnosis of IH who endorsed weekly sleep durations of fewer than 49 hours (i.e., average of 7 hours/night).

2.2 Statistical analysis

De-identified data were obtained from CoRDS. In cases where symptom frequency was assessed as a categorical variable with more than two levels (e.g., every day, weekly, once or twice a month, etc), data were dichotomized as daily or less than daily. Medication use was dichotomized for each medication as currently taking at least once a week or not. Typical nap duration was analyzed after excluding reported nap durations of > 6 hours, as these may have represented major sleep periods rather than naps. For group comparisons between two groups, t-tests were used for continuous variables and chi-square tests for categorical variables. For group comparisons across multiple diagnoses, analysis of variance (ANOVA) was used for continuous variables and chi-square for categorical. Post-hoc pairwise comparisons via Tukey test were performed in the case of significant ANOVA.

3. Results

3.1 Participants

A total of 1,028 participants enrolled in the study and selected a primary diagnosis of idiopathic hypersomnia (n = 812), NT2 (n = 101), or NT1 (n = 115). Of these, 398 were excluded because they did not answer the subsequent question about their diagnosis (n = 342) or because they selected multiple hypersomnia diagnoses (n = 56). An additional 67 participants with preliminary diagnoses of IH were excluded because of self-reported weekly sleep of shorter than 49 hours. Final diagnoses of included participants were: IH (n = 468), NT2 (n = 44), NT1 (n = 51).

Most respondents were women (85.8%), Caucasian (97.2%), non-Hispanic (96.7%), and lived in the United States (88.5%). Respondents from outside the United States were predominantly located in Canada (n = 23, 4.1%), the United Kingdom (n = 15, 2.7%), and Australia (n = 12, 2.1%), with one or two respondents from an additional 11 countries. None of these demographic features differed between those with IH, NT2, and NT1 (all p-values > 0.10). The average age of symptom onset was 19.1 (+/−standard deviation of 11.3) years old, the average age of seeking medical evaluation for symptoms was 26.5 (+/− 10.7) years old,

and the average age at survey completion was 36.5 (+/− 12.8) years, without differences between diagnostic groups (all p-values > 0.10). Eighty-nine percent of participants were diagnosed by sleep medicine specialists, most commonly sleep neurologists. General neurologists diagnosed the next largest number of cases, but only accounted for 3.5% of diagnoses. Diagnoses were rarely made by family physicians (1%).

3.2 Symptoms in IH

Participants were asked about the frequency of symptoms, when symptoms were at their worst. As anticipated, daily excessive daytime sleepiness was reported by virtually all respondents with IH, 457 individuals (97.7%). “Brain fog” (additionally defined for participants as “being unable to think clearly or concentrate at any time throughout the day”) was the second most commonly endorsed symptom, occurring daily in 380 respondents (82.6%). Poor memory was also endorsed as a daily problem by most participants, 326 respondents (71.8%). Sleep inertia/sleep drunkenness was endorsed by most respondents, characterized by daily difficulty waking and functioning with normal alertness (369 participants, 79.0%) and need for multiple alarms (326 participants, 69.8%). Excessive sleep durations, sleeping more than 10 hours at a time or requiring naps, were endorsed by half of participants (daily long sleep in 240, 51.3%, and daily naps in 250, 53.4%). Inadvertent daytime sleep and automatic behaviors were less commonly reported, with unintentional daytime sleep occurring at least daily in 169 participants (36.2%) and automatic behaviors in 100 participants (22.7%).

We then separated participants with IH into those reporting daily sleep durations of 10 hours or more (IH with long sleep, 240 participants, 51.3%) and those reporting habitual sleep durations of 7 to less than 10 hours of sleep (IH without long sleep, 228 participants, 48.7%), when symptoms were at their worst. Those with IH with long sleep time were also more likely to experience daily difficulty with awakening (88.3% versus 69.3%, $p < 0.0001$, Table 1), need for multiple alarms (77.5% versus 61.7%, $p = 0.0002$), daily intentional naps (64.2% versus 42.1%, $p < 0.0001$), and brain fog (86.9% versus 78.1%, $p = 0.01$). They were no more likely than those without long sleep times to endorse unintentional daytime sleep, memory problems, or automatic behaviors. Both groups had similar extension of sleep times on weekends versus weekdays (1.96 hours for those with long sleep, 1.90 for those without). Typical nap duration was significantly longer in those with long sleep, 2.8 +/− 1.3 hours versus 2.0 +/− 1.2 in those without long sleep, $p < 0.0001$.

We then considered sleep duration based on reported sleep durations at the time of the survey, rather than when symptoms were at their worst. Because several different thresholds for long sleep have been proposed (22–24), we considered sleep duration cutoffs of 9, 10, and 11 hours. These thresholds for long sleep were met by 45.9% of participants for 9 hours, 24.0% for 10 hours, and 10.3% for 11 hours. Age and gender did not differ with any cutoff for long sleep. Using current sleep durations of 10 or 11 hours to define long sleep, group differences in difficulty awakening and brain fog remained significant, whereas no group differences in symptoms were seen using a sleep duration cutoff of 9 hours.

We compared those participants with IH who endorsed a current diagnosis of depression to those without depression. The only symptom that differed, when considering symptoms at

their worst, was the need for multiple alarms, less frequent in those with comorbid depression (75.4% of those without depression vs 66.7% of those with depression, 0.049). The only symptom that differed when considering the last 30 days, while on treatment for hypersomnia, was the need for intentional naps, which was more common in those with depression (19.4% with versus 9.3% without depression, p = 0.007).

3.3 Medication use in IH

Three-hundred seventy-nine (82%) participants with IH had taken medication for sleepiness within the 30 days prior to completing the questionnaire. Two-hundred forty participants with IH (51.3%) were taking at least one traditional psychostimulant, most commonly amphetamine-dextroamphetamine (mixed amphetamine salts), in current use by 31.7% of IH respondents, followed by methylphenidate, in current use by 21.8% of IH respondents. A minority (n = 17, 3.6%) of IH respondents were currently treated with more than one traditional psychostimulant. Only 38.0% (n = 178) of IH participants were taking either modafinil or armodafinil, 10.9% in combination with a traditional psychostimulant. IH participants from European countries were significantly more likely to be taking modafinil (11/19, 58%) than IH participants from the United States (98/357, 27%), p = 0.004. Other treatments were used only in a small percentage of IH respondents: melatonin (12.1%), flumazenil (5.7%), clarithromycin (5.0%), and sodium oxybate (2.7%). There were no differences in the frequency of use of these individual medications between those with and without long sleep time, except that clarithromycin was more commonly taken by those with long sleep times (7.9% of those with long sleep time versus 1.9% of those without, p = 0.01).

Eighty-six (18.5%) participants indicated that they had not taken medication for excessive sleepiness or need for sleep within the 30 days prior to completing the questionnaire. Of those providing data on prior treatments, 48 (72.7%) had previously taken modafinil, armodafinil, or both, and 38 (57.6%) had previously taken at least one traditional psychostimulant. A minority had also previously tried, but were no longer taking, other treatments: melatonin (21.2%), flumazenil (7.6%), clarithromycin (13.6%), and sodium oxybate (10.6%).

3.4 Symptoms while taking medications for IH

Considering only those participants with IH currently on treatment, symptoms were improved on treatment versus when they had been at their worst (all p-values < 0.0001, Table 2). However, despite apparent improvement with medication, daily symptoms of IH still were experienced by a substantial proportion of participants while on treatment. Daily excessive daytime sleepiness remained in 243 treated participants (64.1%). A similar proportion continued to experience daily difficulty awakening, either requiring multiple alarms (227 participants, 60.2%) or having difficulty functioning with normal alertness upon awakening (228 participants, 61.1%). Cognitive symptoms persisted in over half of treated participants, brain fog in 201 (54.0%) and difficulty with memory in 189 (51.8%). Long sleep durations, intentional and unintentional daytime naps, and automatic behaviors were all present daily in fewer than 15% of treated participants.

3.5 IH versus narcolepsy types 1 and 2

Virtually all participants, regardless of diagnosis, endorsed daily excessive daytime sleepiness occurring when symptoms were at their worst (occurring in 100% of respondents with either NT1 or NT2, Table 3). Similar percentages of participants in each of the three groups endorsed daily long sleep durations, difficulty waking in the morning, need for multiple alarms, and cognitive symptoms. Intentional and unintentional daytime naps and automatic behaviors were more common in people with narcolepsy type 1 than those with IH, but the only difference between those with narcolepsy type 2 and those with IH was more frequent intentional napping in those with narcolepsy type 2.

Somewhat more group differences emerged when considering symptoms within the last 30 days, limited to those currently on treatment for their central disorder of hypersomnolence (Table 3). Compared to those with narcolepsy type 1, people with IH were more likely to endorse daily difficulty with awakening and less likely to endorse intentional napping. Compared to people with narcolepsy type 2, people with IH were more likely to endorse: a) daytime sleepiness; b) difficulty with awakening: c) requiring multiple alarms; d) brain fog and e) difficulty with memory. People with IH reported a bigger difference in weekday versus weekend sleep duration than did people with either type of narcolepsy (1.93 hours for IH, 0.80 hours for NT1, and 0.59 hours for NT2, $p = 0.0001$). Typical nap duration differed by diagnosis, significantly longer in people with IH than those with NT1 (2.4 +/− 1.3 hours in IH, 1.4 +/− 1.1 hours in NT1, and 1.8 +/− 1.4 hours in NT2, $p < 0.0001$, with significant pairwise differences between IH vs NT1).

Compared to people with either type of narcolepsy, people with idiopathic hypersomnia were significantly less likely to be currently treated with any medication for their excessive daytime sleepiness (82% for IH, 92% for NT1, and 93% for NT2, $p = 0.04$). Participants with IH were also significantly less likely to be currently treated with baclofen (0.9% of IH participants versus 5.5% of narcolepsy participants, $p = 0.02$) or sodium oxybate (2.7% of participants with IH versus 43.9% of participants with narcolepsy, $p < 0.0001$). In contrast, participants with IH and those with narcolepsy had similar rates of current treatment with traditional psychostimulants, modafinil/armodafinil, clarithromycin, flumazenil, and melatonin.

4. Discussion

The overall findings revealed important clinical patterns that demonstrate the value of an online patient registry for people with hypersomnia. Registry participants with IH frequently endorsed symptoms in addition to excessive daytime sleepiness, most frequently brain fog, memory problems, difficulty awakening, and long sleep durations. The latter two are supportive or confirmatory for the diagnosis of idiopathic hypersomnia in current diagnostic criteria (24). However, neither brain fog nor memory problems are currently considered supportive criteria for this diagnosis, likely in part because they are not specific to idiopathic hypersomnia. These two symptoms have not been well characterized in people with idiopathic hypersomnia, but both subjective reports and preliminary objective testing with attentional tasks have suggested that people with IH have difficulty with sustained attention (11, 25). Available data conflict on whether this attentional difficulty is a disease-specific

phenomenon (25) or an effect of decreased vigilance due to sleepiness, regardless of cause (26). A small study has suggested poorer school performance in children with idiopathic hypersomnia (27), but more work is needed to characterize the effects of the cognitive symptoms of IH on school and work performance.

An important, unresolved question in idiopathic hypersomnia is the potential significance of a distinction between those with and without long habitual sleep durations (28). This distinction was embedded in a prior version of the International Classification of Sleep Disorders (23) but subsequently removed (24). Within the Registry, slightly over half of participants with IH endorsed habitual long sleep of 10 hours/night or longer, and those who endorsed long sleep were more likely to endorse sleep inertia, brain fog, and planned naps. Using alternate definitions of long sleep, the associations between long sleep with difficulty waking and brain fog persisted, suggesting an important phenotypic distinction based on sleep duration cutoffs of 10 or 11 hours. This is consistent with the findings of a cluster analysis of hypersomnia disorders, in which those with IH with long sleep times clustered separately from those with IH without long sleep times, with the long sleep cluster having the most difficulty waking from naps (29). Intentional daily naps were only endorsed by half of IH participants, perhaps reflecting their tendency to be long and non-restorative. Another unresolved question is the potential relationship between hypersomnia symptoms and depression, but in our data the presence or absence of reported comorbid depression did not meaningfully change expression of hypersomnia symptoms.

It is presently unknown which medications are most effective in treating IH. In the American Academy of Sleep Medicine (AASM) practice parameter for treatment of IH released in 2007, i.e., the practice parameter that was active during the time period participants responded to the Registry questionnaire, no strong recommendations were given for treatment, but modafinil, amphetamine, dextroamphetamine, methamphetamine, and methylphenidate were all given an ‘option’ level of recommendation based on expert consensus (30). Consistent with these recommendations, the most commonly used treatments by the IH respondents were amphetamine-dextroamphetamine (mixed amphetamine salts, 32%), followed by modafinil (30%) and methylphenidate (22%). Subsequent to the guideline’s publication, two small, randomized, controlled trials of modafinil including patients with IH were published, both showing benefit of modafinil (31, 32). It is perhaps surprising then that the percentage of IH patients in the Registry currently taking modafinil was only 30%. This might reflect cost issues, as insurance coverage that insists on disease-specific Food and Drug Administration (FDA)-labelling can limit IH patients’ access to medications, and until recently, out-of-pocket costs for modafinil and armodafinil were prohibitively expensive for many patients. Although our number of non-US participants was small, those IH participants from Europe were significantly more likely to be taking modafinil than those from the United States, suggesting these insurance coverage differences might play a role. The relatively low rate of modafinil use might reflect the drug-drug interaction between modafinil and oral contraceptive medications, which can affect treatment decisions. However, it may also suggest that modafinil is not fully sufficient for treatment of IH symptoms. Studies of IH to date have focused on excessive daytime sleepiness, which is responsive to modafinil in clinical trials, but the symptoms of IH driving quality of life and functional limitations are much broader than solely excessive daytime

sleepiness. The extent to which modafinil does or does not improve these symptoms may determine whether or not people with IH continue to use it on a chronic basis. Within the Registry, there are several suggestions that modafinil/armodafinil were not sufficient as monotherapy for IH patients. First, one quarter of IH patients taking modafinil/armodafinil were also taking a traditional psychostimulant. Second, respondents with IH frequently reported previously taking these medications but discontinuing them, 41% of participants with modafinil and 33% of participants with armodafinil. This suggests that, despite the evidence in support of modafinil's benefit on IH symptoms, there is a clear need for additional medications. Indeed, the high rate of residual symptoms while on treatment with any of the medications included in the Registry speaks to the current lack of fully effective treatments for IH. Finally, other explanations for low use of particular medications in the Registry also include side effects, prescriber knowledge of and willingness to use off-label treatment for IH, and patient comfort with off-label medication use. These findings highlight specific areas where treatment implementation is sub-optimal and could be targeted for improvement.

Another important finding regarding medication use in this registry was the relatively high proportion of IH respondents who were currently untreated with any medication for IH, nearly one in five. The questionnaire did not specifically ask why participants were not taking medication, although cost, side effects, and lack of sufficient benefit are likely contributing factors. Most participants with IH who were currently untreated had tried at least one IH treatment and many had unsuccessfully tried multiple treatments. This also speaks to the ongoing, unmet clinical need for effective, tolerable treatments for IH. Although two medications were recently FDA-approved for the treatment of narcolepsy, neither has been tested in people with IH and their possible efficacy in this group is unknown.

Symptoms at their worst were similar across hypersomnia diagnoses of IH, narcolepsy type 1, and narcolepsy type 2, including those traditionally ascribed to IH such as sleep inertia and long sleep durations. On treatment, people with IH seem to have more residual symptoms than those with narcolepsy type 2 but similar residual symptoms to those with narcolepsy type 1. However, these diagnostic comparisons should be interpreted with caution, given smaller sample sizes in the narcolepsy groups and reliance on self-reported diagnosis. Additionally, these data should not be used to infer relative prevalence of IH and either type of narcolepsy. The imbalance in sample size may reflect the relative visibility of the Hypersomnia Foundation registry to those with IH compared to those with narcolepsy, rather than underlying population frequencies.

There were several limitations to this study. First, use of self-reported diagnosis of idiopathic hypersomnia rather than employing prospective polysomnographic testing or obtaining prior physician records documenting such testing may have resulted in some diagnostic misclassification. We attempted to mitigate this as much as possible, by requiring several different affirmative responses to consider a patient to have a particular diagnosis. A substantial number (56 people, 5%) of registry participants reported physician-rendered diagnoses of multiple hypersomnia disorders. Although this might reflect uncertainty in diagnosis reporting inherent to self-enrolled registry data, it may also reflect underlying

clinical uncertainties in the diagnostic process. The multiple sleep latency test (MSLT) is now known to have poor test-retest reliability in people with non-cataplectic hypersomnia disorders (33–35), often resulting in a change in diagnosis. Even for NT1, in which MSLT performance is much more stable (34, 35), some patients may initially manifest with a hypersomnia phenotype that resolves over time into that of NT1. Finally, in our experience, it is not uncommon for patients whose testing results are consistent with IH to report previously having been assigned a diagnosis of narcolepsy rather than IH to work around restrictive insurance rules that only allow medication coverage for those with a diagnosis of narcolepsy. In the future, inclusion of patient diagnostic test results, e.g., polysomnography/MSLT results, in registries will improve diagnostic certainty.

Another limitation is that, because the Hypersomnia Foundation Registry is newly formed, this work reports only on cross-sectional data, whereas idiopathic hypersomnia is generally a chronic, often life-long disease. The Hypersomnia Foundation is in the process of collecting follow up data on enrolled participants, which will allow future work investigating change in disease symptomatology and varying success of treatments over time. Such longitudinal follow up of conditions treated with novel and innovative treatments is an acknowledged value of registries (16). Subsequent data collection would also benefit from the inclusion of more details of daytime naps, including number and timing of naps.

Finally, although use of an online registry allowed collection of a larger, potentially more clinically-diverse population of participants than could be obtained from a single clinical site, the people who choose to complete an online disease registry may not be fully representative of the whole population of people with that disease. Our participants were mostly women, overwhelmingly Caucasian, and largely US-based. Idiopathic hypersomnia appears in some studies to be diagnosed more frequently in women than in men, although it is unclear whether this is a biological feature of the disease itself or reflects a sex-difference in REM propensity (36). Separate from demographics, it is possible that people responding to online recruitment may have a more severe or treatment-refractory phenotype. At the same time, use of a registry allows inclusion of people who would not be captured in clinical series, i.e., those who give up on the healthcare system when medications are not successful, not tolerated, or not covered by insurance. As such, despite these limitations, we believe these data provide important preliminary insights into the experiences of people with idiopathic hypersomnia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- Symptoms of Idiopathic Hypersomnia (IH) confirm differences from Narcolepsy type 1
- Hypersomnia Foundation Registry creation yielded hundreds self-identifying with IH
- Brain fog, bad memory, trouble waking, use of multiple alarms all common in IH
- About 50% of IH cases report 10 hours or more of nightly sleep when most severe
- About 20% of IH cases report no current treatment

All authors meet ICJME definition of authorship, with all listed authors meeting all of the following:

- substantial contribution to conception or design of the work or to the acquisition, analysis, or interpretation of data
- drafting the work or revising it critically for important intellectual content
- final approval of this version
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Table 1:

Percent of respondents with idiopathic hypersomnia endorsing daily symptoms, comparing those with and without habitual sleep durations of at least 10 hours

	Idiopathic hypersomnia with long sleep time	Idiopathic hypersomnia without long sleep	p-value
Excessive daytime sleepiness	235 (97.9%)	222 (97.4%)	0.70
Intentional napping	154 (64.2%)	96 (42.1%)	<0.0001
Unintentional daytime sleep	95 (39.8%)	74 (32.5%)	0.10
Requiring multiple alarms to awaken	186 (77.5%)	140 (61.7%)	0.0002
Having trouble waking up and functioning with normal alertness	211 (88.3%)	158 (69.3%)	<0.0001
Brain fog (being unable to think clearly or concentrate at any time throughout the day)	205 (86.9%)	175 (78.1%)	0.01
Difficulty remembering things	170 (73.3%)	156 (70.3%)	0.48
Automatic behaviors	54 (23.8%)	46 (21.6%)	0.58

Table 2:

Comparison of symptoms within the last thirty days and symptoms at their worst, for those participants currently treated for idiopathic hypersomnia

	Number (Percent) endorsing symptom at least daily, within the last 30 days	Number (Percent) endorsing symptom at least daily, when symptoms were at their worst	p-value*
Excessive daytime sleepiness	243 (64.1%)	370 (97.6%)	<0.0001
Long sleep durations	52 (13.7%)	195 (51.5%)	<0.0001
Intentional napping	52 (13.7%)	206 (54.4%)	<0.0001
Unintentional daytime sleep	23 (6.1%)	140 (36.9%)	<0.0001
Requiring multiple alarms to awaken	227 (60.2%)	265 (70.3%)	<0.0001
Having trouble waking up and functioning with normal alertness	228 (61.1%)	301 (80.7%)	<0.0001
Brain fog (being unable to think clearly or concentrate at any time throughout the day)	201 (54.0%)	311 (83.6%)	<0.0001
Difficulty remembering things	189 (51.8%)	262 (71.8%)	<0.0001
Automatic behaviors	42 (12.4%)	88 (26.0%)	<0.0001

*p-values are for McNemar test between the two time points.

Table 3:

Comparison of daily symptoms in those with IH, NT2, and NT1

	IH	NT2	NT1	p-value	pairwise
SYMPTOMS AT THEIR WORST					
Excessive daytime sleepiness	457 (97.7%)	43 (100%)	49 (100%)	0.55	--
Long sleep durations	240 (51.3%)	20 (46.5%)	17 (34.0%)	0.06	--
Intentional napping	250 (53.4%)	30 (69.8%)	35 (71.4%)	0.01	IH < NT2=NT1
Unintentional daytime sleep	169 (36.2%)	22 (51.2%)	33 (67.4%)	<0.0001	IH < NT1
Requiring multiple alarms to awaken	326 (69.8%)	27 (62.8%)	30 (61.2%)	0.33	--
Having trouble waking up and functioning with normal alertness	369 (79.0%)	29 (67.4%)	41 (82.0%)	0.17	--
Brain fog (being unable to think clearly or concentrate at any time throughout the day)	380 (82.6%)	32 (74.4%)	43 (86.0%)	0.31	--
Difficulty remembering things	326 (71.8%)	27 (62.8%)	39 (78.0%)	0.26	--
Automatic behaviors	100 (22.7%)	13 (31.0%)	19 (40.4%)	0.02	IH < NT1
SYMPTOMS WITHIN THE LAST 30 DAYS, ON TREATMENT					
Excessive daytime sleepiness	243 (64.1%)	17 (44.7%)	25 (54.4%)	0.04	IH > NT2
Long sleep durations	52 (13.7%)	4 (10.5%)	3 (6.5%)	0.35	--
Intentional napping	52 (13.7%)	6 (15.8%)	14 (31.1%)	0.01	IH < NT1
Unintentional daytime sleep	23 (6.1%)	3 (7.9%)	3 (6.7%)	0.81	--
Requiring multiple alarms to awaken	228 (60.3%)	9 (23.7%)	21 (46.7%)	<0.0001	IH > NT2, NT1 > NT2
Having trouble waking up and functioning with normal alertness	228 (61.1%)	14 (36.8%)	19 (41.3%)	0.001	IH > NT2 = NT1
Brain fog (being unable to think clearly or concentrate at any time throughout the day)	203 (54.3%)	10 (26.3%)	23 (50.0%)	0.004	IH = NT1 > NT2
Difficulty remembering things	190 (51.5%)	11 (29.0%)	23 (50.0%)	0.03	IH > NT2
Automatic behaviors	45 (12.9%)	5 (13.2%)	9 (20.5%)	0.39	--