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Real-World Experience and Burden of Fatigue in Narcolepsy and Idiopathic Hypersomnia: Survey Results From the ASPIRE Study

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Introduction

- Narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH) are chronic sleep disorders primarily characterized by excessive daytime sleepiness (EDS)[1,2]
- People living with narcolepsy and IH may also experience fatigue as a common and debilitating symptom[3,4]
  - Fatigue is characterized by exhaustion and low energy, which can affect outcomes such as education, employment, social relationships, and overall health-related quality of life (HRQoL)[5,6]
  - Patients may experience symptoms of fatigue even while taking medications for narcolepsy or IH[5,7]
  - It is unclear how fatigue is associated with common measures of HRQoL assessed among those with narcolepsy, including the Functional Outcomes of Sleep Questionnaire - Short Form (FOSQ-10) and EuroQol-5D-5L index (EQ-5D-5L)

Objective

- The ASPIRE study characterized symptoms of NT1, NT2, and IH including fatigue
  - This study also explored the association between fatigue and functional and HRQoL outcomes

Methods

Study design

- The ASPIRE study was an online survey of participants with NT1, NT2, and IH conducted in alignment with the US Food and Drug Administration Patient-Focused Drug Development Guidance on the collection and use of patient experience data (**Table 1**)[8,9]
- Participants were recruited through Rare Patient Voice (RPV, a qualified third-party research panel), the Hypersomnia Foundation, and the Sleep Consortium. Participants who completed and submitted the survey received a nominal honorarium

Table 1: Study population

NT1 (n = 116)	NT2 (n = 127)	IH (n = 123)
Participants were ≥ 18 years of age, resided in the US, and reported a clinician's diagnosis of NT1, NT2, or IH		

IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; US, United States.

Statistical analysis

- No imputation methods were used for missing data. Data from participants who did not complete the survey were not included in analyses
- Descriptive analyses included means and standard deviations (SDs) for continuous variables, and frequencies and percentages for categorical variables
- Differences in patient outcomes were examined using one-sample *t* tests, two-sample *t* tests, and analysis of variance. Statistical significance was defined as $P < 0.05$ (two-sided) without adjustment for multiplicity

Study measures and outcomes

Symptom severity

- Fatigue severity over the past week was assessed using the PROMIS® Item Bank v1.0 - Fatigue - Short Form 6a (PROMIS-Fatigue)

Burden on functional and HRQoL outcomes

- Daily functioning was assessed using the FOSQ-10
- Work and activity impairment were evaluated using the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)
- Self-reported health status was assessed using the EQ-5D-5L, including the visual analogue scale (EQ VAS)

Results

Participant demographics and disposition

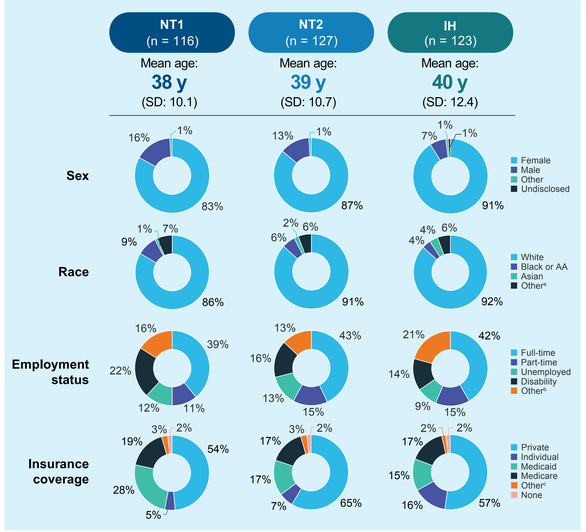
- A total of 366 participants (NT1, n = 116; NT2, n = 127; IH, n = 123) were included. Baseline characteristics are shown in **Figure 1**
- Many participants were taking nonstimulant wake-promoting agents (modafinil, armodafinil, solriamfetol, and pitolisant; 30.1%–48.3%), or stimulants (methylphenidates or amphetamines; 43.1%–48.8%)
  - Almost half (48.3%) of participants with NT1 were taking antidepressants for cataplexy

Fatigue

- The mean (SD) PROMIS-Fatigue T-score for all participants was 65.74 (7.52), which falls into the "moderate fatigue" category (**Figure 2A**)
  - Mean (SD) scores were similar across groups, with each group being categorized as "moderate fatigue" (NT1: 66.08 [7.78]; NT2: 65.03 [7.47]; IH: 66.16 [7.34])
- Ninety-one percent of all participants reported mild-to-severe fatigue (NT1: 90%; NT2: 89%; IH: 95%) (**Figure 2B**)
  - Participants with narcolepsy and IH had similar levels of fatigue

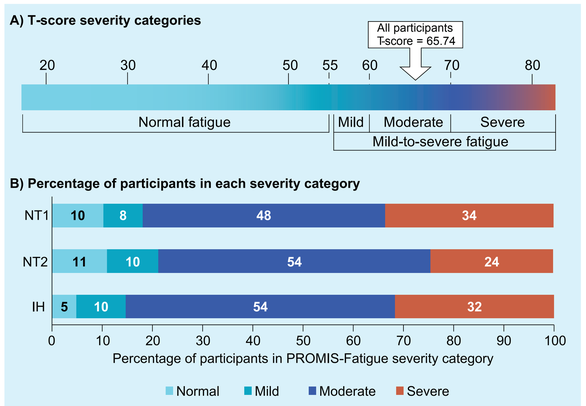
Results continued

Figure 1: Study participant baseline characteristics by diagnosis group



[a]"Other" category includes response options of "American Indian or Alaska Native," "Native Hawaiian or Other Pacific Islander," "Other," and "Prefer not to answer." Percentages may exceed 100% because some participants reported multiple races.
[b]"Other" category includes response options of "Student," "Stay-at-home parent/homemaker," "Retired," "Voluntary job," and "Prefer not to answer."
[c]"Other" category includes response options of "Veterans administration/TRICARE" and "I don't know." Percentages may exceed 100% because participants could report enrollment in multiple types of insurance.
AA, African American; IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation; y, years.

Figure 2: Fatigue as assessed by PROMIS-Fatigue in participants diagnosed with NT1, NT2, and IH



IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PROMIS-Fatigue, PROMIS® Item Bank v1.0 - Fatigue - Short Form 6a.

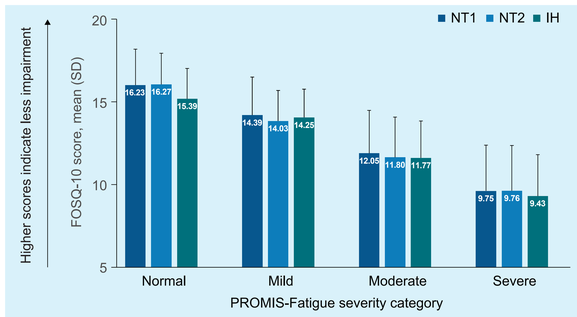
Fatigue and daily functioning

- The mean (SD) FOSQ-10 score for the overall study cohort was 11.79 (3.07)
- Participant scores for the FOSQ-10 were similar across groups, with a mean (SD) of 11.89 (3.28) for NT1, 12.03 (3.09) for NT2, and 11.45 (2.84) for IH
  - Scores demonstrated meaningful impairment on the FOSQ-10, with all groups scoring significantly below the normative value of 17.8 (all $P < 0.001$)[10]
- Participants with mild-to-severe fatigue had lower mean FOSQ-10 scores versus those with normal fatigue (11.38 vs 16.09, $P < 0.001$). Results were consistent across groups (NT1: 11.39 vs 16.23 [$P < 0.001$]; NT2: 11.50 vs 16.27 [$P < 0.001$]; IH: 11.24 vs 15.39 [$P < 0.001$])
- Across all groups, FOSQ-10 scores decreased as fatigue severity increased (**Figure 3**)

Fatigue and self-reported health status

- Participants showed impairment on the EQ-5D-5L and EQ VAS scores, with mean (SD) scores of 0.64 (0.27) and 60.13 (18.52), respectively
- Participant scores for the EQ-5D-5L (NT1: 0.61; NT2: 0.65; IH: 0.65) and EQ VAS (NT1: 58.87; NT2: 61.7; IH: 59.6) were similar across all three groups
  - Scores indicated meaningful impairment on both the EQ-5D-5L index and EQ VAS, with all groups scoring significantly below normative values of 0.85 and 80.4, respectively (all $P < 0.001$)[11]
- Participants with mild-to-severe fatigue had lower mean EQ-5D-5L and EQ VAS scores versus those with normal fatigue (EQ-5D-5L: 0.61 vs 0.88 [$P < 0.001$]; EQ VAS: 58.4 vs 78.13 [$P < 0.001$]).
- Across all groups, EQ-5D-5L and EQ VAS scores were inversely associated with fatigue, with lower scores observed at higher PROMIS-Fatigue severity categories (between group significance for both scales in all diagnosis groups was $P < 0.001$, except for EQ-5D-5L in the IH group, which was $P = 0.027$) (**Figure 4**)
- On average, the most severe EQ-5D-5L dimensions in all diagnosis groups were "Activity," "Pain or Discomfort," and "Anxiety or Depression"

Figure 3: FOSQ-10 scores by PROMIS-Fatigue severity category and diagnosis group



FOSQ-10, Functional Outcomes of Sleep Questionnaire - Short Form; IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PROMIS-Fatigue, PROMIS® Item Bank v1.0 - Fatigue - Short Form 6a; SD, standard deviation.

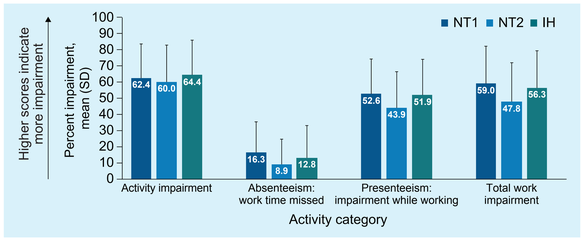
Figure 4: EQ-5D-5L and EQ VAS scores by PROMIS-Fatigue severity category and diagnosis group

EQ-5D-5L, EuroQol-5D-5L index; EQ VAS, EuroQol Visual Analogue Scale; IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PROMIS-Fatigue, PROMIS® Item Bank v1.0 - Fatigue - Short Form 6a; SD, standard deviation.

Fatigue and work

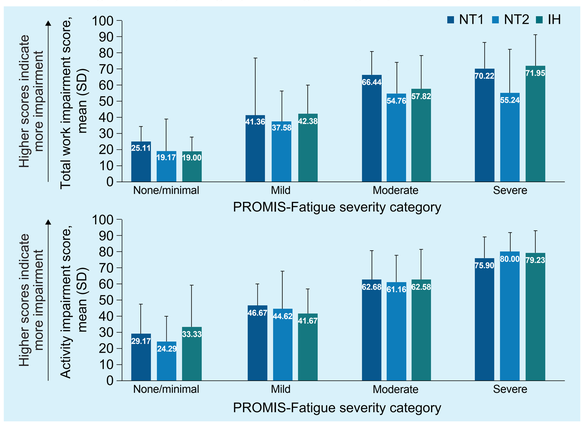
- Participants had high levels of activity impairment, describing 60% or more of their daily activities as being affected by narcolepsy or IH (**Figure 5**)
- Of those employed (NT1: 50%; NT2: 58%; IH: 56%), participants reported over 45% of their work as being impaired (**Figure 5**)
  - Total work impairment was also high across subtypes and was largely driven by presenteeism while at work
- All participants who reported mild-to-severe fatigue had greater impairments in work (59% vs 21%; $P < 0.001$) and activity (66% vs 28%; $P < 0.001$) versus the normal fatigue group
- Total work impairment and activity impairment were higher in participants with more severe fatigue ($P < 0.001$ for all comparisons) (**Figure 6**)

Figure 5: WPAI:SHP scores by diagnosis group



IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

Figure 6: WPAI:SHP total work impairment and activity impairment scores by PROMIS-Fatigue severity category and diagnosis group



IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PROMIS-Fatigue, PROMIS® Item Bank v1.0 - Fatigue - Short Form 6a; SD, standard deviation; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

Study limitations

- Though physician diagnosis of narcolepsy or IH was self-reported, confidence in diagnosis was supported by recruitment from RPV and advocacy groups
- Online survey administration limited participation to those with internet access and those interested in participating
- This study used a convenience sample, which may not reflect overall patient populations
- Participants from advocacy groups may have distinct experiences and a more active role in understanding and managing their conditions compared with the wider populations living with NT1, NT2, and IH

Conclusions

- Fatigue was common across participants with NT1, NT2, and IH
  - Over 90% of all participants reported mild-to-severe fatigue
- Fatigue was associated with significant burden across outcomes
  - The greatest burden was observed among participants with more severe fatigue
- This study highlighted the need to address the common and burdensome symptom of fatigue for those living with NT1, NT2, and IH
  - It also highlighted the importance of using established and relevant patient-reported outcome measures in research to support standardized interpretation and characterization of disease burden and treatment benefit

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Disclosures
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