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ORIGINAL RESEARCH

Symptom and Treatment Satisfaction in Members of the US and Canadian GBS/CIDP Foundations with a Diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy

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ABSTRACT

Introduction: Current guidelines for defining good outcomes in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) are predominately defined by experts. At present, we do not have a patient-anchored definition of what constitutes a "good" outcome. Our study aimed to assess the symptom burden of people living with CIDP, as well as satisfaction with treatments and clinical outcomes.

Methods: We conducted an online-survey in CIDP patients registered with the US and Canadian GBS/CIDP foundations. Respondents answered general demographic and clinical questions, as well as satisfaction with current symptom burden and treatments, plus validated outcome measures.

Results: A total of 318 individuals with self-reported CIDP completed the online survey, of whom 128 (40%) considered their current disease burden as satisfactory while 190 (60%) did not. Of 305 patients who answered the treatment satisfaction question, 222(74%) were satisfied with their treatments. Patients who were satisfied with their current symptoms had, on average, better scores in quality of life and disease severity scales, although regression modeling showed that only ability to walk, stable symptoms, and health utility scores were associated with symptom satisfaction. Treatment satisfaction was associated with stable symptoms, use of IVIG, and use of one versus no medication.

Conclusions: A high proportion of members of the US and Canadian GBS/CIDP Foundations reporting a diagnosis of CIDP were unsatisfied with current symptoms, despite a high level of overall satisfaction with treatments. There is an unmet need for improving long-term outcomes in people with a diagnosis of CIDP, and for studying patient-centered long-term treatment goals.

Keywords: CIDP; Quality of life; PASS; Patient acceptable symptom state; Patient satisfaction

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Key Summary Points

Why carry out this study?

There are few studies assessing the preferences and satisfaction of people living with chronic inflammatory demyelinating polyneuropathy (CIDP).

Understanding what factors are associated with satisfaction with treatments and disease status can improve patient care.

We aimed to assess satisfaction with current treatments and disease status in people with CIDP to incorporate the patients' perspective into future studies and clinical practice.

What did we learn from this analysis?

We found that a large number of people reporting a diagnosis of CIDP are dissatisfied with their current symptoms, despite overall higher satisfaction with treatments.

Having stable symptoms, being able to walk, and having high utility scores were associated with symptoms satisfaction.

There is a need to improve long-term outcomes in CIDP and to incorporate patient-meaningful outcomes to research.

INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired autoimmune disease predominantly affecting the peripheral nervous system [1]. CIDP is characterized by progressive or relapsing symptoms which include paresthesia, muscle weakness, sensory dysfunction, and neuropathic pain [1].

At present, the assessment of long-term outcomes in patients with CIDP is often centered on expert opinions of a "good" outcome. Although several patient-reported measures are available for CIDP, a patient-anchored definition of what constitutes a good outcome during treatment has yet to be established [2]. In addition, changes in patient-reported measures may only denote when a patient feels "better" and may not be sufficient to determine if a patient is doing "well". Previous studies have shown that feeling "well" is valued more by patients than just feeling "better", which highlights the importance of establishing a patient-anchored definition of a good outcome [3].

The patient acceptable symptom state (PASS) evaluates the patient's satisfaction with their overall disease burden and identifies factors that are associated with patients who feel "well", rather than just "better", after treatment [4]. Understanding what patients consider as being "well", and what influences this outcome, can have a considerable impact on medical decisions and help to determine optimal treatment strategies for CIDP.

To date, self-reported patient satisfaction and PASS thresholds has been evaluated for numerous chronic illnesses, such as rheumatoid and psoriatic arthritis, systemic sclerosis, and myasthenia gravis [5–14]. However, there are limited data for CIDP. Therefore, we aimed to investigate the factors that influence patient satisfaction and to establish PASS thresholds for commonly used health scales in CIDP.

METHODS

We developed an electronic survey and invited patients 18 years or older with CIDP to participate in the study from January 2019 to June 2020. The initial draft of the CIDP survey was reviewed by a small group of patients with confirmed CIDP during pilot testing at the Ellen and Martin Prosserman Centre for Neuromuscular Disease, Toronto General Hospital, Canada, to ensure the clarity and relevance of the questionnaire. The final version of the CIDP survey was an anonymous, online questionnaire asking demographic and clinically relevant questions about a patient's CIDP health status. This included patient-reported outcomes (PROs), a symptom satisfaction item, and a question on treatment satisfaction. We invited

members of the GBS/CIDP foundations in Canada and the US to participate in the online open survey. The survey link was distributed by the Canadian and US GBS/CIDP foundations directly to all their registered members through an email with the survey link. Cookies were used so that participants were able to save answers and resume later, and were able to navigate back to previous questions; cookies were stored for the duration of data collection. Respondents were not forced to complete any answers before moving forward. There was no compensation offered to answer the survey. IP data were not collected, as it can be considered potentially identifying data.

Patient Reported Outcomes

1. To assess satisfaction with symptom burden, we used a four-level Likert question, modified from a previously validated PASS query used during a rheumatoid arthritis study [3]. We asked patients: "Considering all the ways your CIDP symptoms have affected you over the last month, how do you feel about your current CIDP symptom severity?".
   The PASS question prompts patients to reflect on their current symptoms and indicate if they were dissatisfied, somewhat dissatisfied, somewhat satisfied, or satisfied. We considered an answer of "somewhat satisfied" or better as being satisfied, (PASS-positive) and an answer of "somewhat dissatisfied" or worse as PASS-negative.
2. To assess patient satisfaction with treatments and the relationship with overall disease state satisfaction, we asked patients: "Considering the positive and negative effects of your CIDP medication, how satisfied are you with your current CIDP medication?" Possible answers ranged between dissatisfied and satisfied, with 4 options in total. We considered an answer of "somewhat satisfied" or better as being satisfied and an answer of "somewhat dissatisfied" or worse as dissatisfied.
3. The EuroQoL Five-Dimension Five Level (EQ-5D) is a multi-attribute measure including domains on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [15–17]. The EQ-5D-5L is scored as a utility value, where 0 represents death and 1 represents perfect health; negative values represent health states worse than death. The EQ-5D-5L also includes a visual analogue scale (VAS), anchored between 0 and 100, where 0 denotes worst possible health and 100 best possible health.
4. Short-Form Twelve-Dimension (SF-12) is a 12-item quality of life scale which can be scored as a preference-based, 6-dimension (SF-6D) utility score [18]. The SF-6D utility score ranges from 0 which represents death and 1, representing perfect health.
5. The Chronic Acquired Polyneuropathy Patient-Reported Index (CAPPRI) is a 15-item patient reported scale on daily activities and mental health with three response categories [19]. The total score can range between 0 and 30, where higher scores indicate worse quality of life.
6. The Rasch Overall Disability Scale (RODS) is a 24-item patient-reported scale on daily activities with four response categories [20]. The total RODS raw score can range between 0 and 48, where higher scores reflect better quality of life. Alternatively, raw scores can be converted into a centile metric value which can range from 0 (most severe limitations) to 100 (no limitations).
7. The Overall Neuropathy Limitation Scale (ONLS) is a neurological disability scale which focuses on upper and lower limb function [21]. Upper limb scores range from 0 to 5 and lower limb scores range from 0 to 7, where 0 indicates no impairment and maximum ratings indicate inability to perform purposeful movements. Upper and lower limb scores can be combined to a total score where higher scores reflect greater physical impairment.
8. The Inflammatory Neuropathy Cause and Treatment (INCAT) is a disability scale similar to the ONLS [2, 22]. Upper and lower limb scores range from 0 to 5 and can be combined for a total INCAT score where higher values indicate more disability. As

the INCAT and ONLS questionnaires are near identical, we omitted the INCAT questionnaire from our survey to avoid item repetitiveness. INCAT scores were then calculated using participant responses to the ONLS questionnaire.

Statistical Analysis

We describe continuous data through mean and standard deviation, and categorical data through counts and percentages. We calculated significant differences between satisfaction groups by Student's *t* test for continuous values, Wilcoxon rank sum test for median distributions, and Fisher's exact test for categorical variables. We adjusted *p* values for multiple testing by the Bonferroni method when appropriate, considering $p < 0.05$ as significant. Associations between satisfaction status and clinical characteristics were evaluated using logistic regression analysis. We built one model for symptom and one for treatment satisfaction. We chose model variables based on theory, including demographics (e.g., age, gender, employment status) and clinical variables (e.g., disability scores, medications). In case of multiple measures for the same construct, such as the INCAT, ONLS, and RODS for CIDP-related disability, or the SF-6D and EQ-5D utility scores for quality of life, we chose only one measure per model, to avoid overfitting due to multicollinearity. We chose to use health utility scores over VAS, since utility scores are obtained through population-based scoring norms using patient preferences, whereas VAS scores reflect a single domain on overall health. As a form of sensitivity analyses, we also built models with the other variables. Missing data were imputed according to the instructions of each PRO, when applicable.

We estimated optimal thresholds to classify patients as being on PASS for all CIDP survey PROs by receiver operating characteristic (ROC) curves using the "closest top-left" method and PASS-positive and -negative classifications as the gold standard. We chose the "closest top-left" method because it selects thresholds nearest to the top left of the ROC curve, which maximizes both sensitivity and specificity.

We also estimated thresholds through two alternate methods, the 75th percentile of PASS-positive patients and by identifying thresholds which have 80% specificity on a ROC curve.

The sample size for the electronic survey was based on the ROC to estimate PASS thresholds: for a minimum AUC)of 0.7, with a standard error of 0.05, 120 patients are needed [23, 24].

All statistical analyses were conducted with R statistical software v.3.60 (R Statistical Foundation, Vienna, Austria).

Compliance with Ethics Guidelines

This study was reviewed and approved by the University Health Network Research Ethics Board and conforms to the World Medical Association Declaration of Helsinki. Participants of the pilot test provided written consent, and answering the anonymous electronic survey was considered as implicit consent.

Permissions

We obtained written permission from the developers of the INCAT, ONLS, RODS, and CAPPRI to use the measures in this study. We obtained a license for the use of the SF-12 from QualityMetric, and we registered our study to use the EQ-5D-5L with EuroQoL (non-commercial, fast-track digital, no license needed).

RESULTS

Survey Participants

The survey email was sent to approximately 3600 individuals registered with the US and Canadian GBS/CIDP foundations. A total of 342 individuals launched the survey (9.5% response rate), but 24 were excluded because they answered only a few or no items; 318 individuals completed the electronic survey (93% completion rate) and were included in the analyses. All items had < 10% missing answers, with the ONLS (7.5%) and CAPPRI (8.5%)

having the highest proportion of missing data points; the remaining demographic and clinical variables had < 5% missing data. The mean age was 59.6 ± 13.7 years and 174 (55%) were female. Additional demographic and clinical characteristics are summarized in Tables 1 and 2.

Regarding current symptom burden, 128 (40%) patients reported that they were satisfied or somewhat satisfied with their current symptom severity, while 190 (60%) were dissatisfied or somewhat dissatisfied with current symptoms. Of the 305 individuals who answered the treatment satisfaction question, 109 (36%) reported being satisfied with their medication, while 113 (37%) were somewhat satisfied. The remaining 83 (27%) patients were either dissatisfied or somewhat dissatisfied with their medications.

Characteristics Associated with Symptom Burden Satisfaction

Compared to satisfied patients, patients dissatisfied with their symptoms had a higher proportion of worsening disease and walking difficulties (Table 1). Dissatisfied patients also had, on average, worse quality of life and disability scores than satisfied patients (Table 1). Individuals reporting dissatisfaction with current symptom burden also reported more treatment dissatisfaction (Fig. 1; symptom burden satisfied vs. dissatisfied, $p < 0.0001$). However, most patients (59%) dissatisfied with their symptoms still considered their treatment regimen as satisfactory (Fig. 1). We found no differences in age, sex, employment, disease duration, medication duration, or medical regimens between symptom burden satisfied and dissatisfied patients (Tables 1 and 2).

Logistic regression analysis showed that higher EQ-5D utility scores, having none, stable; or improved symptoms (compared to worsening), and maintained ability to walk were associated with a higher probability of being satisfied with current symptom burden, as summarized on Table 3. Age, sex, disease duration, number of medications, and IVIG and RODS scores were not associated with symptom burden satisfaction in this model. An alternative model using the SF-6D instead of EQ-5D utility scores, showed similar findings (Table 4).

Patient Characteristics Associated with Treatment Satisfaction

Compared to treatment-satisfied patients, patients dissatisfied with their treatments were more likely to have worsening disease, worse quality of life, and worse disability scores (Table 1). In addition, treatment-dissatisfied patients took medication and IVIG less often than treatment-satisfied patients (Table 2). We found no differences in age, sex, employment, duration of disease, medication duration, or difficulty walking between treatment-satisfied and -dissatisfied patients (Tables 1 and 2).

Logistic regression analysis showed that stable disease status, receiving one medication, and IVIG treatment were associated with a higher probability of being satisfied with treatment, as summarized in Table 5. Age, sex, disease duration, receiving more than one medication, RODS and EQ-5D utility scores were not associated to treatment burden satisfaction in this study. In the alternative model, using SF-6D instead of EQ-5D utility scores, we found that SF-6D scores were significantly associated with treatment satisfaction, along with being on IVIG and being on one treatment (Table 6).

Estimation of Patient-Anchored Thresholds for PASS

PASS thresholds for the EQ-5D utility, EQ-5D VAS, SF-6D utility, RODS, ONLS, INCAT, and CAPPRI total scores were estimated by ROC curves, with the 75th percentile and 80% sensitivity summarized in Tables 7 and 8

DISCUSSION

To our knowledge, this is the first study to evaluate satisfaction with current symptom burden and treatment satisfaction in people with CIDP. We found that a high proportion of members of the US and Canadian CIDP/GBS

Table 1 Demographic and clinical data

	Mean ± SD or *n* (%)			
	Symptom satisfied (*n* = 128)	**Symptom dissatisfied (*n* = 190)**	**Treatment satisfied (*n* = 222)[a]**	**Treatment dissatisfied (*n* = 83)[a]**
Age (years)	58.2 ± 13.45	60.5 ± 13.8	58.8 ± 13.4	60 ± 14
Female	62 (48)	112 (59)	121 (55)	48 (58)
Employment				
Employed	47 (37)	44 (23)	67 (30)	20 (24)
Unemployed/disability	24 (19)	55 (29)	50 (23)	27 (33)
Retired	40 (31)	71 (37)	77 (35)	29 (35)
Other	16 (12)	20 (11)	27 (12)	7 (8)
Disease duration (years)				
Less than 1	0	8 (4)	5 (2)	3 (4)
Between 1–2	17 (13)	24 (13)	30 (14)	11 (13)
Between 3–5	29 (23)	46 (24)	51 (23)	20 (24)
Greater than 5	82 (64)	111 (58)	135 (61)	49 (59)
Disease status		*		*
No symptoms or stable	91 (71)	85 (45)	131 (59)	34 (41)
Improved in the last 6 months	23 (18)	17 (9)	34 (15)	6 (7)
Worsened in the last 6 months	12 (9)	85 (45)	53 (24)	42 (51)
Difficulty walking	63 (49)	173 (91)*	159 (72)	72 (87)
EQ-5D utility	0.69 ± 0.23	0.36 ± 0.28*	0.54 ± 0.29	0.33 ± 0.3*
EQ-5D VAS	70 ± 17	52 ± 18*	61 ± 20	52 ± 19*
SF-6D utility	0.7 ± 0.1	0.58 ± 0.12*	0.64 ± 0.12	0.56 ± 0.1*
RODS (total raw score)	37.66 ± 7.8	28.41 ± 7.91*	33.5 ± 8.9	28 ± 7.9*
RODS (centile metric)	68.3 ± 16.7	54.5 ± 12.1*	60.5 ± 16.4	50.5 ± 12.1*
ONLS total	2.82 ± 1.43	4.18 ± 1.42*	3.5 ± 1.6	4.2 ± 1.4*
INCAT total	1.73 ± 1.51	3.1 ± 1.5*	2.4 ± 1.6	3.14 ± 1.56*
CAPPRI total	10.25 ± 6.46	19.31 ± 6.12*	14.4 ± 7.6	20.1 ± 5.7*

EQ-5D EuroQoL Five-Dimension Five Level, *VAS* visual analog scale, *SF-6D* Short-Form 6- Dimension, *RODS* Rasch Overall Disability Scale, *ONLS* Overall Neuropathy Limitation Scale, *INCAT* Inflammatory Neuropathy Cause and Treatment, *CAPPRI* Chronic Acquired Polyneuropathy Patient-Reported Index

*Significant difference between symptom-satisfied vs. -dissatisfied, and treatment-satisfied vs. -dissatisfied ($p < 0.01$)

[a]Patients who answered both Symptom burden and Treatment Satisfaction questions

[b]Patients currently on medication (Symptom satisfied: $n = 96$, Symptom dissatisfied: $n = 146$, Treatment satisfied: $n = 193$, Treatment dissatisfied: $n = 49$)

[c]Other medications: azathioprine, mycophenolate and cyclosporine

Table 2 Current treatments

	Symptom satisfied ($n = 128$)	Symptom dissatisfied ($n = 190$)	Treatment satisfied ($n = 222$)[a]	Treatment dissatisfied ($n = 83$)[a]
Number of current medications per patient				*
None	32 (25)	44 (23)	29 (13)	34 (41)
One	67 (52)	110 (58)	148 (67)	29 (35)
Two or more	29 (23)	36 (19)	45 (20)	20 (24)
Medication duration[b]				
1 yr or less	18 (19)	33 (23)	37 (19)	14 (29)
Between 1–5 yrs	33 (34)	60 (41)	78 (40)	15 (31)
Greater than 5 yrs	45 (47)	53 (36)	78 (40)	20 (41)
Current medications				
IVIG	71 (55)	112 (59)	152 (68)	31 (37)*
PLEX	4 (3)	5 (3)	4 (2)	5 (6)
SCIG	12 (9)	14 (7)	22 (10)	4 (5)
Prednisone	21 (16)	26 (14)	30 (14)	17 (20)
Rituximab	4 (3)	7 (4)	9 (4)	2 (2)
Other medications[c]	14 (11)	21 (12)	25 (12)	11 (13)

Data expressed as counts and (%)

IVIG intravenous immunoglobulins, *PLEX* plasma exchange, *SCIG* subcutaneous immunoglobulins

*Significant difference between symptom-satisfied vs. -dissatisfied, and treatment-satisfied vs. -dissatisfied ($p < 0.01$)

[a]Patient who answered both Symptom burden and Treatment Satisfaction questions

[b]Patients currently on medication (Symptom satisfied: $n = 96$, Symptom dissatisfied: $n = 146$, Treatment satisfied: $n = 193$, Treatment dissatisfied: $n = 49$)

[c]Other medications: Azathioprine, Mycophenolate, and Cyclosporine

Foundations carrying a diagnosis CIDP were unsatisfied with their current symptom burden. However, most individuals reported being satisfied with their treatments, although those dissatisfied with their symptoms had a higher proportion of treatment dissatisfaction. This discrepancy may have several explanations. For example, some patients who have had some improvement can be satisfied with their treatments, but if their symptoms are still bothersome, they will still be dissatisfied with their overall symptoms. This difference between "being better" and "being well" has been documented in many diseases [5–14].

This difference also suggests that, when asked about symptom and treatment satisfaction individuals, consider these as different concepts, even though they may share some commonalities. For example, when looking at the groups with symptom and treatment dissatisfaction, both had more individuals with worsening disease status compared to those satisfied, suggesting that disease stability is important both in relation to symptoms and to treatments. Disease stability is often a milestone during routine care and serves as a metric to determine treatment dependency in patients with CIDP [1, 25]. This observation further

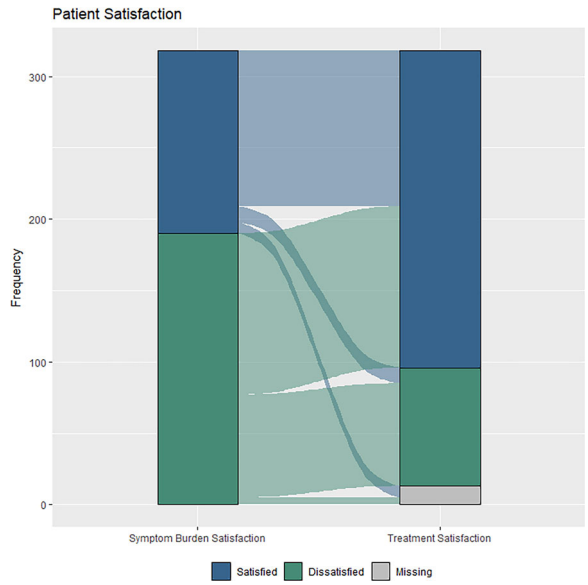

Fig. 1 Proportion of treatment satisfaction. Patients satisfied with their symptom burden, 109 (85%) satisfied and 11 (9%) dissatisfied with treatments; patients dissatisfied with symptom burden, 113 (59%) satisfied and 72 (38%) dissatisfied with treatments; 13 patients did not report their satisfaction with treatment

highlights that, in patients with continued worsening of symptoms, treatment regimens may need further optimization.

Unfortunately, our data do not allow for the assessment of the root cause for treatment dissatisfaction, which can include side effects, treatment efficacy, and other factors, such as depression. The similar treatment durations between patient groups would suggest that the differences in treatment satisfaction may not have been caused by treatment acclimation. Work in rheumatoid arthritis has shown that patients place higher value on treatment benefits over side effects, cost, or mode of administration [26]. Whether patients with CIDP have similar treatment preferences remains to be seen. At present, the treatment preferences in CIDP have not been specifically investigated [27]. A recent review of preferences in chronic autoimmune diseases showed that patients were more likely to choose subcutaneous (SC) over intravenous (IV) treatments [28], driven by a desire for at-home treatment and hospital avoidance. However, some patients did prefer IV over SC treatments due to lower frequency, presence of healthcare professionals, and dislike of self-injection. Therefore, treatment dissatisfaction may have also been influenced by the mode of administration or logistical burden of treatments, a topic we did not explore in this study. The potential role of depression, which is common in chronic diseases including CIDP, in treatment satisfaction also needs further investigation.

Treatment dissatisfaction could have also been driven by the lack of treatment efficacy due to misdiagnosis. A recent survey of self-reported CIDP patients has shown that a common reason for IVIG discontinuation was lack of efficacy [29]. Almost 40% of treatment-dissatisfied participants in our study reported receiving IVIG; if dissatisfaction were due to IVIG inefficacy, then perhaps this would indicate a misdiagnosis of CIDP requiring further investigation.

The use of IVIG was associated with treatment satisfaction, which is not surprising as IVIG is considered as a first-line maintenance treatment for CIDP [30]. However, this difference may also reflect the treatment preferences of CIDP patients, preferring IVIG over other treatments such as corticosteroids [30]. Future work will be aimed to better understand the treatment preferences of CIDP patients and to identify other variables leading to treatment dissatisfaction. In patients reporting treatment dissatisfaction, 34 (41%) were not currently receiving any treatment. As we did not ask about reasons for being off treatment, we do not know if this reflects lack of access to medication (e.g., lack of insurance and/or ability to pay out-of-pocket costs), adverse events requiring stopping treatment, or prior treatment failure. Interestingly, the original model with EQ-5D as a covariate did not show a correlation between utility score on treatment satisfaction; however, the model using SF-6D did show that utility scores were associated with treatment satisfaction. The SF-6D has different domains than the EQ-5D, with a specific vitality domain and a social function domain, and these differences may explain some of these findings.

Surprisingly, disease-specific measures, such as the RODS, did not have a strong association

Table 3 Symptom burden satisfaction logistic regression analysis

	Coefficient	SE	Odds ratio	95% CI	*p* value
Age	− 0.0215	0.0125	0.66	0.40–1.06	0.07
Sex (female)	− 0.0828	0.3339	1.11	0.57–2.15	0.75
Disease duration	0.3391	0.2251	1.47	0.95–2.34	0.09
Reference: "Worsened in the past 6 months"					
Improved in the past 6 months	1.4982	0.5587	5.03	1.66–15.18	0.007
No symptoms or stable	1.2367	0.4074	3.73	1.64–8.51	0.002
Reference: "no treatments"					
One	− 0.4285	0.5162	1.54	0.56–4.22	0.41
Two or more	0.0484	0.5832	1.61	0.75–3.48	0.93
Difficulty walking (yes)	− 1.2556	0.4495	0.36	0.15–0.89	0.02
On IVIG	0.7455	0.4074	2.05	0.93–4.49	0.07
RODS total	− 0.0128	0.0319	0.83	0.33–2.08	0.68
EQ-5D utility	4.5769	1.1095	6.84	2.72–16.59	< 0.0001

C-statistic: 0.871, $p < 0.0001$
IVIG intravenous immunoglobulins, *RODS* Rasch Overall Disability Score, *EQ-5D* EuroQoL Five-Dimension Five Level

Table 4 Symptom burden satisfaction logistic regression analysis, using SF-6D

	Coefficient	SE	Odds ratio	95% CI	*p* value
Age	− 0.019	0.013	0.69	0.43–1.02	0.12
Sex (female)	− 0.084	0.332	1.08	0.56–2.09	0.80
Disease duration	0.341	0.221	1.40	0.91–2.16	0.12
Reference: "Worsened in the past 6 months"					
Improved in the past 6 months	1.652	0.557	5.22	1.76–15.5	0.007
No symptoms or stable	1.378	0.405	3.96	1.79–8.78	0.003
Reference: "no treatments"					
One	− 0.279	0.571	0.76	0.27–2.06	0.58
Two or more	0.386	0.571	1.47	0.48–4.51	0.49
Difficulty walking (yes)	− 1.03	0.437	0.36	0.15–0.84	0.018
On IVIG	0.669	0.387	1.95	0.91–4.17	0.08
RODS total	0.039	0.026	1.73	0.84–3.57	0.14
SF-6D utility	6.436	2.028	2.95	1.51–5.74	0.001

C statistic: 0.86, $p < 0.0001$
IVIG intravenous immunoglobulins, *RODS* Rasch Overall Disability Score, *SF-6D* Short-Form 6-Dimension

Table 5 Treatment satisfaction logistic regression analysis

	Coefficient	SE	Odds ratio	95% CI	*p* value
Age	− 0.0146	0.0136	0.76	0.46–1.26	0.28
Sex (female)	0.1094	0.3420	0.89	0.46–1.75	0.75
Disease duration	0.1248	0.2093	1.13	0.75–1.71	0.55
Reference: "Worsened in the past 6 months"					
Improved in the past 6 months	1.1696	0.5731	3.22	1.05–9.90	0.041
No symptoms or stable	0.7719	0.3595	2.16	1.07–4.38	0.031
Reference: "no treatments"					
One	1.3634	0.4719	3.91	1.55–9.86	0.004
Two or more	0.5537	0.5285	1.74	0.62–4.90	0.29
Difficulty walking (yes)	− 0.0462	0.5267	0.95	0.34–2.68	0.93
On IVIG	1.1942	0.3945	3.30	1.52–7.15	0.003
RODS total	0.0336	0.0319	1.60	0.67–3.84	0.29
EQ-5D utility	1.7138	0.8895	2.04	0.99–4.23	0.05

C statistic: 0.807, $p < 0.0001$

IVIG intravenous immunoglobulins, *RODS* Rasch Overall Disability Score, *EQ-5D* EuroQoL Five-Dimension Five Level

Table 6 Treatment satisfaction logistic regression analysis, using SF-6D

	Coefficient	SE	Odds ratio	95% CI	*p* value
Age	− 0.013	0.013	0.78	0.47–1.29	0.33
Sex (female)	− 0.005	0.339	1.00	0.52–1.95	0.99
Disease duration	− 0.016	0.208	0.98	0.65–1.75	0.94
Reference: "Worsened in the past 6 months"					
Improved in the past 6 months	0.988	0.574	2.68	0.87–8.26	0.08
No symptoms or stable	0.682	0.352	1.98	0.99–3.95	0.05
Reference: "No treatments"					
One	1.274	0.457	3.57	1.46–8.75	0.005
Two or more	0.549	0.508	1.73	0.64–4.68	0.28
Difficulty walking (yes)	0.101	0.528	1.11	0.39–3.11	0.85
On IVIG	1.176	0.386	3.24	1.52–6.90	0.002
RODS total	0.045	0.027	1.86	0.89–3.86	0.09
SF-6D utility	4.464	1.879	2.12	1.14–3.93	0.02

C statistic: 0.81, $p < 0.0001$

IVIG intravenous immunoglobulins, *RODS* Rasch Overall Disability Score, *SF-6D* Short-Form 6-Dimension

Table 7 Patient acceptable symptom state (PASS) Thresholds for Common CIDP Outcome measures

Outcome measure	AUC (95% CI)	Threshold	Specificity (%)	Sensitivity (%)	Accuracy (%)	NPV (%)	PPV (%)
EQ-5D utility	0.83 (0.78–0.88)	≥ 0.57	75.00	76.00	75.4	82.14	67.37
EQ-5D VAS	0.78 (0.72–0.83)	≥ 60.5	67.37	71.09	68.89	77.30	59.87
SF-6D utility	0.78 (0.73–0.83)	≥ 0.63	67.20	79.69	72.29	82.78	62.58
RODS raw score	0.79 (0.74–0.85)	≥ 32	71.05	78.12	73.9	82.82	64.51
RODS centile	0.79 (0.74–0.85)	≥ 56	71.05	78.12	73.9	82.82	64.51
ONLS total	0.74 (0.69–0.8)	≤ 3	72.83	64.46	69.39	74.56	62.40
INCAT total	0.76 (0.71–0.82)	≤ 2	66.28	77.6	71.04	80.28	62.58
CAPPRI total	0.84 (0.79–0.88)	≤ 14	76.00	77.59	76.63	83.65	68.18

AUC area under curve, *EQ-5D* EuroQoL Five-Dimension Five Level, *VAS* visual analog scale, *SF-6D* Short-Form 6-Dimension, *RODS* Rasch Overall Disability Scale, *ONLS* Overall Neuropathy Limitation Scale, *INCAT* Inflammatory Neuropathy Cause and Treatment, *CAPPRI* Chronic Acquired Polyneuropathy Patient-Reported Index

with symptom satisfaction after adjusting by other variables, although mean scores were significantly different in satisfied versus dissatisfied patients before adjustment. In our model, maintained ability to walk, stable symptoms, and utility scores (EQ-5D or SF-6D scores) were the main drivers of symptom satisfaction. This suggests that current CIDP-specific disability measures may not capture all the relevant impacts of CIDP in patients, which has also been seen in other studies [31]. Additionally, it stresses the importance of independence in mobility as an important goal of treatment. Future work is needed to determine how the variables we identified in this study can be incorporated into outcomes. For example, a composite outcome including regaining the ability to walk, stable symptoms and reaching utility score PASS thresholds (e.g., ≥ 0.57 for EQ-5D) could be studied as a long-term outcome in CIDP research, as these were the variables associated with patient satisfaction in this study.

Our estimated PASS thresholds for commonly used outcome measures in CIDP, are centered on patient symptom satisfaction and represent a holistic viewpoint on disease severity and quality of life, reflecting when a patient is feeling "well" rather than just "better" [3]. These estimates can be used alongside known minimum clinical important difference (MCID) values for CIDP during long-term clinical research [32]. The combination of PASS thresholds with MCID will aid in the identification of patients who not only respond to treatment but also consider themselves as "well". Gaining a better understanding of when a patient considers themselves as "well" can have a large impact on medical decisions to maintain or escalate treatment. These thresholds, however, are exploratory, and should be confirmed in future studies with clinical cohorts, where a diagnosis of CIDP can be confirmed.

As an exploratory application of CIDP-PASS thresholds, we applied our INCAT threshold of 2 (Table 7) to a study on the long-term efficacy and safety of intravenous immunoglobulins (IVIG) in CIDP [33]. Patients who responded to IVIG had a mean INCAT score of 2.8 ± 1.9 at week 28, and continued to improve with an average INCAT score of 1.9 ± 1.3 by week 52. Although the INCAT scores at week 28 were significantly less than the average baseline INCAT scores (4.1 ± 1.4), the average score at week 28 is above our INCAT threshold (≤ 2). Therefore, patients may not have been satisfied with their current disease burden, despite feeling "better". In contrast, by week 52, the

Table 8 Alternate PASS thresholds for outcome measures in CIDP

Outcome measure	AUC (95% CI)	Threshold	Specificity (%)	Sensitivity (%)	Accuracy (%)	NPV (%)	PPV (%)
EQ-5D utility							
80% specificity	0.83 (0.78–0.88)	≥ 0.63	82.06	66.4	75.73	78.24	71.55
75th percentile	–	≥ 0.84	98.37	27.2	69.58	66.54	91.89
EQ-5D VAS							
80% specificity	0.78 (0.72–0.83)	≥ 71	86.1	54.69	73.33	73.92	72.92
75th percentile	–	≥ 83.2	97.32	25	67.94	65.47	86.49
SF-6D utility							
80% specificity	0.78 (0.73–0.83)	≥ 0.69	82.26	58.59	72.61	74.27	69.44
75th percentile	–	≥ 0.75	94.62	27.34	67.2	65.43	77.78
RODS raw score							
80% specificity	0.79 (0.74–0.85)	≥ 36	80	64.06	73.58	76.77	68.33
75th percentile	–	≥ 44	96.84	25.78	68.24	65.95	84.61
RODS centile							
80% specificity	0.79 (0.74–0.85)	≥ 61	80	64.06	73.58	76.77	68.33
75th percentile	–	≥ 80	96.82	25.78	68.24	65.95	84.61
ONLS total							
80% specificity	0.74 (0.69–0.8)	≤ 2	89.02	40.49	69.05	68.14	72.06
75th percentile	–	≤ 4	38.73	89.25	59.52	83.75	50.47
INCAT total							
80% specificity	0.76 (0.71–0.82)	≤ 1	86.62	52	72.05	71.29	73.86
75th percentile	–	≤ 2	66.28	77.6	71.04	80.28	62.58
CAPPRI total							
80% specificity	0.84 (0.79–0.88)	≤ 13	80	73.27	77.32	81.87	70.83
75th percentile	–	≤ 14	76.00	77.59	76.63	83.65	68.18

AUC area under curve, *EQ-5D* EuroQoL Five-Dimension Five Level, *VAS* visual analog scale, *SF-6D* Short-Form 6-Dimension, *RODS* Rasch Overall Disability Scale, *ONLS* Overall Neuropathy Limitation Scale, *INCAT* Inflammatory Neuropathy Cause and Treatment, *CAPPRI* Chronic Acquired Polyneuropathy Patient-Reported Index

average INCAT score of patients is below the INCAT threshold. Overall, by the end of the study, patients not only felt better than they did at week 28, but also, on average, met the threshold for being "well". We argue that, as a long-term outcome, becoming "well" is more important than just feeling "better", and strengthens the evidence showing the long-term benefits of IVIG for CIDP patients.

A notable strength of this study is the content validity of our patient satisfaction questions; patients who were satisfied with their current symptom burden and treatments had better health scores than individuals who were dissatisfied. In addition, our patient-anchored satisfaction question allowed for the holistic assessment of symptom burden through the patient's perspective, considering all impairments when determining a good outcome

instead of a single indicator. Additionally, we developed the treatment and symptom satisfaction questions with patient input, which also strengthens their content validity.

We acknowledge that this study has limitations. First, all survey participants were invited through the Canadian and US GBS/CIDP Foundations which limit the generalizability of our results to people living in other countries. Additionally, it is possible that individuals with more severe disease or with poor response to treatments are more likely to participate in this type of study, which may bias the findings. We had a response rate of ~ 10% which is in keeping with typical published rates for online surveys, but it does affect generalizability. Symptom and treatment satisfaction may also have been influenced by regional differences in healthcare access and financial coverage. Study participation required the self-completion of the online survey which introduces the possibility of recall bias within our data. The self-reported nature of our survey inhibited the collection of examination-dependent measures such as grip strength and manual muscle tests [34, 35]. Therefore, variables such as "disease stability" are based on subjective parameters, which will need to be validated using objective measures of disease stability and progression, including neurological exam, grip strength, and even electrophysiology. Future work will investigate how objective measures of disease burden correlate with patient satisfaction and which of these are associated with patient satisfaction.

Another limitation of using a patient registry in CIDP research is the high frequency of misdiagnosis, whereby many patients diagnosed with CIDP may ultimately have an alternative diagnosis [36]. Therefore, it is possible that some survey participants self-reporting a diagnosis of CIDP may not have CIDP at all. Given the nature of the survey, we cannot assess the rate of misdiagnosis in this study. Furthermore, 5–10% of patients presenting as CIDP have paranodal antibodies. Autoimmune nodopathies are now classified as distinct entity from CIDP, and patients are often refractory to typical CIDP treatments such as IVIG [37]. Therefore, it is possible that our cohort included individuals with autoimmune nodopathy, which can affect satisfaction ratings. To address limitations regarding possible misdiagnosis, we are incorporating the symptom satisfaction questions during routine in-person care of patient with confirmed CIDP attending our clinic.

To improve the response rate and avoid participant fatigue, we shortened the length of our online survey. Therefore, we were limited in our ability to collect additional data on health characteristics such as comorbidities. Recent work in CIDP has shown that fatigue is associated with increased self-reported disability and reduced quality of life [38]. The higher disability and lower quality of life of dissatisfied patients would suggest that these patients may also experience more fatigue than satisfied patients. We also did not measure symptoms of depression or anxiety to assess the correlation between mood disorders with symptom and treatment satisfaction.

Due to the high proportion of survey participants with CIDP duration longer than 5 years, our threshold estimates may not appropriately reflect patients who have been recently diagnosed. Work in other chronic conditions have shown that symptom adaptation can influence the interpretation of symptom satisfaction questions and alter threshold estimates over time [3, 39]. It would be of interest to determine if PASS estimates similarly evolve in recently diagnosed CIDP patients.

CONCLUSIONS

We found that, in members of the Canadian and US GBS/CIDP foundations with a diagnosis of CIDP, a large proportion are dissatisfied with their current CIDP symptoms. Most individuals dissatisfied with their symptoms were, however, satisfied with their treatments. There is an unmet need to improve long-term outcomes in CIDP. Incorporating patients' self-reported satisfaction and/or PASS thresholds in clinical research can help identify factors associated with better patient-meaningful outcomes.

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Declarations

Conflict of Interest. Meg Mendoza reports no disclosures. Christopher Tran reports no disclosures. Hans D. Katzberg has been a consultant to Grifols, CSL Behring, UCB, Takeda (Shire), Alnylam, Octapharma, Akcea, Alexion, Pfizer, Biogen and Terumo: he has received research support from Takeda (Shire) and CSL Behring. Vera Bril has been a consultant to Grifols, CSL Behring, UCB, Argenx, Takeda (Shire), Alnylam, Octapharma, Powell Mansfield Inc., Akcea, Immunovant and Alexion; she has received research support from Grifols, CSL Behring, UCB, Argenx, Takeda (Shire), Octapharma, Baxalta and Biogen. Carolina Barnett-Tapia has been consultant to Alexion, Argenx, UCB and Sanofi; she has received grant support from Grifols and Octapharma. She is the developer of the MGII and may receive royalties.

Ethical Approval. This study was reviewed and approved by the University Health Network Research Ethics Board (Study number: 18-5514) and conforms to the World Medical Association Declaration of Helsinki. Participants of the pilot test provided written consent and answering the anonymous electronic survey was considered as implicit consent. We obtained written permission from the developers of the INCAT, RODS and CAPPRI to use the measures in this study. We obtained a license for the use of the SF-12 from QualityMetric, and we registered our study to use the EQ-5D-5L with EuroQoL (non-commercial, fast-track digital, no license needed).

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