

# Health-related quality of life in chronic inflammatory neuropathies

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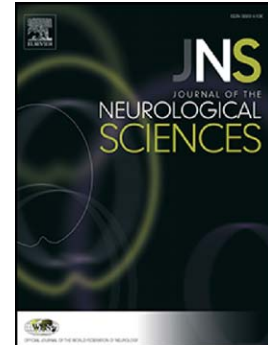
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# Health-related Quality of Life in Chronic Inflammatory Neuropathies: A Systematic Review

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## Highlights:

- Few studies have evaluated HRQoL in chronic inflammatory neuropathies
- HRQoL is lower in chronic inflammatory neuropathies than in healthy subjects
- HRQoL measures improve in conjunction with strength and function with treatment
- HRQoL measures may contradict results obtained with traditional outcome measures

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**Abstract:**

Chronic inflammatory neuropathies represent a heterogeneous group of disorders which affect patients' functional status and quality of life. We conducted a systematic review of the scientific literature on the effects of both disease and treatment interventions on health-related quality of life (HRQoL) in this patient population. The available data are limited, as few studies have systematically considered HRQoL in patients with inflammatory neuropathies. Moreover, in treatment trials, HRQoL measures have exclusively been used as secondary outcome measures. There is some evidence suggesting that baseline pre-treatment HRQoL reports are lower in patients with chronic inflammatory neuropathy than in age and gender-matched controls. Following treatment interventions, improvements in self-reported measures were consistently documented in the physical domain of HRQoL, which in turn correlated with improvements in traditional strength and functional scales. The impact of available treatments on the quality of life of patients with inflammatory neuropathies remains largely under-investigated. Interestingly, recent, although limited evidence from generic HRQoL measures may partly or completely contradict the results found with the primary, traditional outcome measures used (rituximab for anti-MAG neuropathy; immunoglobulins versus corticosteroids for chronic inflammatory demyelinating polyneuropathy). Similarly, HRQoL measures may suggest superiority, rather than equivalence, of certain drug administration methods (subcutaneous over intravenous immunoglobulins). Further research is needed to assess HR-QoL in patients with untreated chronic inflammatory neuropathies in comparison to normative values, as well as precisely quantify treatment benefit. The role of both generic and disease-specific HRQoL measures in the evaluation of patients with chronic inflammatory neuropathies is also worthy of further consideration.

**Introduction.**

Health-related Quality of Life (HRQoL) is a concept that reflects subjective individual perceptions of the effects of an illness and its treatment on physical, mental and social aspects of life [1]. As a result, HRQoL appears to be directly indicative of reduced level of patients' well-being from their disease. Changes may otherwise indicate genuine and meaningful effects of treatments administered. Therefore, use of HRQoL scales has been proposed as an appropriate method to ascertain actual effects on patients' lives, resulting from disease as well as from therapeutic interventions, and should at least complement other health status measurements in neuromuscular conditions. Although an earlier study, which will be detailed as part of the current review, had demonstrated the Medical Outcome Study 36-item short form health status scale (SF-36) Questionnaire as a potentially valuable instrument in inflammatory neuropathies [2], the extent to which HRQoL evaluations have been used subsequently in the research setting has appeared variable.

Chronic inflammatory neuropathies are a broad and heterogeneous group of conditions manifesting in focal, multifocal or generalized sensory and/or motor deficits, evolving in a progressive or relapsing and remitting manner. In chronic inflammatory neuropathies, different therapies have demonstrated favourable effects on muscle strength and/or neurological function. How relevant these can be in actually improving the day-to-day living of treated patients may however be difficult to ascertain. Furthermore, baseline pre-treatment quality of life characteristics are uncertain in this group of disorders and how that may compare with normative values is unknown. We conducted a systematic review of the literature relating to use of

instruments measuring HRQoL in chronic inflammatory neuropathy, focusing in particular on chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN). We aimed to specifically analyze the use of HRQoL measures in the studied populations, in relation to baseline function as well as therapeutic benefit and its clinical correlates.

## Materials and Methods.

Our search methodology followed the standard guidelines for systematic literature reviews outlined in the PRISMA statement [3]. We conducted a Medline search of all English language articles published between 1966-October 2014 on HRQoL in all forms of chronic inflammatory neuropathies. We used Medline with the search MeSH terms “inflammatory neuropathy”, as well as “chronic neuropathy”, “paraproteinaemic demyelinating neuropathy” (“PDN”), “POEMS” (“Polyneuropathy, Organomegaly, Endocrinopathy, M-Protein, Skin”) syndrome, “CANOMAD” (“Chronic Ataxic Neuropathy with Ophthalmoplegia, M-protein and Disialosyl antibodies”) syndrome, each combined with “Quality of Life” and “Health Status”. Reference lists of each retrieved paper were screened for additional relevant publications. All papers discussing specifically ascertainment of HRQoL in any aspect of baseline clinical manifestations, treatment effects or disease monitoring, were analyzed. Articles were included irrespective of disease subtype or course, number of patients studied, main purpose of the analysis considered, type of monitoring otherwise performed/described in addition to HRQoL, or type of therapeutic intervention utilized. Papers considered were read in full-text version and analyzed in detail in relation to HRQoL evaluations, results and conclusions. Reference lists of retrieved articles were searched for any additional relevant publications in the field. The findings are presented here in a descriptive manner following the chronological development of this rapidly expanding field.

## Results.

We retrieved a total of 23 articles which had descriptions of use of instruments measuring HRQoL in patients diagnosed with chronic inflammatory neuropathy. The reviewed articles, summarized in Table 1. showed heterogeneity in terms of study focus. Some studies described the results of a cross-sectional analysis of HRQoL in patients with CIDP. In other studies, changes in HRQoL were described as part of a therapeutic intervention for CIDP or MMN, with intravenous immunoglobulin (IVIg) treatment versus corticosteroids/placebo, or subcutaneous immunoglobulin (SCIg) versus IVIg/placebo, as a secondary outcome measure. In few studies, HRQoL was evaluated as part of the IVIg-related benefit in small treated cohorts, outside the setting of a drug trial. Finally in a single recent study, HRQoL was used as secondary outcome measure in a trial setting of rituximab versus placebo for anti-myelin associated glycoprotein (MAG) antibody neuropathy.

The first relevant study was published in 2001 and presented the results of a multicentre double-blind cross-over randomized controlled trial (RCT) of IVIg versus oral corticosteroids, in 25 patients with chronic inflammatory neuropathy [4]. Both treatments provided significant, but not significantly different, improvements at 2 weeks in the primary outcome measure, the 11-point Inflammatory Neuropathy Cause and Treatment (INCAT) scale. The study participants also completed the SF-36, a generic HRQoL questionnaire consisting of 36 items encompassing the domains of physical functioning (10 items), role functioning-physical (4 items), role functioning-emotional (3 items), social functioning (2 items), body pain (2 items), mental health (5 items), vitality (4 items), general health perception (5 items), and change in health,



which is scored separately. In this study there were no significant changes of HRQoL according to the SF-36 physical functioning scores after 6 weeks in either treatment group. In a separate publication [5], the authors detailed the results of their assessments using the EuroQol (EQ)-5D instrument to ascertain the broader impact of the two interventions. The EQ-5D is a shorter generic HRQoL measure consisting of 5 domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each of which has three levels of severity (1, no problem; 2, some problem and 3, serious problem). As opposed to the findings of treatment equivalence for the primary outcome measure, the EQ-5D was unchanged for the prednisolone group, whilst there was a relatively large improvement in quality of life for the IVIg group. Treatment with IVIg resulted in a consistent, albeit non-significant, improvement in quality of life compared with prednisolone.

Merkies et al. used the SF-36 and other measures including the Medical Research Council sum score, sensory sum score, INCAT score and Hughes functional scale, to assess 23 stable patients with CIDP and 8 with paraproteinaemic demyelinating neuropathy (PDN) [2]. In addition they performed serial evaluations as part of an open-label 1-year longitudinal study, in 13 of the patients with CIDP. The reported mean SF-36 domain scores and summary values for a random, nationwide sample of 1,742 healthy individuals in the Netherlands were used as comparator. In the stable group, mean SF-36 subscales and summary scores (Physical Component Score: PCS; and Mental Component Score; MCS) were compared with the reported mean normal values for the Dutch population. Correlations were ascertained with various other scales used and the impact of age and duration of symptoms was also determined. In the longitudinally examined patients, mean SF-36 subscale and summary scores were

analysed and compared at various arbitrarily chosen follow-up points (weeks 0, 26, 52) with the reported SF-36 normative Dutch data. The mean SF-36 subscale scores with corresponding mean PCS and MCS scores for the stable group were found to be significantly lower compared with the mean normal values, although this included a large group of 83 patients with Guillain-Barré (GBS) syndrome. Precise breakdown data for CIDP and PDN were not provided. In the longitudinal study, all patients demonstrated a general increase in HRQoL at follow-up. The SF-36 adequately captured improvement in these patients, demonstrating a gradual shift of all scores towards normal values in the whole group. At entry, all dimensions and summary measures were substantially lower compared with the corresponding normal values. All SF-36 components, except for the “physical functioning” and “role functioning-physical” domains, as well as PCS score, reached normal values at 6 and 12 months of follow-up. Interestingly, the statistical analysis showed that general strength only explained 12% and sensory functions only 16%, of the SF-36 physical summary scores. Otherwise, no significant association was obtained between weakness and sensory deficit and SF-36 mental summary scores. The authors concluded that the SF-36 could be considered as an adjunct outcome measure for future studies, complementing traditional strength and sensory scales. In addition, they indicated that variables such as depression and fatigue may, as previously suggested, represent potential contributors to decrement in HRQoL.

In a heterogeneous population consisting of 8 patients with CIDP and 3 with MMN, but also 3 with GBS and 10 with myasthenia gravis, improvements of the Italian version of the SF-36 were reported after IVIg therapy [6, 7]. Analysis of changes in SF-36 subscores indicated highly significant differences of vitality, physical role, and

physical function subscores from normal, which all improved after IVIg therapy. On the other hand, the comparison of mental scores between the baseline evaluation and the follow-up evaluation revealed no differences, leading the authors to conclude that IVIg did not improve psychological distress. The lack of data regarding the exact breakdown of different diseases makes it difficult to reach any further conclusions from these two papers. However it is likely that the expected major post-IVIg improvements in patients severely disabled in the acute stages of GBS and myasthenic crises could have biased the results.

In a study of physical training, a 12-week bicycle exercise programme was implemented in 16 patients with GBS with relatively good recovery and 4 with stable CIDP [8]. All were severely fatigued. Besides the Fatigue Severity Score (FSS), Fatigue Impact Scale (FIS), GBS disability score, Hospital Anxiety and Depression Scale (HAD), Rotterdam Handicap Scale (RHS), the SF-36 was also utilized. Significant improvements from baseline were obtained for FSS, FIS, HAD and RHS for the whole cohort. The PCS, but not the MCS, of the SF-36 improved significantly ( $p < 0.05$ ). Interestingly, in comparison with healthy controls, only PCS were significantly different to baseline in patients, whereas MCS were comparable, although still improved with the intervention. Unfortunately, precise breakdown of results for the SF-36 was not provided in relation to CIDP patients specifically.

The ICE Trial, a randomized, double-blind, response-conditional crossover study of immune globulin IV, 10% caprylate/chromatography purified (IGIV-C [Gamunex®]) versus placebo was published in 2008 [9]. This was a multicentre international study involving 117 patients recruited across 33 centres. During the first

period, 32/59 (54%) patients treated with IGIV-C and 12/58 (21%) patients who received placebo had an improvement in adjusted INCAT disability score that was maintained through to week 24 ( $p=0.0002$ ). Significant improvements from baseline to endpoint were also recorded for grip strength in both dominant and non-dominant hands. Results were similar during the crossover period. During the extension phase of the study, participants who continued to receive IGIV-C had a significantly longer time to relapse than patients treated with placebo. This study used HRQoL evaluations as secondary outcome measure, and the results were published separately in two additional papers [10, 11]. The SF-36 Questionnaire was administered at baseline and at each study endpoint. The lowest scores for SF-36 domains at baseline were in role-physical and physical functioning in both the IGIV-C and placebo groups. Treatment with IGIV-C significantly improved the physical component summary score of the SF-36 from baseline compared with placebo. Larger improvements from baseline were observed across all domains in patients treated with IGIV-C than with the placebo group, with differences in physical functioning, role-physical, social functioning, and mental health domains achieving statistical significance. During the cross-over period, treatment with IGIV-C significantly improved the physical component summary score of the SF-36 from baseline compared with placebo to a similar degree as seen during the first period. Larger improvements from baseline in all domains were observed with IGIV-C versus placebo, with physical functioning, bodily pain, and social functioning all reaching significance. Mean improvements in SF-36 scores reported during the first period or the crossover period were maintained or even amplified in the extension period by the participants who continued treatment with IGIV-C. However, general decrease in SF-36 scores was observed in participants re-randomized to the placebo group.

Additionally the authors carried out a detailed analysis and interpretation of the effects of CIDP in terms of HR-QoL-related impairments to activity and participation restrictions, using correlates with the SF-36 [11]. At baseline, PCS correlated highly with MRC sum score, grip strength of both dominant and non-dominant hand, INCAT disability score and Rotterdam handicap scale. The MCS on the other hand failed to correlate at baseline with any strength or functional parameter, but showed a degree of association with electrophysiological proximal motor conduction block, which is of uncertain significance. However, interestingly, change from baseline demonstrated on univariate analysis at end point showed that changes in MCS as well as PCS were significantly associated to changes in INCAT disability score, INCAT sensory sum score and MRC sum score. A number of associations with electrophysiological parameters were also ascertained, including averaged motor amplitude and degree of conduction block, although the practical relevance of these findings appears, again, uncertain.

Harbo et al. performed a cross-sectional study on 14 patients with CIDP using isokinetic strength, muscle strength as evaluated clinically, neurological symptom score, Overall Disability Sum Score, 10-metre walk and 40-metre walk, as well as the physical components of the validated Danish version of the SF-36 [12]. After correction for multiple comparisons, there was a significant impairment in patients with CIDP compared to healthy controls on the physical function and vitality scales, but interestingly not for role physical, bodily pain, general health perception, social functioning, role emotional, or mental health. The PCS was reduced in patients with CIDP, whereas the MCS was similar to that of healthy controls. The PCS, but not the MCS, correlated significantly with isokinetic strength. In relation to global HRQoL

findings in this cross-sectional analysis, the authors felt that their results may have been influenced by the social and cultural context, including the high standards of social care provision in Denmark, and concluded that their findings may, as a result, not be applicable to all CIDP cohorts.

In another analysis, Harbo et al. evaluated the acute motor response following a single IVIg treatment course in 11 patients with CIDP [13]. Various assessment tools were used, including isokinetic strength, NIS (neuropathy impairment score)-strength score, functional tests such as the nine-hole peg test and 40-metre walk test, and in addition, the SF-36 Questionnaire. During the immunoglobulin treatment withdrawal period, significant correlations were ascertained between change in the combined isometric performance score and change in NIS-strength score and 40-metre walk test. However no correlations with SF-36 subscales were reported. Following immunoglobulin treatment, the increase in isometric strength was significant at day 5 and progressed between days 5 and 10 without further increase at day 15. The clinical NIS-strength score improved at day 5 without further improvements. The physical subscales of SF-36 (physical function and role physical function) increased significantly at assessment on day 15, whereas the pain, social, emotional, and mental categories were unchanged.

More recently, few trials of subcutaneous immunoglobulin therapy (SCIg) have been conducted in chronic inflammatory neuropathies and have used HRQoL measures as secondary outcome measures. In a single-blind randomized cross-over trial, 9 patients with MMN on regular IVIg treatment were recruited and randomized to receive either IVIg or SCIg and then crossed over to the other treatment [14]. The primary outcome

was the combined dynamometric strength score expressed relative to normal strength in 5-6 affected muscle groups at three joints and at hand grip. Functional scales were utilized as secondary outcomes. In addition, HRQoL was assessed using a validated Danish version of the SF-36 questionnaire. The items were summarized for PCS and MCS. The treatment methods were found to be equally effective with regard to the primary outcome, and, functionally, there were no significant performance differences for the nine-hole peg test or the 10-metre walk between SCIg and IVIg treatment arms. No differences were otherwise ascertained between the two treatments with regard to SF-36 PCS and MCS scores. In another, prospective, single-centre, open-label interventional study from the Netherlands, 10 patients with MMN were switched from IVIg to SCIg at 50% or 100% of the previous intravenous dose [15]. Results showed that the primary outcome measure, the MRC sum score, was unchanged at equivalent doses of treatment, and that HRQoL assessment carried out using the SF-36 Questionnaire showed no differences between IVIg and SCIg. In a further, open-label, proof-of-concept multicentre study, 8 patients with MMN were switched from IVIg to SCIg, with primary outcome measure being muscle strength at 24 weeks [16]. Disability and HRQoL were also assessed using another scale, the Life Quality Index (LQI) along with a visual analogue scale (VAS) to evaluate health status. The LQI is a 14-item self-reported questionnaire which provides scores on 4 major dimensions of patients' perceptions on daily activities and satisfaction with medication: effectiveness, side effects, convenience and global satisfaction are rated on a 0-100 scale (0 = not satisfied; 100 = fully satisfied). Scoring is arranged so that the more positive side of the pair gains highest scores. The LQI improved on SCIg in 6/8 patients and VAS remained stable or improved in 7/8. No details of scores and comparisons of these with normative data were provided. In another prospective

longitudinal study from Italy, Cocito et al. demonstrated in 5 CIDP patients previously on IVIg, equivalence of SCIg on the primary end-points which consisted of MRC scores, ONLS (Overall Neuropathy Limitation Score), Grip strength and sensory sum score, as well as, for secondary outcomes, the SF-36 PCS and MCS and Modified LQI [17]. The same authors later reported significant quality of life improvements in 10 patients with CIDP, as measured by the LQI with use of 20% SCIg versus 16% SCIg which had allowed reduction in infusion rate [18]. In a single study specifically focusing on quality of life from the U.K., the SF-36 and LQI were used in 16 patients with MMN treated with either SCIg or IVIg [19]. Overall the mean LQI score for the SCIg group was higher than the IVIg group but this did not reach a significant difference ( $p=0.06$ ). All individual mean item scores were higher in the SCIg group except for the item related to pain, where the SCIg was rated as causing more pain than IVIg. For the SF-36, overall the IVIg patient group had a lower, although non-significant, total score than the SCIg patient group ( $p=0.22$ ). A significant difference was observed between IVIg patient group and SCIg patient group on the MCS ( $p=0.03$ ), however no significant difference was observed on the PCS ( $p=0.38$ ), although this was higher for the SCIg group. Of the 8 domains, a significant difference favouring SCIg was only observed for the vitality component ( $p=0.004$ ). Disease duration was the only factor found to significantly correlate with lower SF-36 ( $p=0.02$ ), PCS ( $p=0.03$ ), MCS ( $p=0.02$ ) and for the specific dimensions of physical function ( $p=0.02$ ), general health ( $p=0.003$ ), social function ( $p=0.02$ ) and vitality ( $p=0.02$ ). Social class, work status, age, gender, and travel time to treatment centre were found not to be confounding factors.



In the most recent RCT for CIDP from the Italian group, IVIg treatment was compared to intravenous pulsed corticosteroids, using the difference in the proportion of patients discontinuing treatment with IVIg or intravenous methylprednisolone during the 6 months of therapy because of side-effects, intolerance, or inefficacy (defined as the absence of improvement after 2 months or worsening after 15 days) as primary outcome [20]. The results showed that more patients stopped methylprednisolone (11/21) than IVIg (3/24). This result was highly significant ( $p=0.0085$ ). When adjusted for sex, age, disease duration, comorbidity, modified Rankin scale and ONLS scores at enrolment, as well as previous treatment with IVIg and steroids, the difference between the two groups remained significant ( $p=0.007$ ). Reasons for discontinuation were lack of efficacy (8 in the steroid group vs. 3 in the IVIg group), adverse events (1 in the steroid group), or voluntary withdrawal (2 in the steroid group). Despite these results in favour of IVIg, SF-36 ratings revealed an improvement of 16.7 points at 6 months with steroids ( $p=0.0008$ ) and of 14.2 points with IVIg ( $p=0.011$ ), with no significant difference comparing the two treatment arms ( $p=0.3634$ ), this result contrasting with the previous comparative analysis performed [1].

A recent cross-sectional analysis from the south-east of England, U.K., studied specifically HRQoL using the EQ-5D instrument, which was completed by 43/50 of patients with CIDP, 26/37 of patients with PDN and 9/19 of patients with MMN to whom it was sent [21]. In all three diseases, limitations in ability to self-care or carry out daily activities and pain were reported in at least 75% of cases. Anxiety and/or depression affected nearly 50% of patients. Difficulty with mobility was experienced in 83% of patients with CIDP, 81% of patients with PDN and 38% of patients with

MMN. Combining data from the three diseases, the utility scores were not significantly related to gender, age, disease duration or, interestingly, IVIg treatment. The mean utility scores of each of the three diseases were lower than the U.K. average, but higher than the scores obtained from a cohort of 737 patients with multiple sclerosis and from a cohort of 97 patients with Parkinson's disease from the same country. In keeping with correlations described in other studies with neurological function, HRQoL was significantly higher in patients who were independently mobile or had no upper limb disability.

A Canadian study specifically analysed the relationship between social support and quality of life, as assessed by a disease-specific HR-QoL scale, the Peripheral Neuropathy Quality of Life Instrument-97, in a population of 154 patients with neuropathy, amongst whom 31.9% had diabetic polyneuropathy, 16% CIDP and 9% PDN, most having [22]. Comparison of quality of life between the patients with neuropathy and a Canadian normative sample showed highly significantly lower scores for all eight SF-36 domains in patients with CIDP ( $p < 0.001$ ). Physical and psychological quality of life were related to pain and to autonomic symptoms. Social support was otherwise associated with psychological aspects of quality of life when adjusting for other factors. Male gender and severity of neuropathy were independent predictors of impairment in physical health dimensions of quality of life. As acknowledged by the authors, major limitations for this study were the clinical heterogeneity of the neuropathic population and the absence of detailed findings for patients with CIDP and PDN.

Another recent cross-sectional study from Brazil specifically focused on the minimal status examination (MMSE) and SF-36 scores in a cohort of CIDP patients [23]. The results were unfortunately not adequately detailed for meaningful conclusions. Although scores for various domains were provided, normative values for the relevant Brazilian population were not available for analysis. Comparisons were made with data from Denmark [13], although, as acknowledged by the authors, these comparisons were likely to be biased cultural differences.

HRQoL measures have only been used rarely in studies of chronic inflammatory neuropathies other than CIDP. In a RCT of cyclophosphamide with prednisolone for polyneuropathy with IgM monoclonal gammopathy involving 35 patients stratified on the basis of their anti-MAG status, the SF-36 was used as a secondary outcome measure [24], with the Revised Rivermead Mobility Index used as primary outcome. Interestingly, although no effect could be demonstrated on the primary outcome, the MRC sum score, the sensory sum score and the SF-36 scores significantly improved in the first study phase of 6 months. The SF-36 itself improved by 31 points in treatment group vs. 5 points in placebo group ( $p=0.03$ ). Similarly, in the latest placebo-controlled RCT of rituximab for anti-myelin-associated-glycoprotein (anti-MAG) neuropathy [25], no effect could be demonstrated for the primary outcome measure, the INCAT sensory score at 12 months. Although improvement of the SF-36 PCS, utilized as secondary outcome, only approached significance in favour of rituximab ( $p=0.08$ ), subscores for physical functioning and role emotional improved significantly with the drug versus placebo ( $p=0.0069$  and  $p=0.02$ , respectively). Of note, improvement of subscores for mental health, social functioning and bodily pain also approached statistical significance ( $p=0.08$ ,  $p=0.07$  and  $p=0.09$ , respectively).

**Discussion.**

This review aimed to analyze the use of measures of HRQoL in all forms of published research in relation to chronic inflammatory neuropathies. The first striking finding is the relative scarcity of literature on this topic. This made further analysis of the data gathered, in addition to the purely descriptive one we have attempted to perform here, unfortunately unfeasible. Furthermore, variable use of scales, absence of normative values, and lack of longitudinal data, all represent major drawbacks in studies that have used HRQoL in their assessments of patients with chronic inflammatory neuropathies.

The SF-36 appears to be a useful generic instrument to evaluate HRQoL adequately in CIDP and PDN [2], as shown by its performance across the studies analyzed in this review. Although the SF-36 was the most popular, other non-validated scales have also been used in the studies considered in our review. The results with these scales are however clearly more difficult to interpret. With the SF-36 itself, absence of age-dependent reference values specific to the clinical population under study can make interpretation and meaningful inter-study comparisons impossible. Exclusive mention of aggregate PCS or MCS without the detailed breakdown also represents a limitation in some studies.

The studies we have considered show that patients with CIDP in particular demonstrate lower baseline HRQoL measures, especially with regard to the physical component. However, from the limited available data, the degree of impairment may be lesser than in other neurological disorders and other HR-QOL domains such as

pain and general health perception, social functioning and mental health appear to be relatively spared. It cannot be ruled out that this finding reflects the fact that the reviewed studies were carried out in countries with high standards of healthcare and ready access to a wide range of currently available pharmacological and non-pharmacological therapies. Improvement of the physical component of HRQoL otherwise appears to consistently occur with effective therapies such as IVIg, SCIg or steroids.

One important finding of this review relates to the comparative therapeutic studies. Although it appeared possible that IVIg may offer a better option than steroids for patients with CIDP on the basis of short-term HRQoL data [1], this was not confirmed with the 6-month data from the latest comparative study [20]. In the economic context of the high costs of IVIg, this latter result, not consistent with the main study findings on the primary outcome, may raise important questions on the appropriateness of choice of first-line therapy for CIDP. Interestingly, in keeping with these findings, the recent cross-sectional U.K. study equally raises the issue of utility of long-term immunoglobulin therapy which, surprisingly, was not found to influence HRQoL [21]. Likewise, SCIg could be of actual greater benefit than IVIg for CIDP and MMN, from a broader HRQoL perspective, from specific standpoints such as the psychological component, the importance of which cannot be discounted when treating disabling diseases. Correlations of HRQoL measures were otherwise consistently found at baseline with strength scores, isokinetic strength and functional scores in CIDP. Longitudinally, changes in HRQoL also correlated with changes in these scales, interestingly including changes in the psychological domain in the

largest study performed to date [11]. This would appear to confirm the applicability and suitability of HRQoL measures and the SF-36 in particular in this setting.

In therapeutic studies for CIDP, the HRQoL findings suggest that these measures, while correlating closely to traditional scales, may in addition provide useful information, not captured by these. The improvement of the MCS on active therapy in the ICE study demonstrates this [11]. The SCIg versus IVIg trials also revealed improved HRQoL for the former, while other scales showed equivalence. Similarly, the latest placebo-controlled trial of rituximab for anti-MAG neuropathy shows a similar positive impact of the active drug on several components of the HRQoL measures [25]. The results may have been also significant globally on the SF-36, with a greater sample size, contrasting again with the results for the primary outcome for this study.

In conclusion, this review indicates that despite the limited data, HRQoL measures may be a useful clinical tool and represent a potentially important component of the assessment of patients with chronic inflammatory neuropathies. Disease-specific Rasch-built Overall Disability Scales (R-ODS) have become the preferred and most popular recently proposed assessment tool for inflammatory neuropathies [26] and appear to have superseded consideration of HRQoL scales in recent literature.

Comparison of the suitability of traditional disability scales such as the INCAT Scale or ONLS, the R-ODS and HRQoL scales such as the SF-36 in the assessment and monitoring of clinically different entities such as CIDP, MMN and PDN, is not straight forward. As such, it is possible that use of HRQoL issues may be of greater relevance in conditions where clinically-relevant measurable changes are more difficult to predict or elicit. Conversely, in disorders where functional changes are of

large magnitude and more easily quantifiable, the relevance HRQoL measures may be may be more apparent in specific contexts, e.g. when making therapeutic decisions. However, use of a homogeneous validated scale such as the SF-36 may remain generally desirable and appears invaluable in capturing subjective aspects of baseline clinical presentations, as well as allow comparative analyses with other patient populations/healthy controls and contribute in determining meaningful treatment effects. Over the last few years, disease-specific HRQoL instruments have also been developed and validated for use in a number of common neurological conditions, ranging from multiple sclerosis (e.g. MSQOL-54 [27]) to epilepsy (e.g. QOLIE-10 [28]) and movement disorders (e.g. PDQ-39 [29], PSP-QOL [30], GTS-QOL [31]). Specifically for neuropathy, a HRQoL instrument was developed using the SF-36 as framework [32]. However this 97-item tool has not been used in subsequent studies in chronic inflammatory neuropathies, with the exception of the wider Canadian study described in this review [22]. Its reappraisal for this subset of neuropathic disorders may prove to be helpful in dissecting the selective impact on different HR-QoL domains. Although these disease-specific psychometric tools do not allow comparisons between quality of life in the target condition and other disorders or healthy state, they often capture aspects of HRQoL which are important to particular patient populations and can be overlooked or underestimated when using generic instruments. The development of a disease-specific HRQoL instrument for patients with chronic inflammatory neuropathies, alongside the recently developed R-ODS scales, might likewise allow a more comprehensive assessment of the impact of the condition and its treatment on patients' wellbeing. In general, further prospective studies are needed to ascertain the exact place and potential future role of HRQoL measures in chronic inflammatory neuropathies. Although limited, current available

data are of great interest as we believe this review highlights, and raise many questions, including that of the right choices for the primary outcome measures for future therapeutic studies in the field.

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**Table 1. Studies on Health-Related Quality of Life in chronic inflammatory neuropathies (Medline search of English language articles 1966-2014).**

Authors	Publication Year	Chronic Inflammatory Neuropathy Subtype(s)	Study Type	Number of Participants	Main Outcome/Finding regarding HRQoL
Hughes et al. [4]	2001	CIDP	Therapeutic	25	No improvement on IVIg or steroids
McCrone et al. [5]	2003	CIDP	Therapeutic	25	More improvement on IVIg than on steroids
Merkies et al. [2]	2002	CIDP, PDN	Cross-sectional	31	Lower than in controls; Improvement with treatment
Padua et al. [6]	2004	CIDP, MMN	Prospective cohort	11	Improvement with IVIg
Padua et al. [7]	2005	CIDP, MMN	Prospective cohort	11	Improvement with IVIg
Garssen et al. [8]	2004	CIDP	Interventional: Physical Training	4	Improvement with training
Hughes et al. [9]	2008	CIDP	Therapeutic	117	Improvement with IVIg
Merkies et al. [10]	2009	CIDP	Therapeutic	117	Improvement with IVIg
Merkies et al. [11]	2010	CIDP	Therapeutic	117	Correlation with strength, grip, disability
Harbo et al. [12]	2008	CIDP	Cross-sectional	14	Impairment; Correlation with isokinetic strength
Harbo et al. [13]	2009	CIDP	Therapeutic	11	Improvement with IVIg
Harbo et al. [14]	2009	MMN	Therapeutic	9	SCIg equivalent to IVIg
Eftimov et al. [15]	2009	MMN	Therapeutic	10	SCIg equivalent to IVIg
Misbah et al. [16]	2011	MMN	Therapeutic	8	Improvement on SCIg
Cocito et al. [17]	2012	CIDP	Therapeutic	5	SCIg equivalent to IVIg
Cocito et al. [18]	2013	CIDP	Therapeutic	10	Improved with 20% SCIg compared to 16% SCIg
Braine et al. [19]	2012	MMN	Therapeutic	16	SCIg equivalent to IVIg
Nobile-Orazio et al. [20]	2012	CIDP	Therapeutic	45	IV Steroids equivalent to IVIg
Mahdi-Rogers et al. [21]	2014	CIDP, MMN, PDN	Economic, HRQoL	106	Impaired compared to average Unrelated to treatment received
Maxwell et al. [22]	2013	CIDP, PDN	HRQoL, Social	39	Impaired compared to normal
dos Santos et al. [23]	2014	CIDP	HRQoL, cognitive	41	Impaired compared to non-matched normal subjects
Niermeijer et al. [24]	2007	PDN	Therapeutic	35	Improved with Cyclophosphamide + prednisone
Léger et al. [25]	2013	PDN (anti-MAG neuropathy only)	Therapeutic	54	Significantly improved physical domains with Rituximab

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