Relationship between Health-Related Quality of Life, Pain, and Functional Disability in Neuropathic Pain Patients with Failed Back Surgery Syndrome

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ABSTRACT

Objectives: Patients with failed back surgery syndrome (FBSS) and chronic neuropathic pain experience levels of health-related quality of life (HRQoL) that are considerably lower than those reported in other areas of chronic pain. The aim of this article was to quantify the extent to which reductions in (leg and back) pain and disability over time translate into improvements in generic HRQoL, as measured by the EuroQol-5D and SF-36 instruments.

Methods: Using data from the multinational Prospective, Randomized, Controlled, Multicenter Study of Patients with Failed Back Surgery Syndrome trial, we explore the relationship between generic HRQoL—assessed using two instruments often used in clinical trials (i.e., the SF-36 and EuroQol-5D)—and disease-specific outcome measures (i.e., Oswestry disability index [ODI], leg and back pain visual analog scale [VAS]) in neuropathic patients with FBSS.

Results: In our sample of 100 FBSS patients, generic HRQoL was moderately associated with ODI (correlation coefficient: -0.462 to -0.638) and mildly associated with leg pain VAS (correlation coefficient: -0.165 to -0.436). The multilevel regression analysis results indicate that functional ability (as measured by the ODI) is significantly associated with HRQoL, regardless of the generic HRQoL instrument used. On the other hand, changes over time in leg pain were significantly associated with changes in the EuroQol-5D and physical component summary scores, but not with the mental component summary score.

Conclusions: Reduction in leg pain and functional disability is statistically significantly associated with improvements in generic HRQoL. This is the first study to investigate the longitudinal relationship between generic and disease-specific HRQoL of neuropathic pain patients with FBSS, using multinational data.

Keywords: EuroQol-5D, failed back surgery syndrome, neuropathic pain, quality of life, SF-36.

Introduction

Neuropathic pain is a prevalent [1–4] and often underdiagnosed [5] condition estimated to affect up to 2% to 3% of the general population [2,5,6]. Back and legs are the most common location of pain of neuropathic origin [7]. Treatment options vary in nature and success rate, with the appropriate treatment depending on individual circumstances. Nonsurgical medical therapy (that can include a spectrum of rehabilitative and drug therapies) is often the treatment of choice for the management [2] of individuals presenting with neuropathic back and leg pain. Of these, 10% to 40% will still experience persistent or recurrent pain [7,8], a condition often referred to as “failed back surgery syndrome” (FBSS).

Patients with neuropathic pain experience levels of health-related quality of life (HRQoL) which are considerably lower than those of chronic heart failure patients [9] and the general population [10,11]. Increased pain severity is typically associated with lower levels of HRQoL [12], and high levels of functional disability [13] in patients with FBSS.

The impact of neuropathic pain (of different origin) on HRQoL has been the focus of a recent study [13], which reviewed 52 high-quality published reports on the subject. The authors found strong evidence that the presence (and severity) of neuropathic pain are associated with greater impairments in a number of HRQoL domains. Furthermore, the degree of association between pain and HRQoL decrement was found to depend on both the type of instrument (generic vs. disease specific) used and the HRQoL domain being investigated (physical, emotional, role, or social functioning). For instance, the authors found weaker associations between neuropathic pain and measures of the quality of patients’ social relationships than between neuropathic pain and measures of other HRQoL domains. Similarly, it was found that associations between pain severity and disease-specific measures of HRQoL are generally stronger than those between pain severity and generic measures of HRQoL.

We report the results of a longitudinal analysis of the association between generic and disease-specific outcome measures based on the first 6 months follow-up data from the recently published multinational Prospective, Randomized, Controlled, Multicenter Study of Patients with Failed Back Surgery Syndrome (PROCESS) trial. The PROCESS trial [14] investigated the addition of spinal cord stimulation (SCS) to conventional medical management (CMM) in patients with FBSS suffering from chronic neuropathic back and leg pain [15].

The aim of this article was to quantify the extent to which reductions in (leg and back) pain and disability (as measured by the Oswestry disability index [ODI] score) over time translate into improvements in generic HRQoL as measured by the EuroQol-5D [16], and the mental and physical components of the SF-36 [17] instrument.
Methods

Study Design, Patient Recruitment, and Data Collection

The design and results of the PROCESS trial have been described previously in detail [14,15,18]. Briefly, a total of 100 patients were recruited from 12 centers in Europe, Canada, Australia, and Israel between April 2003 and June 2005. Eligible subjects were randomly assigned to CMM alone (n = 48; CMM group) or CMM with SCS (n = 52; SCS group). Eligibility criteria included patients 18 years or older suffering from predominant neuropathic pain of radicular origin in the legs (radiating in dermatomal segments L4 and/or L5 and/or S1) with or without associated less severe back pain. The intensity of leg pain was at least 50 mm on a visual analog scale (VAS: 0 equaling no pain, to 100 mm representing the worst possible pain) for at least 6 months after at least one anatomically successful surgery for a herniated disk. All patients had a documented history of nerve injury (i.e., root compression by herniated disk, compatible with the pain complaint). The neuropathic nature of the pain was confirmed according to the routine clinical practice of each investigator and included mapping the pain distribution, examining sensory/motor/reflex changes, and EMG. All patients randomized to the SCS group underwent a screening trial. Those experiencing at least 80% overlap of their pain with stimulation-induced paresthesia and at least 50% leg pain relief received an implantable neurostimulation system. CMM included oral medication (i.e., opioids, nonsteroidal antiinflammatory drugs, antidepressants, anticonvulsants/antiepileptics, and other analgesic therapies), nerve blocks, epidural corticosteroids, physical and psychological rehabilitative therapy, and/or chiropractic care. In either group, the use of intrathecal drug delivery systems and re-operation were not allowed.

Using case report forms, the investigators prospectively collected detailed information on patients’ baseline age, gender, prior back operations, and source of major pain. Patients’ HRQoL, pain, and functional capacity were assessed before randomization (baseline), and at 3 and 6 months follow-up.

Instruments aimed at measuring a subject’s HRQoL fall under one of two categories: generic and disease-specific instruments [19]. The former attempt to measure the extent to which an individual’s health status affects a broader set of dimensions with respect to quality of life, and the generic (as opposed to the disease-specific) nature of the instruments makes them suitable for general use to compare HRQoL status across disease areas [20]. On the other hand, disease-specific outcome measures are designed to focus only on a reduced set of dimensions that are relevant to the subjects and conditions under study. Typically, these instruments are more sensitive than their generic counterparts to minimal changes in health status. The disadvantage is that they do not facilitate comparison of results across different disease areas. Examples of generic HRQoL instruments include the EuroQol-5D [16] and the SF-36 [17], while examples of disease-specific measures in patients with FBSS neuropathic pain are the ODI [21] and pain indices measured using a VAS approach.

Generic HRQoL Instruments

For the purposes of the present study, generic HRQoL was assessed using the physical (PCS) and mental (MCS) component summary scores of the SF-36 and the EuroQol-5D instrument. These instruments were completed by the patient the week before or on the day of the visits (baseline, 3 and 6 months follow-up).

The SF-36 is a general measure of health intended to capture HRQoL through eight different dimensions, including the ability to function and complete everyday tasks, perform usual physical and social activities, as well as capturing aspects relating to an individual’s mental well-being, such as energy and fatigue. Two summary measures of physical and mental health can be constructed from the eight scales [22]. The PCS and MCS typically range from 0 to 100 (with 0 = worst possible state), but norm-based interpretations, in which scores are understood in relation to typical values (norms) with respect to the US general population, are also possible. These two summary scales for the SF-36 are recommended when a general effect (across subscales) in the physical or mental health domain is expected.

The EuroQol-5D comprises five questions, each relating to a different dimension: mobility, self-care, ability to undertake usual activity, pain/discomfort, and anxiety/depression. Each dimension has three possible levels of severity: no problems, moderate problems, and severe problems. Based on their combined answers to the EuroQol-5D questionnaire, participants can be classified as being in one of 243 possible health states (not including unconsciousness and death). Each of these health states has an associated score ranging from −0.594 (worst possible health state) to 1 (perfect health) [16].

Disease-Specific Outcome Measures

During 4 days preceding each study visit, the patients were asked to record their level of pain, measured using a VAS (0 equivalent to no pain, and 100 equivalent to worst possible pain), three times per day separately for back and leg pain [23]. The week before or on the day of the follow-up visit, the patients completed the ODI (version 2) [21] questionnaire, to assess pain-related disability. The ODI questionnaire covers 10 domains of functional ability (e.g., personal care, lifting, traveling, sex life, walking, social life), each having six possible levels of severity ranging from zero (no limitation) to five (greatest possible limitation). The respondent is asked to select the severity level that best describes his/her perception for each of the 10 domains. The percentage of disability (i.e., total ODI score) is obtained by adding up the domain-related points, dividing the total by 50, and multiplying the result by 100. A score between 0 and 20% indicates minimal disability, 21% to 40% is moderate disability, 41% to 60% reflects severe disability, 61% to 80% indicates level of pain that impinges on all aspects of the patient’s life requiring positive intervention, and finally scores between 81% and 100% indicate patients who are bed bound [21].

Statistical Analysis

A three-stage approach was followed to analyze the HRQoL data in the PROCESS trial.

Assessing changes from baseline. First, we looked at the trend over time of generic and disease-specific outcome measures, plotting their mean (and 95% confidence interval) values at baseline and at each follow-up time. In addition, we estimated—for each HRQoL instrument—the change from baseline values at 3 and 6 months follow-up. To address the risk of “regression to the mean” fallacy [24], changes from baseline were estimated using an analysis of covariance approach [25].

The first stage of the analysis was used to assess whether or not there was any practical justification (other than the theoretical one referring to a repeated measure design), to a more sophisticated statistical analysis, than a change from baseline. Statistically significant changes from baseline at 3 and 6 months follow-up would, for instance, indicate the presence of a strong correlation over time, suggesting that the EuroQol-5D of a given
subject observed at follow-up can be predicted by the EuroQol-SD value reported by the same subject at baseline.

**Assessing between instrument correlation.** The second stage of the statistical analysis included scatter plots of individual patient scores at baseline and estimation of relevant pair-wise Pearson correlation coefficients to assess the pair-wise association between generic HRQoL and pain (leg and back) or disability (ODI) measures. Although the first stage of the analysis assessed the within-measure correlation over time, the second stage was used to define the extent of between-outcome correlation at a given time point.

The presence of such a correlation structure would then justify the use of a regression framework to include several predictors of outcome at once, while accounting for the observed between- and within-HRQoL instrument correlation.

**Multilevel modeling for longitudinal data analysis.** Such a regression framework takes the name of multilevel (also known as hierarchical or repeated measures or random effects) modeling [26, 27], and the advantages deriving from its use for the analysis of HRQoL are well recognized [28, 29]. The basic structure of a multilevel regression model for longitudinal data can be written as follows:

\[
y_{ij} = \beta_0 + \beta_1 r_{ij} + \cdots + \beta_{i0} + u_{ij} + \epsilon_{ij}
\]

where \( y \) represents the value of the dependent variable (e.g., EuroQol-SD) of patient \( i \) at time \( j \). The intercept term (\( \beta_0 \)) represents the mean value of the outcome variable across all patients at baseline, while the coefficient (\( \beta_1 \)) captures the average change in \( y \) at each measurement occasion, denoted by the variable \( r_{ij} \).

The model allows subject-specific HRQoL (at baseline and at each follow-up point) to depart (at random) from the overall mean trend represented by (\( \beta_0 + \beta_1 r_{ij} \)). The extent to which a given subject’s HRQoL departs from the overall mean at a particular time point is governed by the “random” part of the model (hence, the name “random effects” model) represented by (\( u_{ij} + \epsilon_{ij} \)).

The term \( u_{ij} \) captures the subject-specific random deviation from the overall mean outcome, while the random term \( \epsilon_{ij} \) indicates the subject-specific departure from the average change in \( y \) at each measurement occasion (\( r_{ij} \)). Finally, \( \epsilon_{ij} \) represents the between-subjects variability. The total variability in the data is therefore decomposed as between and within-subjects variability. More elaborated model specifications, like the one implemented in this article, can also include a series of subject-specific characteristics (e.g., age, gender).

By appropriately accounting for both the between- and within-subjects’ correlation, the use of a multilevel modeling framework facilitates the correct estimation of the standard errors for the regression parameters in the model and correct quantification of the \( P \)-values for hypothesis testing. Furthermore, the inclusion of several explanatory variables within the multilevel regression model helps quantify the contribution of a given predictor (e.g., leg pain) to the observed outcome, conditional on a set of other factors (e.g., age, clinical status, functional disability).

Thus, the third step of the analysis consisted of a series of multilevel regression models developed with the aim to quantify the extent to which the dynamics of generic HRQoL measures can be predicted by disease-specific measures such as pain (back and leg) and disability (ODI) scores, after controlling for patient-specific baseline characteristics (i.e., age, gender, number of previous back surgeries, time since last surgery, location of the pain). The set of predictors included in the analysis was not selected on statistical grounds, but based on evidence from published literature, integrated by the expert clinical, health economic, statistical, and epidemiological opinion of the coauthors. The rationale for this is twofold. First, the “best” prediction model on statistical grounds may lack clinical meaning, and second, there are a number of factors that are known to be important predictors regardless of their statistical significance in the data set at hand.

Two different specifications of the multilevel model were compared: one in which the HRQoL was assumed to follow a linear trend over time, and the second where the HRQoL followed a quadratic (i.e., nonlinear) trend. The latter was achieved by including an additional term (i.e., \( \beta_2 r_{ij}^2 \)) in Equation (1), to capture a possible nonlinear behavior in the dynamics of the HRQoL over time at patient level. Model comparison and model selection were carried out using the Bayesian information criteria (BIC) statistics. The latter can be viewed as a measure that combines model fit and model complexity, through which alternative models can be compared and selected. The model with the lowest BIC should be selected. All analyses were carried out in the statistical software STATA 10.0 [30], and the multilevel regression models were carried out using the STATA command—xtmixed—and the STATA user written package gllamm [31, 32].

**Results**

**Outcomes at Baseline**

Baseline characteristics of the study sample are reported in Table 1. The patients were on average 50 years old, 50% of them having had more than one back surgery (mean number of previous back surgeries: 1.75), their last surgery taking place approximately 4.7 years before recruitment into the trial. The location of leg pain was mostly unilateral (65%). The study sample reported average levels of leg and back pain (on a VAS 0–100 mm scale) of 75 and 50, respectively, and a mean ODI score of 56, which indicates severe disability. Average generic HRQoL scores were: EuroQol-SD: 0.16 (on a −0.594 to 1 scale) and PCS: 27.4 and MCS: 39.5 (both on a scale 0–100).

**Stage 1: Trends in Outcomes**

Figure 1 shows the mean scores for EuroQol-SD (Fig. 1a), SF-36 physical (PCS, Fig. 1b) and mental (MCS, Fig. 1c) component summary measures, ODI (Fig. 1d), leg (Fig. 1e) and back (Fig. 1f) pain at baseline, and at 3 and 6 months of follow-up. Our sample reported improvements in each of the HRQoL and disease-specific measures over the first 6 months of the study period, and these improvements were all statistically significant with the exception of the changes in back pain and MCS.

**Table 1 Baseline characteristics (n = 100)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td></td>
<td>51 (51)</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td></td>
<td>50.3 (10)</td>
</tr>
<tr>
<td>Time since last surgery, years (SD)</td>
<td></td>
<td>4.7 (5)</td>
</tr>
<tr>
<td>&gt;1 Surgery, n (%)</td>
<td></td>
<td>50 (50)</td>
</tr>
<tr>
<td>Unilateral leg pain, n (%)</td>
<td></td>
<td>65 (65)</td>
</tr>
<tr>
<td>Back pain VAS, mean (SD)</td>
<td></td>
<td>49.9 (24)</td>
</tr>
<tr>
<td>Leg pain VAS, mean (SD)</td>
<td></td>
<td>74.7 (13)</td>
</tr>
<tr>
<td>Disability (ODI), mean (SD)</td>
<td></td>
<td>56.3 (14)</td>
</tr>
<tr>
<td>Generic HRQoL, mean (SD)</td>
<td></td>
<td>27.4 (6)</td>
</tr>
<tr>
<td>PCS</td>
<td></td>
<td>39.5 (12)</td>
</tr>
<tr>
<td>MCS</td>
<td></td>
<td>0.16 (0.3)</td>
</tr>
</tbody>
</table>

HRQoL: health-related quality of life; MCS, mental health summary score (SF-36); ODI, Oswestry disability index; PCS, physical health summary score (SF-36); VAS, visual analog scale.
Stage 2: Association between Generic HRQoL and Disease-Specific Measures at Baseline

Figure 2 depicts the matrix of univariate pair-wise scatter plots, and reports the Pearson correlation coefficients for the generic (i.e., EuroQol-5D, PCS, and MCS) and disease-specific (i.e., ODI, leg and back pain) measures of HRQoL at baseline. Consistent with the results of the review by Jensen et al. [13], we found a varying degree of pair-wise correlation between HRQoL measures, which suggests that the explanatory power of the variables...
(leg and back) pain and functional disability might differ depending on the generic HRQoL measures to which they are being related. Figure 2 suggests that greater levels of leg pain are associated with lower levels of generic HRQoL, as measured by the EuroQol-5D (correlation coefficients vs. leg pain: \(-0.436\) \(P < 0.05\)). Furthermore, MCS (vs. leg pain: \(-0.215\); vs. back pain: \(-0.095\)) and PCS (vs. leg pain: \(-0.165\); back pain: \(-0.118\)) displayed a negative (although not statistically significant) association with leg and back pain. Finally, ODI showed a statistically significantly negative correlation with all generic HRQoL measures: EuroQol-5D (correlation coefficient: \(-0.638\) \(P < 0.05\)), MCS (correlation coefficient: \(-0.301\) \(P < 0.05\)), and PCS (pair-wise correlation: \(-0.462\) \(P < 0.05\)), indicating that lower functional disability is associated with higher generic HRQoL.

### Stage 3: Predictors of Outcomes

The third stage of our analysis used multilevel regression to assess the joint relationship between generic HRQoL measures and a set of predictors, which included disease-specific outcomes such as ODI and (leg and back) pain VAS scores. Table 2 reports the results of the multilevel regression analyses relating generic HRQoL (i.e., EuroQol-5D, PCS, and MCS) measures to pain, disability levels, and patients’ baseline characteristics. The results of the EuroQol-5D regression model indicate that, on average, higher leg pain and functional disability are significantly associated with lower EuroQol-5D (coefficient for leg pain: \(-0.039\); coefficient for ODI: \(-0.069\) \(P < 0.001\)). Thus, at the margin, if the other factors such as patient age and number of previous back operations are held constant, a 1 point increase in leg pain (ODI) corresponds to a 0.039 (0.069) reduction in EuroQol-5D. Repeated observations over time on the same individual were strongly correlated; therefore, the baseline outcome score is a strong predictor in our model (coefficient for baseline EuroQol-5D: \(0.529\) \(P < 0.001\)). The same set of predictors was found to be statistically significant in the PCS model (coefficient for leg pain: \(-0.079\); coefficient for ODI: \(-0.089\); coefficient for baseline PCS: \(0.721\) \(P < 0.001\)). In the MCS model, two significant predictors were found: ODI (coefficient: \(-0.137\) \(P < 0.001\)) and baseline MCS score (coefficient \(0.815\) \(P < 0.001\)). None of the other baseline characteristics were found to be statistically associated with the trend of the patients’ HRQoL over the first 6 months of the study period. Statistical comparison between a model with a linear trend and a model with a quadratic trend of the HRQoL over time suggests that the best model fit was...
Multilevel regression analyses of HRQoL scores on patient characteristics, pain, and disability

<table>
<thead>
<tr>
<th></th>
<th>EuroQol-SD</th>
<th>PCS</th>
<th>MCS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coefficient</strong></td>
<td><strong>P-value</strong></td>
<td><strong>Coefficient</strong></td>
<td><strong>P-value</strong></td>
</tr>
<tr>
<td>Age</td>
<td>0.0007</td>
<td>0.571</td>
<td>0.0031</td>
</tr>
<tr>
<td>(female = 0, male = 1)</td>
<td>0.0049</td>
<td>0.104</td>
<td>-0.3951</td>
</tr>
<tr>
<td>Number of previous back surgeries</td>
<td>0.0029</td>
<td>0.922</td>
<td>0.1145</td>
</tr>
<tr>
<td>Two</td>
<td>0.0051</td>
<td>0.909</td>
<td>-1.0663</td>
</tr>
<tr>
<td>Four or more</td>
<td>0.0016</td>
<td>0.976</td>
<td>-0.2668</td>
</tr>
<tr>
<td>Time from last back surgery (years)</td>
<td>0.0025</td>
<td>0.652</td>
<td>0.0883</td>
</tr>
<tr>
<td>Bilateral leg pain (unilateral = 0, bilateral = 1)</td>
<td>-0.0188</td>
<td>0.507</td>
<td>-0.1384</td>
</tr>
<tr>
<td>Back pain (VAS)</td>
<td>0.0004</td>
<td>0.430</td>
<td>-0.0006</td>
</tr>
<tr>
<td>Leg pain (VAS)</td>
<td>-0.0039</td>
<td>&lt;0.001</td>
<td>-0.0785</td>
</tr>
<tr>
<td>ODI</td>
<td>-0.0069</td>
<td>&lt;0.001</td>
<td>-0.0089</td>
</tr>
<tr>
<td>Baseline HRQoL score</td>
<td>0.5290</td>
<td>&lt;0.001</td>
<td>0.7207</td>
</tr>
<tr>
<td>Visit</td>
<td>0.0090</td>
<td>0.070</td>
<td>0.1165</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.6907</td>
<td>&lt;0.001</td>
<td>18.6689</td>
</tr>
</tbody>
</table>

Bayesian information criteria (BIC)

| For models reported here | 33 | 1760 | 2124 |
| For models with quadratic trend (not reported) | 51 | 1773 | 2136 |

Note: These results allow prediction of the mean HRQoL score at a given follow-up time between baseline and 6 months for a hypothetical patient based on the set of covariates included in the model. For instance, at 6 months follow-up, the mean physical component summary score of an individual with the following characteristics male, aged 40 at recruitment in the trial, with three previous back surgeries, unilateral leg pain, who had the last back surgery 2.5 years before, is expected to be, on average, 29.23—which is obtained as: 18.67 [intercept] + 0.7207 × (coefficient for sex) - 0.3951 × (coefficient for age) - 0.0188 × (coefficient for three previous back surgeries) - 0.0039 × (coefficient for leg pain) - 0.0069 × (coefficient for ODI) + 0.5290 × (coefficient for baseline HRQoL score) + 0.0090 × (coefficient for visit) + 0.6907 × (coefficient for intercept) + [0.0031 × (coefficient for mean age in the trial, i.e., (50.39 – 46.07) (coefficient for back pain)] + [0.0449 × (coefficient for male) + (0.7207 × 27.44) (coefficient for baseline PCS × mean baseline PCS)] + [(-0.3951 × 1) (coefficient for male × dummy for male) + [0.0031 × (50.39 – 40)] (coefficient for age × departure from the mean age in the trial, i.e., (50.39 – 40) years)] + (-1.0663 × 1) (coefficient for three previous back surgeries) × dummy for three previous back surgeries) + (-0.0006 × 1) (coefficient for unilateral leg pain × dummy for unilateral) + (0.0893 × 2.5) (coefficient for time since last back surgery × mean time since last back surgery) + (0.00785 × 53.43) (coefficient for leg pain × mean leg pain at 6 months) + (0.0006 × 46.67) (coefficient for back pain × mean back pain at 6 months) + (-0.0893 × 50.21) (coefficient for ODI × mean ODI at 6 months).

HRQoL, health-related quality of life; MCS, mental health summary score (SF-36); ODI, Oswestry disability index; PCS, physical health summary score (SF-36); VAS, visual analog scale.

Discussion

We carried out the longitudinal analysis of the 6-month follow-up (generic HRQoL and disease-specific outcome measures) data from the recently completed multinational PROCESS trial, which compared the addition of SCS to CMM versus CMM alone in patients with chronic neuropathic pain secondary to FBSS [15].

Consistent with the findings of Jensen et al. [13], we found that the degree of association between patient’s levels of pain, disability, and generic HRQoL depends on both the HRQoL measure and the dimensions of HRQoL being investigated. Our results indicate that functional ability (as measured by the ODI) is significantly associated with HRQoL, regardless of the generic HRQoL instrument used. On the other hand, changes over time in leg pain were significantly associated with changes in the EuroQol-5D and PCS scores, but not with the MCS score. A possible explanation for the latter rests on the characteristics of the study population. The high levels of pain reported by patients with chronic neuropathic conditions secondary to FBSS have an undeniable impact on these patients’ physical well-being, limiting their ability to carry out tasks such as lifting or moving objects, climbing stairs or walking, and self-care. Previous evidence suggests that individuals’ mental well-being tends to adjust to chronic disease conditions [33], which might be at the source of our finding regarding the apparent lack of a statistically significant link between leg pain and MCS.

The patients enrolled in the PROCESS trial had lower levels of HRQoL—on each of the eight domains of the SF-36—than those recruited in other studies in this clinical area [10,12]. The mean EuroQol-5D reported by subjects in the PROCESS trial at baseline (0.16) is identical to that reported by the group experiencing the most severe level of pain (i.e., VAS: 7–10) in the survey published by McDermott et al. [12].

Our results suggest there is some level of: 1) pair-wise correlation between HRQoL measures at a given time point (see Methods, Stage 2; and 2) correlation over time within each HRQoL instrument (see Methods, Stage 1). The absolute magnitude of the correlation coefficients though was small (i.e., when expressed as $R^2$ one would only explain a proportion of the variance on one outcome on the basis of knowing the other), and this may be because of the fact that each of them is being considered independently from the others. The third stage of our analysis used multilevel regression to assess the joint relationship between generic HRQoL measures and a set of predictors, which included disease-specific outcomes such as ODI and (leg and back) pain VAS scores.

We did not find changes in back pain to be significantly associated with changes in the EuroQol-5D and SF-36 physical and mental summary scores. This may be explained by: 1) the characteristics of the PROCESS study population, where the predominant pain was leg pain; 2) the multifactorial nature of back pain; and 3) the smaller impact of the interventions on back pain.

Our study found that a number of the baseline patients’ characteristics included in the model, such as age, gender, and location of pain, were not statistically significant predictors of their generic HRQoL. This result is somewhat surprising and may be a simple artifact of the relatively small sample size and the carefully selected nature of the population in the PROCESS trial, which resulted in a homogenous mix of patient characteristics compared to a more broadly drawn sample. This result should therefore be interpreted with caution, and we recommend further research into the identification and selection of predictors of future HRQoL in neuropathic pain patients with FBSS. A further note of caution relates to the interpretation of the multi-

Table 2 Multilevel regression analyses of HRQoL scores on patient characteristics, pain, and disability

Note: These results allow prediction of the mean HRQoL score at a given follow-up time between baseline and 6 months for a hypothetical patient based on the set of covariates included in the model. For instance, at 6 months follow-up, the mean physical component summary score of an individual with the following characteristics male, aged 40 at recruitment in the trial, with three previous back surgeries, unilateral leg pain, who had the last back surgery 2.5 years before, is expected to be, on average, 29.23—which is obtained as: 18.67 [intercept] + 0.16) is identical to that reported by the group experiencing the most severe level of pain (i.e., VAS: 7–10) in the survey published by McDermott et al. [12].
level model results presented here. The EuroQol-5D regression model indicated that, on average, higher leg pain and functional disability are significantly associated with lower EuroQol-5D (coefficient for leg pain: −0.039; coefficient for ODI: −0.069 [all $P < 0.001$]). These results are valid in the context of the study sample, and extrapolation beyond the characteristics of the study sample may lead to biased predictions in terms of improvements in HRQoL following a reduction in pain and/or disability. Furthermore, any extrapolation exercise will need to take into account the underlying correlation structure between the predictors of outcome (regardless of their statistical significance).

Most of the research investigating the relationship between generic and disease-specific outcome measures in neuropathic chronic pain patients comes from either cross-sectional studies (i.e., where relationships are estimated at a given point in time) [10,12], or has focused on slightly different patient groups. We argue that to assess how generic HRQoL measures (e.g., EQ-5D, SF-36) respond to changes in health status, as measured by the disease-specific instruments (e.g., pain, ODI score), requires a longitudinal study design (which is designed to take into account their statistical association over time).

To our knowledge, the only report which has assessed the longitudinal relationship between generic and disease-specific outcome measures in this clinical area, albeit focusing on a slightly different patient group, comes from a case series study conducted in Finland. Hakkinen et al. [34] studied the HRQoL of a sample of 145 lumbar disk surgery patients compared to the general population, assessing the relationships between HRQoL and other outcome measures—such as ODI, short depression inventory (SDI) pain, trunk muscle strength, and mobility of the spine—at 2 and 14 months after surgery. The authors found that the 15D, Oswestry, and SDI scores remained unchanged during the follow-up, while the improvements in the spine mobility and trunk muscle strength were significant. Furthermore, HRQoL, as measured by the 15D instrument, was associated with age, pain, Oswestry, and SDI indices, but not with objective measures of physical function.

Another study conducted in Sweden [10] assessed the psychometric properties of the SF-36 and the Nottingham Health Profile (NHP) in patients with peripheral neuropathic pain of multiple origin. The cross-sectional analysis of the 126 subjects recruited in the study found: 1) SF-36 and NHP to be consistent with each other, showing important correlation between items referring to the same dimension of HRQoL; and 2) demonstrated the burden of illness of this health condition comparing these instruments against the values reported by the general population.

A recently reported large, observational, cross-sectional survey of 602 neuropathic pain patients recruited from general practitioners in 6 European countries [12] has produced further evidence of the burden of neuropathic pain. The authors collected data on the brief pain inventory instrument and the EuroQol-5D, as well as patients’ demographics, treatment information, and frequency of physician visits. Pain severity was found to be associated significantly with poorer EuroQol-5D scores, greater disruption of employment status, and more frequent physician visits. Finally, a small number of other studies conducted in this patient population used disease-specific outcome measures of outcomes only (e.g., McGill pain questionnaire, sickness impact profile) [36].

The generalizability (from one country to another) of the findings of single-country studies is often limited by factors such as the health-care system in which patients are treated, the societal set of values with respect to a given health condition, etc. [37]. It has been shown that self-reported HRQoL for specific groups of patients can vary not only between countries [38,39], but also within the same country [40]. In this sense, by enrolling individuals from different countries and different settings, analyses of quality-of-life data collected alongside multinational trials can be perceived to offer results that are more “generalizable.”

To the authors’ knowledge, this is the first longitudinal analysis of HRQoL data carried out alongside a multinational randomized, controlled, clinical trial to explore the relationship between generic HRQoL and disease-specific outcome measures in the chronic neuropathic pain population with FBSS. This study brings new evidence in support of the hypothesis that pain and disability in patients with FBSS have a strong association with reduced levels of HRQoL. Interventions aimed at reducing pain and disability in FBSS patients are therefore expected to bring considerable HRQoL improvements, thus reducing the burden of disease in this clinical area.

Establishing the relationship between disease-specific outcomes (such as pain and functional ability) and generic HRQoL will aid in efficient data collection strategies in future research studies, minimizing the burden of data collection on patients. The development of such tools would also help address the never-ending problem of missing data, arising from dropout, in longitudinal studies. Further studies in pain are needed to explore the link between disease-specific outcomes and HRQoL.

Conclusions

Generic HRQoL (EuroQol-5D and SF-36) was found to have some degree of association with disease-specific outcome measures (leg pain VAS and ODI) in selected patients with chronic neuropathic pain secondary to FBSS. Further studies in chronic neuropathic pain populations are needed to explore the link between disease-specific outcomes and HRQoL.

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