ORIGINAL ARTICLE

Do General and Multiple Sclerosis-Specific Quality of Life Instruments Differ?

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ABSTRACT: ***Background:*** Quality of life instruments provide information that traditional outcome measures used in studies of multiple sclerosis do not. It is unclear if longer, disease-specific instruments provide more useful information than shorter, more general instruments, or whether patients prefer one type to another. ***Methods:*** We conducted a cross-sectional study of quality of life in a multiple sclerosis clinic population using a mailed questionnaire that combined three different quality of life instruments; the SF-36, the Multiple Sclerosis Quality of Life Instrument-54, and the EuroQol EQ-5D. We assessed the feasability of using each instrument and patient preference for each, calculated correlation coefficients for the summary scores of each instrument and other measures of disease severity, and calculated odds ratios from proportional odds models comparing each instrument with the Expanded Disability Status Scale. ***Results:*** We did not find substantial differences between the three instruments. All were well-received by patients, and over 75% felt that the combination of the three instruments best assessed their quality of life. For each instrument there was substantial variability between patients with similar quality of life scores in terms of their disability (as assessed by the Expanded Disability Status Scale and their own perception of their disease severity and quality of life (on simple 1-10 scales). ***Conclusions:*** Quality of life instruments are easy to use and well-received by patients, regardless of their length. There do not appear to be clinically important differences between general and disease-specific instruments. Each instrument appears to measure something other than a patient's disability or perception of their own disease severity or quality of life.

RÉSUMÉ: Les instruments de mesure généraux de la qualité de vie et ceux utilisés dans la sclérose en plaques diffèrent-ils? ***Introduction:*** Les instruments de mesure de la qualité de vie fournissent de l'information que les mesures d'impact traditionnelles utilisées dans les études sur la sclérose en plaques ne mesurent pas. On ignore si des instruments plus longs et spécifiques pour la maladie fournissent une information plus utile que des instruments plus brefs et plus généraux, et si les patients préfèrent l'un ou l'autre. ***Méthodes:*** Nous avons effectué une étude transversale de la qualité de vie parmi les patients d'une clinique de sclérose en plaques au moyen d'un questionnaire posté à chaque patient, qui combinait trois instruments différents de mesure de la qualité de vie: le SF-36, le Multiple Sclerosis Quality of Life Instrument-54 et le EuroQol EQ-5D. Nous avons évalué la faisabilité d'utiliser chaque instrument et la préférence des patients vis-à-vis de chacun. Nous avons également calculé des coefficients de corrélation pour les scores sommaires de chaque instrument et les autres mesures de sévérité de la maladie et calculé le risque relatif à partir de modèles de risque proportionnel comparant chaque instrument avec le EDSS. ***Résultats:*** Nous n'avons trouvé aucune différence importante entre les trois instruments. Ils ont tous été bien acceptés des patients et plus de 75% d'entre eux considéraient que la combinaison des trois instruments évaluait mieux leur qualité de vie. Pour un score de qualité de vie similaire, il existait pour chaque instrument une variabilité importante entre les patients quant à leur degré d'invalidité (tel que mesuré par le Expanded Disability Status Scale et par leur propre perception de la sévérité de leur maladie et de leur qualité de vie, selon une échelle de 1 à 10). ***Conclusions:*** Les instruments de mesure de la qualité de vie sont faciles à utiliser et bien acceptés par les patients, quelle que soit leur longueur. Il ne semble pas y avoir de différences importantes au point de vue clinique entre des instruments généraux ou spécifiques pour la maladie. Chaque instrument semble mesurer autre chose que l'invalidité du patient, sa perception de la sévérité de sa maladie ou de sa qualité de vie.

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Multiple sclerosis (MS) is a demyelinating disease of the central nervous system.[1] The majority of patients eventually develop progressive neurological disability.[2] Treatment trials in MS[3-7] have used a variety of outcome measures including attack frequency, disease progression as assessed by change in Expanded Disability Status Scale (EDSS) score,[8] and lesion burden on magnetic resonance imaging. However, it is unclear if improvement in these outcome measures translates into improved quality of life (QOL) for individuals suffering from MS. Quality of life instruments can be used as outcome measures in clinical trials.[9-11] In MS, they have been used in one trial of interferon α-2_a[12] and in several small trials of rehabilitation and other nonpharmaceutical treatments.[13-16] A number of disease-specific QOL instruments have been developed for use in MS[17-

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[21] which may be more relevant to, and appropriate for, MS than general QOL instruments.[9,22,23]

Measurements of QOL may also be relevant to the everyday practice of neurologists seeing patients with MS. Quality of life instruments could aid in evaluating quality of care, assessing the acceptability of treatment, and in determining the need for physiotherapy or psychological support. Quality of life instruments would complement, rather than replace, clinical evaluation by demonstrating the importance of signs or symptoms to the individual patient. In the clinic setting, however, it is not practical to use lengthy QOL instruments. It is therefore important to know whether a simple, general QOL instrument can provide adequate information on QOL.

To examine these questions, we conducted a cross-sectional study of the QOL in an MS clinic population using a mailed questionnaire. The questionnaire included a brief, general QOL instrument, the EuroQol EQ-5D,[24] a longer general QOL instrument, the SF-36,[25] and an MS-specific QOL instrument, the Multiple Sclerosis Quality of Life Instrument (MSQOL-54).[17] Previous authors have compared the psychometric properties of these instruments[17,22,26-28] and their correlation with each other.[29-30] The purpose of this study was to determine whether one would be more useful in clinical practice. Usefulness requires ease of use, acceptability to subjects, and generation of information that is important to caregivers. We therefore compared their ease of use when administered as a simple mailed questionnaire, subject's preference for each (which has not been well-reported), and correlation with the EDSS and patient ratings of disease-severity and QOL on simple 1-10 scales.

The study protocol was approved by the Research Ethics Committee of the Montreal Neurological Institute.

Methods and materials

Design

This was a cross-sectional study using a mailed questionnaire.

Subjects

Subjects were selected from the clinic database of the McGill Multiple Sclerosis Clinic at the Montreal Neurological Institute and Hospital. Inclusion criteria were clinically definite MS according to the criteria of Poser,[31] of any subtype and any duration, with at least one clinic visit in the year 2001. This latter criterion was applied to ensure that a recent EDSS score would be available. Exclusion criteria were age < 18 or > 65, the presence of any significant comorbid illness (i.e. likely to impact on the patient's QOL, such as a previous stroke or rheumatoid arthritis), and the presence of cognitive impairment. A standard history and examination form is completed for all patients at each visit to the McGill MS clinic and intellectual function and memory are graded from 0 (normal) to 4 by the evaluating physician. For example, a patient with mild memory difficulty would be graded 1, while a patient with severe memory difficulty would be graded 4. Only those patients receiving a grade of 0 (normal) for both intellectual function and memory at their most recent clinic visit were included in the study. This was done primarily for ethical reasons, as there was concern that subjects with cognitive impairment could not properly consent to inclusion in the study. Where this information was not included in the database, hand searches of patient's charts were conducted. The use of medications other than disease-modifying agents was not documented. Medications could alter mental status but the effect should have been accounted for with the physician's evaluation of cognitive function.

The MS clinic at the Montreal Neurological Institute has been in operation since the early 1970s and, at the time of the study, information on approximately 2,800 patients was contained in the clinic database. Of these, 575 fulfilled the inclusion criteria. Random number tables were used to select an equal number of male and female patients to produce a sample of 240 patients. Of these subjects, 42 were excluded because of the presence of cognitive impairment and 15 were excluded because insufficient data were available (such as cognitive function or EDSS not being recorded in the database, or a correct address not being available). A final sample of 183 patients was available for analysis.

QOL Instruments

Three different QOL instruments were used: the SF-36, the MSQOL-54, and the EuroQol EQ-5D. The SF-36 is a generic, 36 question, QOL instrument developed from the Medical Outcomes Study in the United States[32] and takes approximately 15 minutes to complete. The subject's response to each question is coded, and then the questions are combined to form eight scales covering different aspects of QOL: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The scale scores are then transformed to a 0 to 100 score,[33] with higher scores indicating better QOL. These eight scales are then weighted and combined into two summary scales, the Physical Component Summary and the Mental Component Summary.[34] The summary scores are also scored from 0 to 100, with higher scores indicating better QOL. The SF-36 has been widely used and well-validated in diverse patient populations,[25,33] including MS.[35-37]

The MSQOL-54[17] is composed of the SF-36 supplemented by 18 questions specific for MS. Five of the original SF-36 scales remain unchanged, three are altered by the addition of one question to each (bodily pain, vitality, and social functioning), and five new scales are added (cognitive function, health distress, sexual function, satisfaction with sexual function, and overall QOL). As with the SF-36, the individual questions are summed to form the scales, the scores are transformed to a 0 to 100 score and combined into Physical and Mental Summary Scores, and higher scores indicate better QOL. The MSQOL-54 has been used in several different populations, and initial results support its reliability and validity.[22,26,38-41]

The EuroQol EQ-5D is a five-question, general QOL instrument developed in four European countries.[24,42] It requires at most a few minutes to complete, and can easily be administered during an office visit. Subjects respond to questions on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression by indicating whether they have no problems (score of 1), some problems (score of 2), or extreme problems (score of 3) in these areas. Unlike the SF-36 and MSQOL-54, the scores are not summed but instead form a five-digit descriptor representing one of 243 possible health states. For example, a subject experiencing some pain but no other problems would

have a descriptor of 11121. Numerical values for each of these health states have been derived from a representative survey conducted in the United Kingdom,[43] and are available from the EuroQol group. These values range from –0.594 for 33333 (lowest QOL) to 1.000 for 11111 (highest QOL). Like the SF-36, the EuroQol EQ-5D has been widely used and well-validated in diverse patient populations,[24,42] including MS.[30]

Data collection

The three QOL instruments were included in a single questionnaire. The English and French Canadian versions of both the SF-36 and the EuroQol EQ-5D were used. For the MSQOL-54, both the original version and the French translation developed by Vernay et al[40] were used. Permission to use each of the instruments was obtained from the authors. The final questionnaires (English and French versions) consisted of an introduction with demographic/background questions, including self-rating of QOL and symptom severity (on simple 1-10, nonvalidated, visual-analog scales, where 10 is better QOL or milder symptoms); three parts corresponding to the SF-36 alone, only the MS-specific items from the MSQOL-54 (i.e. the SF-36 was not repeated), and the EuroQol EQ-5D; and a series of concluding questions in which the subjects were asked how acceptable, easy, and relevant they found each instrument. The order of the instruments in the questionnaires was varied, such that half of the questionnaires began with the SF-36 and half with the EQ-5D. Both English and French questionnaires were mailed to each of the 183 subjects, and they were requested to complete and return the questionnaire (in the language of their choice) along with a signed consent form.

Covariates

Other data collected in the questionnaire included subject age, sex, disease duration, living status, and education level.

Data analysis

In order to assess the acceptability and feasibility of use of each QOL instrument, the results for response rate, average number of missing items, the difficulty of completing each instrument, the time to complete each instrument, and the subject's preferred instrument are presented using descriptive statistics. Each summary measure (SF-36 Physical and Mental Scores, MSQOL-54 Physical and Mental Scores, and overall EQ-5D score) was correlated with the subject's own rating of QOL and symptom severity (on 1-10 visual analog scales), the number of days missed from school or work in the previous month, and the EDSS. Comparison to the visual analog scales was done to evaluate whether the instruments measure what they purport to measure, namely a subject's QOL. Comparison to the EDSS was done because it is currently the most widely used tool for the evaluation of MS severity and there is no gold standard for QOL. It is important to know if the instruments measure disease severity in the same way as the EDSS, a scale based primarily on neurological signs and physical disability, or if they measure something completely different. The object was not to identify the single instrument which best correlated with the EDSS, but simply to see if any of them did and whether they differed in their degree of correlation.

Scatter plots of the comparisons were produced and correlation coefficients were calculated. Proportional Odds models were constructed in which the relationship between the EDSS and the individual QOL measures was examined, while accounting for possible confounding variables (i.e. disease duration, living status, level of education, order of instruments in the questionnaire, and patient age and sex). For this purpose the EDSS was stratified into categories of less than 3, 3 to 6, and greater than 6. The odds ratio (OR) measures how predictive the instruments are of the EDSS. The further the OR is from 1, the more strongly that instrument predicts the EDSS. A value less than 1 is inversely predictive (a low QOL score predicts a high EDSS, or a high QOL score predicts a low EDSS), while values greater than 1 are positively predictive (a low QOL score predicts a low EDSS, while a high QOL score predicts a high EDSS). Ninety-five percent confidence intervals for the OR were also calculated.

Results

Of the 183 mailed questionnaires, 114 were returned with a signed consent form (for a response rate of 62%). The demographic characteristics of the responders are shown in Table 1. Responders and nonresponders did not differ in terms of age, sex, or the proportion of relapsing or progressive disease (data not shown). The average scores for each of the QOL instruments are presented in Tables 2 to 4.

Acceptability

Table 5 shows the percentage of questionnaires in which any items from the SF-36, the MS-specific questions of the MSQOL-54, or the EQ-5D were missed (not completed), as well as the percentage that were missing more than one item. Thirteen percent of the questionnaires had at least five (of a total of 18) of the MS-specific questions from the MSQOL-54 missing. By far the most commonly missed questions were those relating to sexual function. Also shown in the Table is the percentage of subjects who needed help to complete each part of the questionnaire, the percentage who found each instrument easy to complete, and the percentage who found each instrument acceptable.

The average time required to complete each instrument was 20.5 minutes for the SF-36, 36.3 minutes for the MSQOL-54 (meaning time to complete the SF-36 plus the extra MSQOL-54 questions), and 10 minutes for the EQ-5D.

When asked which instrument best summarized their quality of life, 76% of respondents preferred all instruments together (i.e. the combination of the SF-36, plus the MS-specific questions of the MSQOL-54, plus the EQ-5D), 17% preferred the MSQOL-54 (the SF-36 plus the MS-specific questions of the MSQOL-54), 5% preferred the SF-36 alone, and 2% preferred the EQ-5D alone.

Quality of Life

Correlation coefficients for the summary measures of each instrument and alternative measures of disease severity or QOL are shown in Table 6. Results for days of school or work missed are not reported because too few subjects reported missing any days for a meaningful analysis. The largest correlation was between the SF-36 Physical Score and the EDSS (r=-0.69, 95% CI: -1.00, -0.64), while the smallest correlation was between the SF-36 Mental Score and the EDSS (r=-0.06, 95% CI: -0.26,

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Table 1: Patient Characteristics

Variables	EDSS < 3.0 (n=51)	EDSS 3.0 – 6.0 (n=37)	EDSS > 6.0 (n=26)	Total (n=114)
Mean age [years (SD)]	40 (10)	47 (12)	51 (11)	45 (11)
Sex [number female (%)]	33 (65)	21 (57)	9 (35)	96 (55)
Mean time since diagnosis [years (SD)]	7.5 (6.1)	11.2 (9.4)	15.9 (10.2)	10.6 (8.8)
Clinical course [n (%)]				
Primary progressive	2 (4)	2 (5)	4 (15)	8 (7)
Relapsing remitting	47 (92)	21 (57)	3 (12)	71 (62)
Secondary progressive	2 (4)	14 (38)	19 (73)	35 (31)
Recent or current Exacerbation [n (%)]*	23 (45)	14 (38)	5 (19)	42 (37)
Treatment [n (%)]				
Betaseron	7 (14)	12 (32)	2 (8)	21 (18)
Avonex	7 (14)	2 (5)	1 (4)	10 (9)
Rebif	8 (16)	9 (24)	3 (12)	20 (18)
Copaxone	6 (12)	3 (8)	2 (8)	11 (10)
Total	28 (55)	26 (70)	8 (31)	62 (54)
Previous Treatment [n (%)]	19 (37)	12 (32)	9 (35)	40 (35)
Marital status [number married (%)]	25 (49)	26 (70)	14 (53)	65 (57)
Education level [n (%)]				
Greater than high school	34 (67)	25 (68)	14 (53)	73 (64)
Employed or in school [n (%)]	32 (63)	10 (27)	4 (15)	46 (40)
Living alone [n (%)]	21 (41)	6 (16)	5 (19)	32 (28)
Satisfied with Income (%)	34 (67)	28 (76)	16 (62)	78 (68)

*within the previous month

Table 2: SF-36 Assessment of QOL. Results are expressed as mean score (SD)

Variables	EDSS < 3.0 (n=51)	EDSS 3.0 – 6.0 (n=37)	EDSS > 6.0 (n=26)	Total (n=114)
Physical function	75.8 (21.9)	40.0 (22.4)	16.7 (26.4)	50.5 (33.5)
Role-physical	56.4 (40.9)	23.5 (35.9)	25.0 (35.4)	39.1 (41.1)
Bodily pain	73.9 (23.6)	63.0 (28.4)	56.0 (25.4)	66.5 (26.4)
General health	62.6 (18.8)	49.1 (21.9)	45.5 (21.9)	54.3 (21.7)
Vitality	48.4 (20.0)	36.3 (18.1)	37.3 (20.6)	41.9 (20.2)
Social function	70.8 (20.1)	57.8 (26.4)	55.5 (25.8)	63.1 (24.5)
Role-emotional	64.3 (38.7)	56.2 (46.3)	59.3 (41.4)	60.6 (41.6)
Mental health	64.5 (15.4)	65.2 (21.4)	66.7 (14.8)	65.2 (17.3)
Summary Scores				
Physical	**49.4 (8.6)**	**36.2 (7.7)**	**31.1 (8.5)**	**41.5 (11.3)**
Mental	**44.0 (10.3)**	**45.2 (13.8)**	**49.0 (10.6)**	**45.4 (11.6)**

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Table 3: MSQOL-54 Assessment of QOL. Results are expressed as mean score (SD).

Variables	EDSS < 3.0 (n=51)	EDSS 3.0 – 6.0 (n=37)	EDSS > 6.0 (n=26)	Total (n=114)
Physical function	75.2 (21.8)	38.8 (22.8)	16.7 (26.4)	50.0 (33.3)
Role-physical	55.9 (41.4)	24.8 (36.1)	25.0 (35.4)	39.1 (41.2)
Role-emotional	64.7 (38.9)	56.2 (46.3)	58.7 (42.3)	60.6 (41.9)
Pain	78.1 (22.0)	68.6 (27.8)	60.4 (27.7)	71.0 (26.1)
Emotional well-being	64.5 (15.4)	65.2 (21.4)	66.3 (14.7)	65.1 (17.3)
Energy	48.5 (19.2)	38.9 (17.3)	38.3 (17.5)	43.1 (18.7)
Health perceptions	58.9 (20.2)	47.0 (21.3)	45.3 (20.8)	51.9 (21.5)
Social function	47.8 (13.2)	39.2 (17.5)	37.4 (16.9)	42.6 (16.1)
Cognitive function	69.1 (23.3)	68.0 (24.1)	72.9 (21.7)	69.6 (23.1)
Health distress	65.8 (23.5)	56.6 (25.3)	53.3 (23.4)	60.0 (24.4)
Overall QOL	73.5 (17.0)	63.2 (21.6)	56.8 (18.5)	66.3 (20.0)
Sexual satisfaction	60.6 (28.9)	50.9 (34.4)	33.0 (37.3)	51.3 (34.1)
Sexual function	72.5 (26.0)	56.7 (34.5)	47.8 (37.2)	61.6 (33.1)
Change in health	60.8 (24.1)	43.9 (24.6)	41.0 (22.7)	50.9 (25.4)
Summary Scores				
Physical	**61.8 (16.0)**	**44.3 (15.3)**	**38.5 (12.8)**	**50.9 (18.1)**
Mental	**66.5 (17.5)**	**61.2 (21.6)**	**61.4 (15.3)**	**63.6 (18.5)**

Table 4: EuroQol EQ-5D Assessment of QOL. Results are expressed as mean summary score (SD). (The five individual questions do not have a numerical value. Rather, the combined responses give a unique 'health state', for which numerical equivalents have been determined)

EDSS < 3.0	EDSS 3.0 – 6.0 (n=51)	EDSS > 6.0 (n=37)	Total (n=26)	(n=114)
	0.74 (0.21)	0.59 (0.25)	0.42 (0.34)	0.61 (0.28)

Table 5: The acceptability of each instrument to the subjects.

Variables	SF-36	MSQOL-54*	EuroQol EQ-5D
Questionnaires with missing items (%)	13	30	3
Questionnaires missing more than one item (%)	5	16	1
Subjects needing help to complete questionnaire (%)	13	13	13
Average time to complete in minutes (mean)	20.5	36.3	10
Subjects who found instrument easy or very easy to complete (%)	93	88	97
Subjects who found instrument acceptable or very acceptable (%)	92	85	93

*For the purposes of this table, the column MSQOL-54 refers only to the MS-specific items of the MSQOL-54 with the exception of time to complete, which refers to the MSQOL-54 as a whole (SF-36 plus MS-specific questions)

Table 6: Correlation between summary scores of quality of life instruments and alternative measures of disease severity and quality of life. [Correlation (95% Confidence Interval)].

Measure of severity or QOL	SF-36 Physical	SF-36 Mental	MSQOL-54 Physical	MSQOL-54 Mental	EQ-5D
Patient's QOL Rating	0.47 (0.30,0.72)	0.29 (0.09,0.50)	0.65 (0.59,0.96)	0.57 (0.46,0.83)	0.49 (0.35,0.72)
Patient's severity rating	0.38 (0.18,0.62)	0.18 (-0.03,0.40)	0.48 (0.33,0.72)	0.32 (0.14,0.53)	0.36 (0.18,0.58)
EDSS	-0.69 (-1.00,-0.64)	-0.06 (-0.26,0.14)	-0.60 (-0.88,-0.51)	-0.20 (-0.39,-0.02)	-0.56 (-0.82, -0.44)

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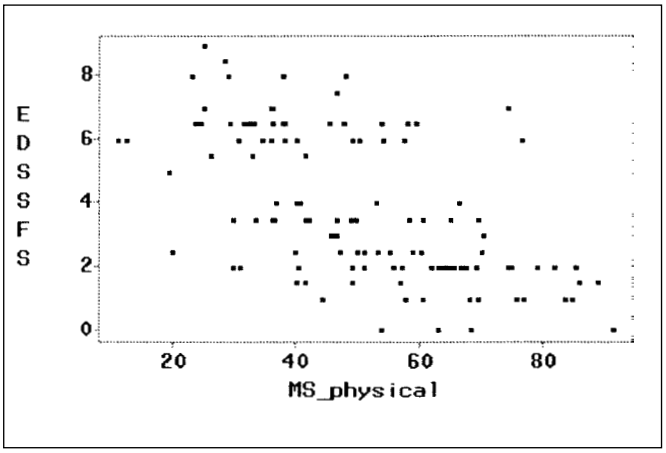

Figure: *Scatter plot comparing the EDSS Functional Scale and the MSQOL-54 Physical summary scale. Correlation coefficient is given beneath the plot.*

Correlation=-0.60 , 95% CI: -0.88, -0.51

0.14). The MSQOL-54 appeared to correlate better than the SF-36 with these alternative measures, but it did not differ greatly from the EQ-5D. Scatter plots of the raw data for the comparison between EDSS, patient rating of QOL, or patient rating of symptom severity and the summary measures of each instrument revealed that, even when a moderate correlation existed, there was still tremendous variability in the data. One example is shown in the Figure, comparing the EDSS and the MSQOL-54 Physical summary scale. As can be seen from the figure, subjects with an EDSS of 6 scored between 5 and 74 on the MSQOL-54 Physical summary scale. This degree of variability was similar in all the plots.

Proportional odds models were constructed that examined the relationship between the recoded 3-level EDSS and each of the summary measures, accounting for possible confounding variables such as living status (alone or not), duration of disease, age, sex, education (beyond high school or not), and the order of the questionnaires. The calculated OR are presented in Table 7. The physical summary scores of the SF-36 and MSQOL-54 were both inversely predictive of the EDSS (OR < 1), while the 95% confidence intervals for the mental summary scores included the null value of 1.0. The EQ-5D uses a different scoring scale than the 0 to 100 scale of the SF-36 and MSQOL-54. This affects the calculated OR for the EQ-5D, and makes it difficult to compare with the others.

Table 7: Odds ratios comparing quality of life instrument summary measures and the EDSS.

Instrument	Odds Ratio	95% Confidence Interval
SF-36 Physical	0.86	0.81-0.91
SF-36 Mental	1.02	0.98-1.06
MSQOL-54 Physical	0.94	0.91-0.96
MSQOL-54 Mental	0.99	0.97-1.01
EuroQol EQ-5D	0.07	0.01-0.35

Discussion

We found the assessment of QOL by mailed questionnaire to be feasible. A response rate of over 60% was achieved, similar to previous studies.[44] The number of questionnaires with missing responses was small, and rarely was more than one question missed. Few subjects reported needing help to complete the instruments. We excluded subjects with cognitive impairment so we would not have expected a large number of subjects to have difficulty. It is still important to document, however, that the instruments are not perceived by subjects as being difficult to complete.

The major goal of this study was to determine if a simple generic QOL instrument (the EuroQol EQ-5D), a longer generic instrument (the SF-36), or a disease-specific instrument (the MSQOL-54) would be most useful in clinical practice when assessing QOL in MS. All three instruments have been previously studied for reliability and validity, and this was not the aim of the present study. Instead, we compared the instruments based on their ease of use, patient preference, and correlation with simple measures of disease severity in order to determine, in a very practical manner, if the instruments differed in terms of how easily they could be used in a clinical setting and what they could tell us.

The majority of subjects who responded found each instrument easy to use and acceptable. More than 75% felt that the combination of the three instruments was most reflective of their QOL. The only clear difference between instruments from the subject's perspective, apart from differences in time to complete, was in the greater number of missing responses seen with the MSQOL-54. This was almost entirely due to questions relating to sexual function being left blank, a problem that has been noted previously.[38,44] An obvious explanation is that sexual function is a highly personal issue, and subjects did not feel comfortable answering these questions. This would not seem to be merely a cultural issue, as previously suggested,[44] as it has now been noted in Italian, French, and Canadian populations. However, it would be wrong to conclude from our results that sexual function is not important to an MS patient's QOL.[26,45,46] The majority of subjects did answer these questions, and of the 25% of subjects who did express a preference for one (as opposed to all) of the instruments the majority preferred the MSQOL-54. A number of subjects also provided written comments in which they expressed their appreciation at these questions being included (data not shown). Rather than neglecting this area, future questionnaires should instead provide a statement explaining the inclusion of such questions and encouraging subjects to complete them. Input from individuals with MS may be useful in revising the wording of such questions.

The summary scores of each instrument correlated positively with the subject's own rating of QOL and of symptom severity (on simple 1-10 scales), and inversely with the EDSS. Comparing the instruments, the MSQOL-54 had the highest

correlation coefficients. However, the EQ-5D, which is far simpler than either of the other two instruments, produced similar results. Also, there was tremendous variation at a given QOL score for any of the instruments. This means that subjects with similar QOL scores on these instruments had different levels of disability (based on the EDSS) and viewed their own QOL and disease severity very differently. Conversely, subjects with similar EDSS scores, or similar scores on the 1-10 scales, had very different QOL scores on the instruments. This is important, because it means that not only do these instruments measure something else about a subject's life than what is found in standard measures of disease severity such as the EDSS, but they also measure something other than a subject's perception of their disease severity or even what a subject perceives their own QOL to be. All three instruments make the basic assumption that the questions they ask are relevant to each subject's QOL. However, QOL is a highly personal entity and it may be that these instruments are unable to capture this individuality. Different subjects may cope better with their disease, and therefore view their QOL very differently.

As a final analysis we developed proportional Odd's models to examine the relationship between the QOL scores and the EDSS, while accounting for potentially confounding variables. All scores were inversely predictive of EDSS (OR < 1) except the SF-36 Mental score, although the 95% confidence interval for the MSQOL-54 included the null value of 1.0. There was no major difference between instruments, although it is difficult to compare the OR for the EQ-5D because of its different scoring scale.

In conclusion, using QOL instruments is feasible, a good response can be obtained by mailed questionnaire, and they are well-received by subjects. The length of the instruments does not appear to be an issue for subjects. Special attention may need to be paid to questions addressing sexual function. All instruments performed similarly when compared with other QOL measures, with tremendous variation between patients with similar QOL scores. Each instrument appears to measure something other than a patient's disability or perception of their own disease severity or QOL. If they were to be used in clinical trials, very large sample sizes would be needed.

It is not clear that there are important clinical differences between simple and complex, or general and disease-specific instruments, when used cross-sectionally. What will be important to confirm for each instrument is their responsiveness to change, as has been shown for the EDSS. In addition to the cross-sectional design, another limitation of this study is that no effort was made to increase the response rate. If the nonresponders differ from the responders in a manner that we could not measure, then this would bias the results. A larger sample size may have allowed the detection of subtle differences between instruments that we may have missed. Also, we separated the MS-specific questions of the MSQOL-54 (that had been added to the SF-36) from the SF-36. It could be argued that this alters the MSQOL-54, but the change to the original MSQOL-54 structure is minimal. We also felt that structuring the questionnaire in this manner would be more acceptable to patients than having them complete the SF-36, followed by the entire MSQOL-54 (in effect having them complete the SF-36 twice). However, our structuring of the questionnaire in this way, while allowing us to compare the three instruments, limits the generalizability of the results as we would not expect other investigators to use the three instruments together in this way. The final limitation is the lack of a gold standard to which we can compare the QOL instruments, thus making it far more difficult to judge whether one is superior to the others.

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