Review

Quality of life and its assessment in multiple sclerosis: integrating physical and psychological components of wellbeing

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Health-related quality of life (HRQoL) has been more intensively studied in multiple sclerosis (MS) than in any other neurological disorder. Traditional medical models of impairment and disability are an incomplete summary of disease burden. Quality of life can be thought of as the sum of all sources of satisfaction (including anticipated sources) minus all threats (including anticipated threats). Many psychosocial factors—including coping, mood, self-efficacy, and perceived support—influence the quality of life of patients with MS more than biological variables such as weakness or extent of MRI lesions. Neuropsychiatric complications such as cognitive impairment and fatigue are also important predictors, even in those patients in the early stages of the disease. We review generic and specific HRQoL measures to help clinicians choose the most appropriate therapies. Subjective (self-report) HRQoL measures may serve to alert clinicians to areas that would otherwise be overlooked. Studies of new interventions should include an assessment of HRQoL not just impairment or disability alone.

Introduction

Multiple sclerosis (MS) is one of the most common chronic neurological diseases in young adults, affecting about one in 1000 people. There are an estimated 1·1 million patients worldwide.[1] In most cases, the disease is episodic with full remission separated by unpredictable relapses. With time, 80% of patients experience a transition towards persistent disability in the secondary progressive phase.[2] Only one in five patients will either remain stable or avoid substantial disability during their lifetime. Even those patients with very early clinically isolated MS-related syndromes are likely to have disseminated lesions on brain MRI[3] together with subtle neuropsychological deficits.[4] MS is a disorder with early involvement of the brain and higher function, resulting in important consequences for living a full and independent life. As a neuropsychiatric disease affecting young people, MS threatens personal autonomy, independence, dignity, and future plans.[5] As a relapsing-remitting disorder patients face an unpredictable course;[6] as an incurable progressive disease patients have to respond to multiple new setbacks over time. Collectively these features mean that MS can threaten wellbeing to a particularly severe extent.[7]

The neurological complications of MS are well documented and have a major role in the personal burden of the disease. The disease typically starts with sensory disturbances, unilateral optic neuritis, diplopia, Lhermitte's sign (trunk and limb paraesthesias on neck flexion), limb weakness, poor coordination, and gait ataxia. However, the contribution of each symptom to overall distress or disability has rarely been studied. Additional burdens arise from neuropsychiatric complications that occur in part as a direct manifestation of demyelination and inflammation and in part because of the psychological effect of having to adapt to an unpredictable disease. The main neuropsychiatric features include (in decreasing order of frequency) anxiety, depression, cognitive impairment, irritability, and anger.[8] Less common symptoms include disinhibition, delirium, psychosis, dementia, apathy, emotionalism, and behavioural disturbances.[9] For many years these psychological and psychiatric dimensions have interested only specialists and have rarely featured in clinical trials or have been used by clinicians when assessing the effect of the disease.[10] However, there is now increasing recognition that psychological, social, and psychiatric issues form vital segments of health-related quality of life (HRQoL), which is distinct from physical disability alone. For those involved in assessing new treatments, quality of life (QoL) measures may be more sensitive to change compared with conventional disability instruments. In this review we look at the clinical importance of HRQoL in MS, namely its practical measurement and its inter-relationship with psychosocial and emotional domains. We view QoL as a multidimensional index of wellbeing: the sum of all sources of satisfaction (including anticipated sources) minus all sources of worry (including anticipated threats) from the patient's perspective.

HRQoL in MS

HRQoL has been widely examined as an outcome measure in MS. The first study of HRQoL in MS[11] was published in 1990 and the first comparative study appeared 2 years later.[12] At least 90 studies have now measured QoL in patients with MS.[13,14] Studies in Canada,[15] Norway,[16] Spain,[17] and the USA[18] proved that many patients with MS have notable decrements in HRQoL; this is because the effect of disability in daily living is greater in MS (especially in its progressive form) than in other chronic diseases.[19] Compared with patients with many other chronic diseases, patients with MS have the least favourable ratings of general

health, vitality, physical functions, and social limitations in social roles.[20] At least a third of patients experience a major decline in their standard of living after the diagnosis of MS.[21] Up to 70% of community-dwelling patients with MS are unemployed, half of these due to the consequences of their disease.[22] Within 10 years of onset, half of all patients with MS are unable to fulfil household and employment responsibilities; within 15 years, half are unable to walk unaided; and within 25 years, half require a wheelchair.[23] Clinicians must understand the moderating factors of these trajectories (panel 1);[24] however, many individuals with MS adapt well to modest disabilities and some individuals cope well even when faced by severe physical setbacks.[25] Resilience factors are important in HRQoL, and remain almost completely unexplored in MS.[26] Similarly, coping styles (both adaptive and maladaptive) are notable moderating variables for patient and carers, re-inforcing that psychological and personality variables are becoming part of mainstream practice.

Even though almost all clinicians acknowledge the advantages of using the concepts of impairment (loss), disability (function), and handicap (participation) to model the impact of disease, some clinicians are sceptical about the additional benefits of HRQoL (panel 2).[27] We know that HRQoL in MS correlates with measures of impairment and disability such as the expanded disability status scale (EDSS). However, this correlation is surprisingly weak, varying from 2–29% (on R^2) depending on the interplay of multiple additional influences (table 1).[28–32] Therefore, QoL assessment might alert health professionals to less obvious burdens of disease.

Predictors of HRQoL in MS

HRQoL is not just a measure of perceived health; however, research has focused largely on disease-related threats rather than sources of satisfaction.[33] Studies in other areas of medicine illustrate that many distal factors have an influence that is greatly moderated by numerous proximal variables.[34] Proximal measures of distress (such as hopelessness and depression) are among the strongest predictors, but many threats associated with a disease will be greatly reduced in the presence of external help and internal resilience factors (panel 3).[33] Health-related anticipated threats also have an important effect and can hugely affect the patient; for example, a patient who meets another with a rapidly progressive form of MS might fear their illness will follow the same course. Some individuals not only fear the "worst case scenario" but also become preoccupied by it. This type of fear has also been recognised in cancer care and is one reason why simple interventions such as bibliotherapy or group therapy can be rapidly successful.[35]

Psychiatric influences

Depression is undoubtedly the most significant predictor of low HRQoL in all neurological diseases including tumours of the CNS,[36] head and spinal-cord injury,[37] epilepsy,[38] headache,[39] motor neuron disease,[40] Parkinson's disease,[41] and stroke.[42] In these studies, even modest symptoms of depression have an appreciable effect on HRQoL. In accordance with these findings, depression is one of the strongest predictors of HRQoL in MS;[30–32,43] there are at least five reasons for this. First, depression impairs motivation, interest, and concordance, therefore retarding physical progress. Second, depression tends to occur when an individual's own coping resources are exhausted and can therefore be thought of as sensitive marker for "stresses getting beyond the patient's point of no return". Third, depression can distort an individuals view of the world and their health so that their assessment is more negative than it would otherwise be—although, HRQoL ratings from observers are also low in depressed patients. Fourth, factors that impair HRQoL will also affect mood, even if a mood disorder is not present

Study	HRQoL measure	Depression R²	EDSS R²	Others (domain)	Sample
Fruehwald et al (2001)[30]	Quality of Life Index (QoL)	43% (Zung)	29%	NS (anxiety)	60 patients from an outpatient clinic
Merkelbach et al (2002)[31]	SF-36 mental	26% (BDI)	0·03%	18% (fatigue)	87 unselected patients with clinically definite MS (56% RR)
Patti et al (2003)[29]	SF-36 RL*	15% (BDI)	8%	12% (time)	308 patients diagnosed at least 4 years before (51% RR)
Benedict et al (2005)[32]	MSQoL54P	8% (BDI)	2%	53% (fatigue)	120 patients (75% RR)

In short form 36 (SF36), role limitations are markers of HRQoL. RR=relapsing-remitting; BDI=Beck depression inventory; NS=not significant.

Table 1: Strength of predictors of HRQoL and disability (unadjusted R² data) in MS

syndromally. Finally, poor HRQoL and depression are both typically associated with similar facets of experience—such as distress and suffering.

Anxiety is also a known risk factor for poor HRQoL in many disorders but has rarely been studied in patients with MS. Anxiety comes in different forms, such as background worry (generalised anxiety disorder), episodic anxiety (panic disorder), and focused anxiety (phobias). However, health anxiety involving fears of disease progression is most troubling for many patients with a physical disease.[44] In MS, anxiety has been linked with low HRQoL in some,[45] but not all studies.[46] In a study of subtypes of fear and worry in MS, patients had high levels of both intrusion and related avoidance in a preliminary report.[47] More work is needed to clarify which elements of anxiety disorder (intensity, duration, somatic symptoms) most affect HRQoL.

The possible role of agitation, disinhibition, irritability, and apathy in determining HRQoL in

Panel 3: Predictors of reduced HRQoL[33]

Strong predictors
Depression
Demoralisation or hopelessness
Cognitive impairment
Lack of autonomy
Lack of support
Pain

Moderate
Fatigue
Anxiety
Communication difficulties
Rapidly progressive disease
Low self esteem

Weak
Long duration of disease
Neurological symptoms
Subtypes of disease
Forced unemployment
MRI disease burden

patients with MS and carers has only been examined by one group, despite its importance in other areas of neurology. Benedict and colleagues[32] showed that agitation, irritability, apathy, and behavioural problems (aberrant motor behavior) had an influence on employment status in MS and that disinhibition had a small effect on overall HRQoL.

Psychosocial influences
An individual's perception of their own circumstances is critical to their rating of overall QoL. A person's perception of their future, whether accurate or inaccurate, has a substantial influence. Patients who expect or hope for a favourable future rate higher than pessimistic patients on HRQoL measures, regardless of what doctors think might be more realistic appraisals.[48] One group found that patients with MS overestimated risks of being wheelchair dependent at 2 years and 10 years, but underestimated their lifetime risks.[49,50] These observations suggest that the provision of appropriate information and promotion of independence may help alleviate suffering. Qualitative studies showed that patients commonly resent care they receive, even when they acknowledge it as necessary; many describe it as intrusive and a threat to their dignity.[5] Quantitative studies confirm that intrusiveness is an important mediator of HRQoL.[51] Thus even though deterioration in physical dependence may be inevitable, the degree of autonomy and decision-making control that the individual retains has strong influence on overall HRQoL. This feeling of self-efficacy is the belief that challenges can be overcome by use of innate abilities. Although self-efficacy is eroded by progressive medical disorders, it is moderated by other factors.[52] Self-efficacy strongly predicts psychological adjustment to MS and is interlinked with self esteem, depression, and self-worth.[53,54] In both pretreatment and post-treatment, self-efficacy scores are linked with improvements in self-rated walking ability and physical and psychological effects of MS; suggesting that efforts should be made to involve patients in collaborative treatment.[55] Self-efficacy is rarely adequately assessed in generic or specific HRQoL scales, although, specific scales of self-efficacy in MS have been developed.[56,57]

Beyond perceived control, coping mechanisms used by patients themselves influence HRQoL in both positive and negative directions. Acceptance of MS—"I know it's there, but I don't think much about it"—is associated with good HRQoL.[58] Although coping styles seem to be largely innate, the ability to handle MS might improve with time over the course of the disease.[59] More importantly for health professionals coping style can be positively influenced by treatments such as group therapy.[60] Perception of self-efficacy and different coping styles seem to be refined by feedback and encouragement from friends, professionals, and peers. When this process goes awry, individuals with

MS can feel stigmatised and rejected by society. HRQoL correlates strongly with measures of social stigma and perception of social desirability to which close personal relationships are perhaps the biggest influence.[61] Finally, the ability to sustain worthwhile employment or education is important to almost everyone, including those with chronic disease. Preservation in recreation and social life is equally important. In a seminal publication, Rao and colleagues[62] compared employed and unemployed patients and matched for physical disability and illness duration, and found that those who were not employed or socially active were much more likely to have cognitive impairment. Benedict and colleagues[32] recently confirmed that vocational status is determined in part by cognitive impairment and in part by disease duration. The ability to engage in meaningful activities is a protective factor against depression and impaired HRQoL.[63]

Biological influences

Disease-related physical variables have an effect on QoL in MS. Poor HRQoL has been linked with a progressive disease course and degree of physical disability, but HRQoL is better predicted by measuring social participation (handicap; table 1).[64–67] Some domains may have special importance; those with both biological and psychological components are called neuropsychiatric and include symptoms of both cognition impairment and fatigue.

Cognitive impairment is an important symptom in MS, but the medical profession has only recently acknowledged its relation with HRQoL. Most,[68–70] but not all[67] studies show an association between cognitive deficits and low HRQoL. In a cross-sectional study, Cutajar and colleagues[69] found a relation between both memory impairment and executive function and HRQoL. Gold and co-workers[70] compared 80 patients with MS affected by cognitive dysfunction with 107 unimpaired patients, separated on the basis of the symbol digit modalities test (SDMT); cognitively impaired patients had higher prevalence of depression and anxiety and lower HRQoL. Benedict and colleagues[32] found that cognitive impairment predicted mental health components of HRQoL (in unadjusted analysis) as well as the ability to maintain full employment. Most recently, Benito-León and colleagues[71] examined all degrees of cognitive impairment using neuro-psychological testing, the clock drawing test, and MMSE screening instruments in 191 MS patients. After controlling for depression, comprehensive (but not simple) ratings of cognition distinctly contributed to poor HRQoL. In addition, all degrees of cognitive impairment, severity of fatigue, and higher physical disability were independent predictors of low functional assessment of MS (FAMS) instrument total scores.[71]

Fatigue is a complex and troubling symptom of MS with both physical and mental components. In one community survey, 88% reported moderate or severe fatigue.[72] Fatigue has been linked with both survival and HRQoL in cancer care.[73] Although less intensively investigated in MS, worsening fatigue in the early phase of illness is linked with progressive brain atrophy over subsequent years—strongly suggesting a link with progressive axonal damage.[74] Fatigue scores affect both physical and mental HRQoL even after adjusting for disability.[75] However, fatigue is exacerbated by depression and vice versa, providing a firm link between physical and emotional symptoms.[76]

Given the developments in neuroimaging of MS, it would be interesting to examine its link with HRQoL. Hypointense brain lesions and atrophy on MRI are associated with impaired function, poor mental health, and functional limitations.[77] Depression, anxiety, disinhibition, and fatigue have been weakly linked with MRI brain lesions.[78] Atrophy has been used as a surrogate marker of axonal loss with atrophy, being a better association with disability measurements like the EDSS or the MS functional composite (MSFC) compared with the assessment of focal lesion volume.[79] One possibility is that early MRI findings might predict long-term disability.[80] However, serial brain MRI assessments showed that only about one in ten new or active MS lesions give rise to clinical relapse[81]—and only a small proportion of actual lesions can be seen on MRI. Could HRQoL (or neuropsychiatric) measures be used as a better index of brain involvement than disability scales? If so, this would be important for future drug-effect studies. There are strong associations between brain atrophy and neuropsychological functioning, but it remains to be seen whether a similar link with HRQoL exists.[82,83]

General, specific, and composite HRQoL measures

There has been a proliferation of HRQoL measures and there is now uncertainty about which measure to use in which situations.[84] For clinicians new to the concept of QoL, many find measures of impairment, disability, and handicap easier to understand than HRQoL. Vickrey and colleagues[85] looked at the properties of several HRQoL measures for MS and concluded that no single measure was clearly and consistently best in all situations. Different groups have tended to promote their own scale without head-to-head comparison of accuracy or practicality. Clinically, we suggest a measure should be chosen that captures information across physical and psychological domains together with proven value in relation to a specific aim, whether that is screening, service improvement, or monitoring of treatment. In busy environments where clinicians have no time for formal rating, use of a questionnaire in the waiting room is one option. An alternative is to assess QoL by use of simple questions (panel 4).[86] Repeat measures can also be used.[87]

Measures of broadly defined HRQoL issues are called generic scales because they can be applied to different diseases. The main advantage of generic scales is that they can be used to make comparisons between the degree of deficits in different diseases. Measures that include focused questions about the effects of a single disorder are called specific HRQoL measures. These measures are typically capable of quantifying deficits more precisely than generic scales. Sometimes features from both designs are combined. New developments include measures that ask open questions that patients can refine themselves.

As QoL is predominantly a first-person-perspective concept, many scales rely on a considerable degree of self-report from either patients or carers. This subjective element commonly causes uncertainty for clinicians who are more familiar with objective measures.[88] However, subjectivity should not be thought of us as inherently unreliable—self-reported symptoms can be assessed with high reliability and validity.[89] Subjectivity in this case acknowledges that the perspective of the patient is the primary source of information regarding their own condition. Studies show that patients with MS undergoing rehabilitation who achieve the same "objective" clinician-rated improvement might actually score very differently when asked to assess themselves.[90] In addition, patients might complain of early complications (for example early cognitive impairments) before symptoms and signs are detected by clinicians.[91]

Generic scales

The most widely used is the short form 36 (SF36), although many generic scales now exist. The SF36,

which takes about 10 min to complete was developed from the much longer batteries of items used in the RAND Corporation's health-insurance-study experiment.[92] There are some structural limitations in the SF36, including floor and ceiling effects, and these vary according to the severity of the disease being examined.[93] Several generic HRQoL scales have been used in MS studies (table 2).[94–98]

Specific scales

Disease-specific instruments focus more attention on the concerns of the patients themselves. However, self-completed questionnaires may not be appropriate for severely disabled patients and therefore many such patients have been excluded from studies because of concerns about the validity of proxy responses.[99] In addition, many diseases, including MS, have considerable heterogeneity and therefore specific scales may be needed for different phases of the disease.[100] However, there is a difficulty with patients who have moderate or severe cognitive impairment because they might not be able to complete HRQoL measures. In fact this has been formally tested in MS and in Alzheimer's disease. Severe cognitive impairment does not seem to prejudice HRQoL ratings (although the type and format of the scale may need adjustment).[101]

More than 20 measures that address HRQoL in patients with MS have been developed (panel 5).[102] The most commonly applied measures include the MSQoL54,[103] the disability and impact profile (DIP),[104] functional assessment of MS (FAMS),[105] Hamburg QoL questionnaire in MS (HAQUAMS),[106] Leeds MS QoL (LMSQoL),[107] Multiple Sclerosis Impact Scale (MSIS-29),[108] MS QoL inventory (MSQLI),[109] RAYS,[110] Pfennings HRQoL instrument,[111] QoL index MS version,[112] and performance scales (table 3).[113]

The effect of interventions on HRQoL in MS

HRQoL in randomised drug trials in MS

In the last 8 years, HRQoL scales have gradually been incorporated into randomised controlled drug trials (table 4).[64,98,114–124] To date several studies of interferon beta in patients with relapsing-remitting MS have used generic instruments. Results range from no effect on HRQoL to significant improvement, largely in physical

Scale	Number of items	Time to complete (min)	Physical				Neuropsychiatric				Psychosocial		
			Physical	Mobility	Bladder/Bowel	Sensory	Communication	Sexual	Cognitive	Fatigue	Emotional	Social	Self-efficacy
Nottingham health profile[94]	45	5–10	y	y	n	y	n	n	n	y	y	y	n
Sickness impact profile[95]	136	20–30	y	y	n	n	y	n	y	n	y	y	n
SF36[96]	36	5	y	y	n	y	n	n	n	n	y	y	n
Farmer quality of life index 2[12]	41	15–30	y	y	n	n	n	n	n	y	y	y	n
EuroQoL[97]	5	3	y	n	n	y	n	n	n	n	y	n	n
Functional status questionnaire[98]	34	15	y	y	n	n	n	n	n	n	y	y	n

Table 2: Generic HRQoL scales

dimension subscales.[64,114,116,117,122] In the two studies that assessed the effect of interferon beta in secondary progressive MS, some HRQoL dimensions improved.[118,120] A study, which assessed the HRQoL in patients with MS who had experienced an acute relapse and were treated with intravenous methylprednisolone, showed a statistically significant early improvement of both the EDSS and the incapacity status scale scores and a non-significant trend towards improvement in the SF36 physical and mental composites.[98] Although improvement of disability after intravenous methylprednisolone treatment occurs early, the improvement in HRQoL may be delayed.

HRQoL in non-pharmacological trials in MS

Types of support are important moderators of HRQoL, whether the support is informal or professional. The provision of psychosocial and emotional support has a direct effect on HRQoL in many medical disorders as well as neurological disorders, particularly in MS.[125] The nature, duration, and quality of support are important but these variables have not been tested in MS. In one study, patients who received a peer-support intervention in a randomised trial showed improvements in confidence, self-awareness, self esteem, depression, and role functioning.[126] In a second study, Mohr and colleagues[127] assigned 60 patients with MS (with moderate to severe depression) to 16 weeks of treatment of cognitive behavioural therapy, group psychotherapy, or sertraline. Both fatigue and depression improved in all groups. The nature of the doctor-patient relationship affects long-term HRQoL and satisfaction for cancer patients;[128] this could also be the case with MS. Two studies have shown that exercise training and physical rehabilitation improve patients' HRQoL.[118,121] A recent study has shown that long-term exercise improves functional impairment but not HRQoL in MS.[123] An important question is whether rehabilitation programmes are helpful for HRQoL.[129] The effect of rehabilitation programmes have hardly been studied in MS and requires further attention. In a randomised study, patients were given 3 weeks of inpatient physical rehabilitation or exercise at home; patients in the active arm showed improved disability and mental components of HRQoL.[130] However, these benefits of improved disability were gradually eroded with return to usual care.[131]

Value of HRQoL and neuropsychiatric measures in future clinical trials

Researchers have traditionally relied upon measures of impairment and disability such as the EDSS to assess

Scale	Number of Items	Time to Complete (min)	Physical				Neuropsychiatric				Psychosocial		
			Physical	Mobility	Bladder/Bowel	Sensory	Communication	Sexual	Cognitive	Fatigue	Emotional	Social	Self-efficacy
MS QoL[103]	54	11–18	y	y	n	y	n	y	y	y	y	y	n
Disability and Impact Profile[104]	39	25	y	y	y	y	y	y	n	n	y	y	y
Functional assessment of MS (FAMS)[105]	59	20	y	y	y	y	y	y	y	y	y	y	y
Hamburg QoL questionnaire in MS[106]	38	25	y	y	y	y	y	y	y	y	y	y	n
Leeds MS QoL[107]	8	5	n	n	n	n	n	n	n	y	n	y	n
MS impact scale-29[108]	29	15	y	y	y	n	n	n	y	y	y	y	y
MS QoL inventory[109]	30	45	y	y	y	y	n	y	y	y	y	y	y
RAYS[110]	50	30	y	y	y	y	y	y	y	y	y	y	n
Pfennings HRQoL instrument[111]	40	10	y	y	y	n	n	n	y	y	y	n	n
QoL index MS Version[112]	18	45	y	n	n	n	y	y	y	y	y	n	y
Performance scales[113]	21	10	y	y	y	y	n	n	y	y	n	n	n

Table 3: MS-specific HRQoL instruments

Therapy	MS type (No. of patients)	Sample size	Follow-up	Scale	Results
Intravenous methylprednisolone[98]	Remitting-relapsing	24	3 months	SF36	Trends for improvement of physical and mental dimensions
Interferon beta-1b[114]	Remitting-relapsing	79	12 months	Q-TWIST	No effect on patients' HRQoL
Interferon alfa-2a[115]	Remitting-relapsing	97	12 months	SF36	The adverse events affected the patients' HRQoL
Interferon beta-1b[116]	Remitting-relapsing	117	60 months	SF36	Physical, social, and health dimensions improved especially those with an EDSS <3·0
Interferon beta[117]	Remitting-relapsing	51	6 months	SF36	Physical dimensions improved
Interferon beta-1b[118]	Secondary progressive	718	36 months	SIP	Physical dimension improved
Intramuscular interferon beta-1a[64]	Remitting-relapsing	121	12 months	SF36	No negative effect on MS patients' HRQoL
Aerobic training[119]	Remitting-relapsing	54	15 weeks	SIP	All dimensions improved
Intramuscular interferon beta-1a[120]	Secondary progressive	436	24 months	MSQLI	Benefit on eight of 11 MSQLI subscales
Outpatient rehabilitation[121]	Primary/Secondary progressive	58	6 weeks	SF36	All dimensions improved
Intramuscular interferon beta-1a[122]	Remitting-relapsing	27	12 months	FAMS	No effect on HRQoL
Long-term exercise[123]	Remitting-relapsing	47	6 months	MSQOL-54	No effect on HRQoL
Autologous HSCT[124]	Non-primary progressive MS	19	36 months	MSQOL-54	Improvement in both composite scores and in most of the individual domains

HSCT=Haematopoietic stem cell transplantation; SIP=Sickness Impact Profile

Table 4: **Interventions on HRQoL in MS**

treatment response. Attempts to incorporate MRI data have been only partly successful, enabling an explanation of less than 10% of the variance in disability.[132] Nevertheless axonal pathology present in the earlier stages of the disease may be clinically silent when assessed with traditional methods.[133] There have been many attempts at developing better disability scales.[134,135] For example, the MSFC combines disability information with cognitive measures (a 25 m timed walk, the nine-hole peg test, and the paced auditory serial addition test) and seems to be a more accurate indicator of HRQoL than the EDSS. However, these disability scores still reflect physical health status more than they reflect mental health and thus they are insensitive to important HRQoL domains.[136,137] Further measures will probably link disability, participation, neuropsychiatric, and psychosocial domains. Such measures may actually turn out to be more useful methods of monitoring early disability effects of potential disease-modifying drugs.

Conclusions

Over the past 10 years HRQoL issues have been more intensively studied in MS than in any other neurological disorder.[13] Although increasingly accepted in research, many busy clinicians do not see the usefulness of HRQoL measures when making medical decisions. The development of short and easy-to-use HRQoL instruments may change this. We suggest that ultra-short (panel 4)[87] or short generic instruments (such as the EuroQoL) can be used in most clinical settings as a screening test to rule out patients who are doing well. However, where problems are suspected a more detailed questionnaire (such as the functional assessment of MS)[105] can be used.

Studies of HRQoL show that clinicians are more concerned than patients about the physical manifestation of the disease, whereas patients consider vitality, role limitations, emotional problems, and mental health to be the critical determinants of overall burden.[138] HRQoL assessment can be used as a way of checking if further treatment is required and whether interventions were as effective from the patient's point of view as clinicians believe.[139] A further benefit is that HRQoL might actually be an independent predictor of physical outcomes. For example, during a randomised control trial of interferon α, Nortvedt and co-workers[140] found that low scores on the SF36 correlated with impaired disability scores 1 year later—even after controlling for baseline disease-activity and disability. In the same year Parkin and colleagues[141] found that HRQoL predicted a change in physical disability as measured by EDSS scores over 1 year. Most recently Visschedijk and co-workers[142] showed that SF36 was a notable predictor of change in disability status over 5 years in a mixed group of 81 MS patients. In these studies both the physical and mental dimensions were predictive of decline suggesting that the HRQoL measures were not simply measuring physical impairment more accurately.

Predictors of HRQoL reveal that both physical and psychological concerns are important and interact with each other.[32] Psychological concerns and psychiatric complaints have long been overlooked and undertreated in MS.[143] The burden of living with MS affects patients physical and mental health; it also has a similar effect on carers.[144] Neuropsychiatric symptoms present early in the disease course, and specific cognitive deficits can be seen in over 50% of patients in the earlier phases of disease.[4,145] Even in patients with a short disease duration of less than 2 years, discrete impairment of cognitive function may be seen in up to 60% of patients on neuropsychological testing.[146] Symptoms of depression are also present early in the disease process and have an effect on cognitive performance, particularly processing speed, but do not entirely account for cognitive problems.[147] If seen within the first year of diagnosis 48% of patients and 46% of their partners have clinically relevant levels of either anxiety, depression, or distress.[47] Similarly, up to 50% of patients thought to be normal on routine neurological examination have specific

neuropsychological deficits.[148] Treatment of physical, psychological, and social needs of patients improves HRQoL in most cases, particularly where the interventions are sustained or incremental. Simple interventions such as providing adequate disease-related information or support are likely to be beneficial and should be provided for most patients. Many patients need better quality information than they initially receive. Unmet needs in service provision was reported by 36% of patients in UK.[149] 75% of patients reported inadequacies in information they had been offered about MS.[150]

Historically the management of MS has been predominantly about limiting disability by symptomatic management of acute relapses and attempting to influence the long-term course. Even though this type of management is important, we suggest this is accompanied by an equal effort at improving participation, wellbeing, and QoL. By use of this strategy, many options are available to patients, even if disease-modifying treatments are unavailable or ineffective. For those who remain sceptical about the HRQoL concept, HRQoL can be seen as an opportunity to assess and meet previously unmet needs, to predict previously unpredictable outcomes, and to develop broad interventions with beneficial psychological and physical effects.

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All authors developed the concept of the review. AM and JB-L drafted the review. All authors were involved in revising the article for intellectual content.

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