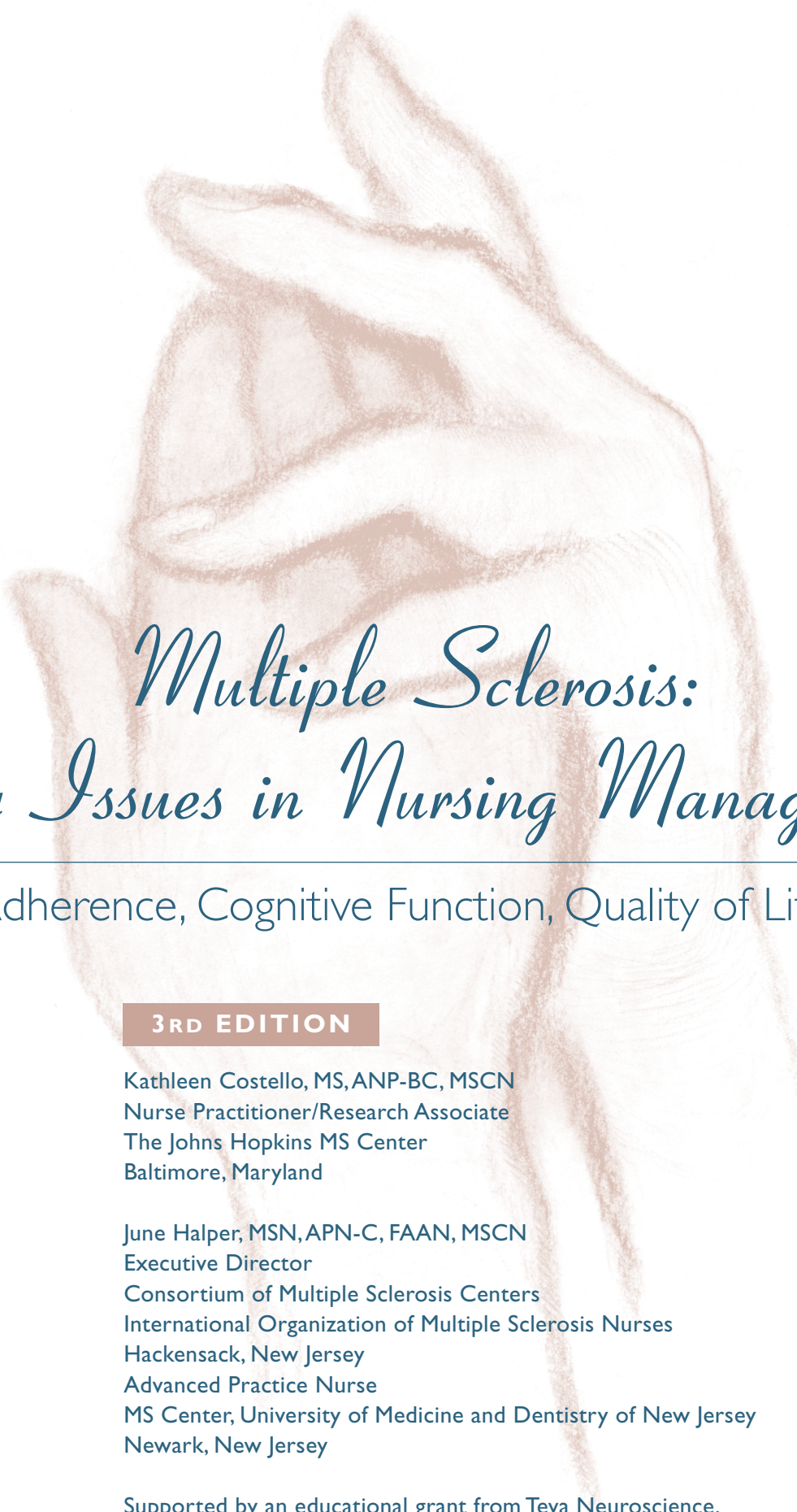




Multiple Sclerosis: Key Issues in Nursing Management

Adherence, Cognitive Function, Quality of Life

3RD EDITION

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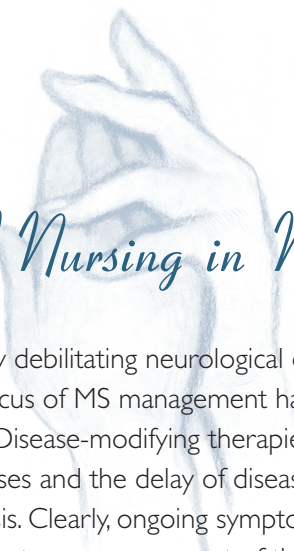
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Preface: The Roles of Nursing in Multiple Sclerosis

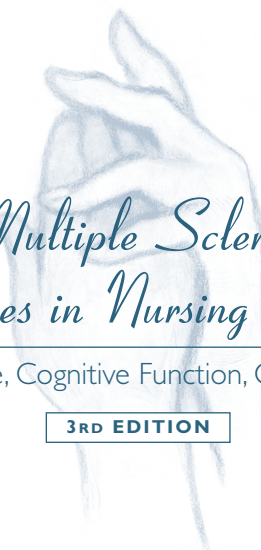
Multiple sclerosis (MS) is a chronic, frequently debilitating neurological disease that affects young adults in the prime of their lives. Over the past 2 decades, the focus of MS management has changed from one of only symptomatic intervention to one of disease modification. Disease-modifying therapies (DMTs) have had an impact on the natural history of MS through the reduction of relapses and the delay of disease progression. The earliest possible initiation of treatment is encouraged following diagnosis. Clearly, ongoing symptomatic management with rehabilitation intervention remains critical to successful long-term management of the disease. Thus, plans of care in MS must be multidimensional and require both pharmaceutical intervention and rehabilitation strategies. The nurse has a vital role to play in the ongoing care of and interaction with patients and their families. Nursing care in MS is a collaboration between the patient/family and the nurse, a partnership centered on the goal of attaining self-awareness, self-responsibility, and the knowledge necessary for a great deal of self-care.

The nurse working in the field of MS is a care provider, facilitator, advocate, educator, counselor, and innovator. The challenges of the disease require many creative interventions in a wide variety of settings. The list of needs for MS care is long and complex. Interventions range from instruction in the use of medications, both oral and injectable, to bowel and bladder management strategies, to the improvement of mobility. The dynamic nature of the disease and the psychosocial, economic, and physical implications of MS call for ongoing skill development and up-to-date information on the part of the nurse interested in MS care.

With the advent of DMTs, new breakthroughs in research, the establishment of worldwide networks of care, and the validation of a new specialty branch of nursing, the MS nurse must adopt a vision of MS that includes empowerment, collaboration, skills development, and team building with an ongoing leitmotif of hope.

The nurse has a vital role as an educator of patients and their family members. It is very important for the nurse to encourage them to move out of a passive role and to assume a proactive stance about their disease. By becoming educated, the patient is more likely to feel a sense of empowerment, acceptance, and well-being. The nurse can assist in this process by referring patients to literature, newsletters, and short-term orientation groups, and by explaining the disease process, symptoms, tests, and technical terms. It is important for a nurse to help establish reasonable expectations for proposed treatments, to educate patients in self-care and wellness, and to explain side effects. A nurse's support, advice, education, and expertise can do much to advance the patient's conception of MS from that of an incurable and uncontrollable disease to that of a manageable problem that is merely a part of his or her life.

This is the 3rd edition of a landmark work on MS, a monograph originally published to document the roles and contributions of MS nurses. Since the first edition, MS care has evolved and expanded, and nurses have continued in their expanded roles.



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Foreword

Multiple sclerosis (MS) continues to be one of the most life-altering diagnoses a patient can receive. A chronic, often debilitating, neurological disease with no cure, it produces motor, sensory, mood, visual, elimination, and cognitive dysfunction. Coupled with this range of deficits, the course of MS is unpredictable—patients must adjust to living with a fluctuating disease characterized by periods of relapses and remissions or unrelenting progression.

Advances in our understanding of MS, the availability of disease-modifying agents, and a wide range of symptomatic therapies have facilitated a comprehensive approach to the management of MS. The underpinning of this model of care is the empowerment of patients with the knowledge and skills needed to minimize the impact of the disease and to maximize patients' control over their lives. Nurses care for people with MS in a variety of settings and address a broad spectrum of physical, emotional, and educational needs. The key issues in MS nursing include the following.

- Promoting adherence to complex protocols.
- Adapting nursing care to recognize and compensate for/monitor cognitive impairment.
- Facilitating assessment of the impact of MS on quality of life despite uncertainty or disability.
- Providing individualized attention to the comprehensive needs of those affected by MS.

This monograph is a revised edition of an earlier version created by the Multiple Sclerosis Nurse Specialists' Consensus Committee (see page 49 for a complete listing of the original committee members, all of whom are nurses specializing in MS care) and now includes updated information. As with the previous editions, this monograph is designed to enhance MS nursing care, particularly with regard to providing a comprehensive review of several key issues that challenge nurses involved in MS care. These issues are pivotal to the patient's ability to adjust to living with MS despite its many challenges. After reading this monograph, which builds upon the groundwork laid by the contributors to the earlier editions, nurses should be able to:

1. Describe the prevalence, diagnosis, and pathophysiology of MS.
2. Describe the role of the nurse in the comprehensive management of MS.
3. Recognize the barriers to adherence to treatment regimens.
4. Identify the signs of cognitive impairment in people with MS.
5. Describe what factors influence quality of life in people with MS.

This monograph is a valuable resource for nurses and other healthcare professionals who care for people with MS in any setting, as well as those who care for other chronically ill patients.



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Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) that has pervasive effects on the lives of over 2.5 million people throughout the world.^{1,2} Patients must adapt to the stress of living with a frequently debilitating illness of unknown etiology, an uncertain prognosis, and a variable disease course.

While technologic and pharmacologic advances in the past decade have brought hope to patients and their families, these advances have also created new complexities in long-term management. Injectable disease-modifying therapies (DMTs), energy management, bladder management techniques, regimens to improve sexual functioning, and cognitive and physical rehabilitation programs have made MS management more challenging, time consuming, and demanding for patients and their families.

With these advances, nurses have taken a leading role in the development of comprehensive care strategies. Philosophically, these strategies focus on empowering patients and promoting self-care. In practice, they pose a challenge to the care team to provide ongoing education on the implementation of complicated regimens and to ensure that patients have adequate support mechanisms. Crucial to the success of these tasks is proper assessment of 3 factors:

- the capacity and/or motivation of patients to adhere to therapeutic regimens,
- the presence and impact of cognitive impairment, and
- the influence of MS and treatment interventions on the patient's/family's quality of life.

Each of these factors alone, and in combination, helps determine how an individual patient will respond to management efforts by the healthcare team. For example, although a patient may be willing to learn about and implement a therapeutic regimen, cognitive and physical impairment may make this difficult. People whose quality of life has been negatively affected by MS may be unwilling to adhere to complicated regimens that further disrupt their lives. Nurses caring for patients and their families should understand how MS has affected each individual. They can help patients and families compensate for the unchangeable aspects of the disease and assist them in addressing those aspects that can be changed. Strategies to promote active participation and adjustment to change are key factors in the nurse–patient partnership.

Overview of Multiple Sclerosis

MULTIPLE SCLEROSIS FACTS AND FIGURES

MS affects an estimated 300,000–400,000 people in the US and approximately 55,000–75,000 people in Canada.^{1,3-5} Although considered a relatively rare disease, MS is of particular interest to healthcare professionals and providers because of its potential to cause severe disability, and because the typical age at onset is young adulthood. In addition, the multifaceted nature of the disease affects healthcare, social service, community support, and economic issues. As a result, patients, families, and the healthcare community are presented with many lifelong challenges.

PATHOPHYSIOLOGY AND ETIOLOGY

MS is characterized by damage to the myelin sheath and underlying nerve fibers within the CNS—that is, the brain, optic tracts, and spinal cord. This damage is caused by inflammation and injury to the myelin sheaths as well as underlying axons. Damaged areas undergo gliosis and appear as lesions or plaques scattered throughout the CNS. These plaques may be found in the periventricular white matter, in the optic nerves, and in the white matter of the spinal cord, brainstem, cerebellum, and cerebrum. Over the past several years, evidence of plaques in the gray matter of the brain and spinal cord, observed mostly post-mortem, has also emerged.^{6,7} The damage and destruction of myelin interferes with the efficiency of electrical conduction within the CNS; thus, the major clinical manifestations of MS relate to sensory and motor dysfunction, as well as cognitive and affective disorders. Damage to the underlying axons is likely the cause of the irreversible neurological disability. This damage was originally thought to occur late in the disease; however, work in the late 1990s by Trapp and colleagues demonstrated that permanent axonal damage occurs early as well as late in the disease.⁸

Although the etiology of MS is not clear, researchers believe that a multigenetic predisposition to the disease

may exist (ie, the disease may result from defects in more than one gene).⁹ In addition, it is hypothesized that the myelin loss associated with MS results from an immunologic attack caused by sensitization to myelin or to an infectious agent (possibly viral or bacterial). Proinflammatory lymphocytes that are autoreactive to self-CNS antigens such as myelin become activated in the periphery, disrupt the blood–brain barrier, and enter the CNS where they become reactivated. The cascade of immunological events that follows causes demyelination and damage to nerve fibers, ultimately resulting in neurological symptoms and disability.

CLINICAL FEATURES AND DIAGNOSIS

Because the damage to myelin and axonal loss is not localized to one particular area of the CNS, MS results in a diverse range of neurological impairments. The symptoms of MS can be classified as primary, secondary and tertiary and vary in intensity from patient to patient and within the patient from time to time. Primary symptoms—such as bowel and bladder dysfunction, tremor, sensory loss, ataxia, and visual disturbances—result from myelin and axonal damage in specific areas of the CNS. These may give rise to secondary symptoms, such as urinary tract infections and decubitus ulcers. Partial treatment or lack of treatment for primary and secondary symptoms can lead to complications of MS or tertiary symptoms such as social isolation, job loss, and deterioration in relationships.

In addition to the classic motor and sensory symptoms of MS, patients may experience a variety of cognitive deficits. The neuropsychological disturbances are probably related to the overall involvement of white matter, particularly in the periventricular frontal regions¹⁰ and in the corpus callosum. Memory or recall problems and slowed information processing are most commonly reported, although abstract reasoning and problem solving can also be affected. Cognitive deficits will impact the ability of patients to adhere to treatment regimens and will impact social, family, and work roles and relationships.

In order to support a diagnosis of multiple sclerosis an individual must demonstrate 2 episodes of neurological

symptoms referable to the CNS with objective evidence separated in space and time. This diagnosis is dependent on a number of factors. The patient history should indicate episodes of symptoms or a progressive course of symptoms. The neurological exam should support the history and lead the provider to order laboratory evaluations. Revised McDonald diagnostic criteria bases diagnosis on attacks that last at least 24 hours and are separated by at least 1 month. Two attacks and evidence of 2 or more lesions require no additional evidence to make a diagnosis of MS. If a patient has had fewer than 2 attacks and/or displayed fewer than 2 lesions, diagnosis requires dissemination of time or space as shown by magnetic resonance imaging (MRI).^{11,12}

Although there is no specific laboratory or radiologic test to definitively diagnose MS, MRI with gadolinium (Gd) has proven useful for imaging cerebral and brainstem lesions and many spinal cord lesions. In patients presenting only with optic neuritis, MRI has frequently demonstrated asymptomatic lesions elsewhere in the CNS.¹³ More current suggested guidelines recommend that baseline brain MRIs be conducted in all patients with suspected MS, as detected brain lesions provide evidence of dissemination in both time and space.¹⁴ If the brain MRI is nondiagnostic or presenting symptoms are at the spinal cord level, a spinal cord scan should also be obtained.¹⁴

According to the revised McDonald diagnostic criteria, MRI evidence that shows dissemination of space must have at least 3 of 4 of the following findings (1 spinal cord lesion can be substituted for certain brain lesions): 1) 1 Gd-enhancing lesion or 9 T2 hyperintense lesions if Gd lesions are not present, 2) at least 1 infratentorial lesion, 3) at least 1 juxtacortical lesion, and/or 4) at least 3 periventricular lesions.¹¹ If a patient presents with a single episode of neurological symptoms and an MRI suggestive of MS, the diagnosis cannot be made because the criteria for dissemination in time has not been met. According to revised McDonald criteria, there are 2 ways to show dissemination of time: 1) the presence of a Gd-enhancing lesion at least 3 months following the initial MRI or 2) the presence of a new T2 lesion 30 days after the initial MRI scan.¹¹

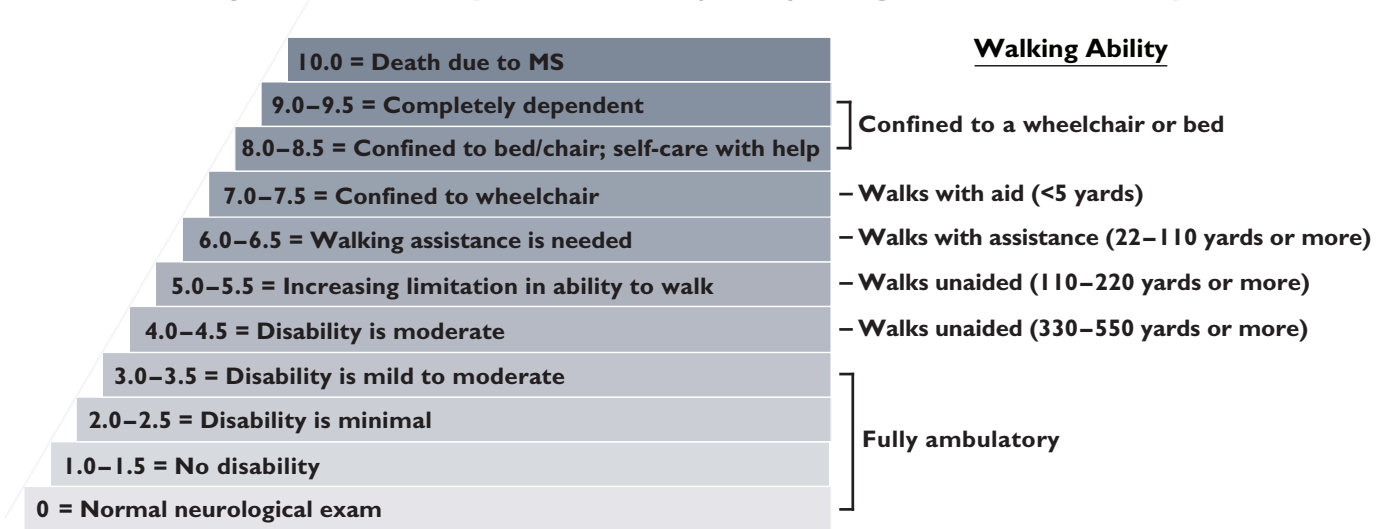
However, despite its usefulness in detecting asymptomatic lesions, there are circumstances when clinical presentation or MRI alone does not allow an MS diagnosis. These include cases in which active evidence of brainstem, optic nerve, or spinal cord disease on neurological examination is absent, a patient presents with fewer attacks or only insidious neurological progression suggestive of MS, or there is clinical evidence of only 1 lesion.⁵ Hence, in cases where clinical presentation is unusual or the imaging criteria are not fulfilled, cerebrospinal fluid (CSF) and/or abnormal visual evoked potential (VEP) testing are used to provide additional diagnostic support.¹¹

Neurological deficit, both at diagnosis and over the course of the disease, can be quantified by the Kurtzke Expanded Disability Status Scale (EDSS).¹⁵ This is a standard scale (0 = normal function and 10 = death due to MS) used to rate the degree of MS-related neurological disability (Figure 1); however, this scale is heavily weighted toward ambulation and may not provide a true picture of the patient's functional status. Another measure that may be used clinically is the MS Functional Composite, which consists of the Paced Authority Serial Addition Test (PASAT), a 9-hole peg test, and a 25-foot timed walk.¹⁶

DISEASE COURSE

The course of MS is unpredictable, differing from patient to patient and within a given individual over time. At one extreme, some patients may have 2 or 3 relapses and never become disabled; rarely, a small number of patients may experience frequent attacks and die within several months of diagnosis.¹³

Many patients diagnosed with MS initially present with clinically isolated syndrome (CIS), an acute episode indicative of pathology in the white matter of the CNS. The presentation of CIS typically involves the spinal cord, brain stem, or a single optic nerve. According to a recent panel of MS experts, CIS should be defined as a single (monophasic) presentation of relatively rapid onset, with the suspicion of underlying inflammatory demyelinating disease; there may be evidence of clinical or paraclinical indications of lesion dissemination in space, but not in time.¹²

FIGURE 1. Expanded Disability Status Scale (EDSS): Progression to Disability

Adapted with permission from Kurtzke J. *Neurology*. 1983;33:1444-1452.¹⁵

Rarely, a patient may present with MRI evidence of abnormalities typical of demyelination but without neurological symptoms; this is called radiologically isolated syndrome or subclinical MS. For such patients, a diagnosis of MS cannot be made using the current McDonald criteria, and further clinical evaluation and follow-up MRI are suggested.¹⁷

Four distinct clinical courses of MS have been identified: relapsing-remitting, primary-progressive, secondary-progressive, and progressive-relapsing.¹⁸ These courses are depicted in Figure 2. The typical pattern, affecting approximately 90% of those diagnosed with MS, is relapsing-remitting at onset, with relapses occurring randomly over many years. Relapses are followed by complete, partial, or no improvement. These unpredictable neurological events constitute an important and distressing element of the disease. During relapse, transient neurological dysfunction occurs, with or without complete recovery.^{19,20}

Secondary-progressive disease begins with a relapsing-remitting course followed by progression at a variable rate, in some cases interspersed with acute attacks. Primary-progressive MS is characterized by progression

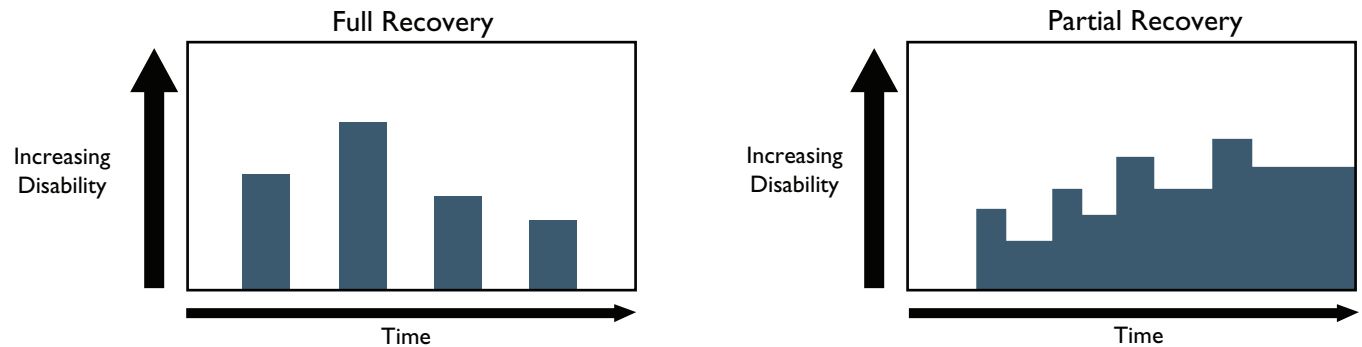
from onset, but without relapses or remissions. This course of MS affects approximately 10% of those diagnosed with MS. Finally, a progressive-relapsing disease course is marked by progression from onset, which is later punctuated by clear, acute relapses.

ADVANCES IN MULTIPLE SCLEROSIS TREATMENT

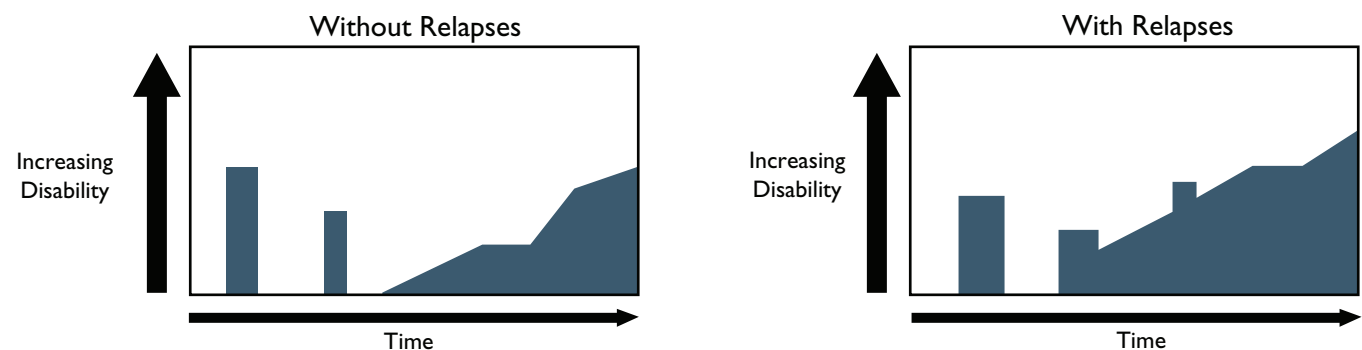
Advances in MS management focus on both disease modification and symptom management. Treatment regimens have become more complex and therefore more challenging to the patient, the care partner, and the healthcare team. An important goal in the nurse–patient relationship is patient and care-partner empowerment. This requires skills and knowledge that the nurse can help provide. Nurses provide education so that patients can make informed choices. In addition, an important part of the nurse's role in caring for people with MS is to ensure that the patient can make informed treatment decisions. Because there is an inherent relationship between the medication a patient is prescribed and the patient's adherence to a treatment regimen, level of cognitive functioning, and quality of life, the disease-modifying treatments available as of this printing are discussed later in this monograph.

FIGURE 2. Types and Courses of Multiple Sclerosis

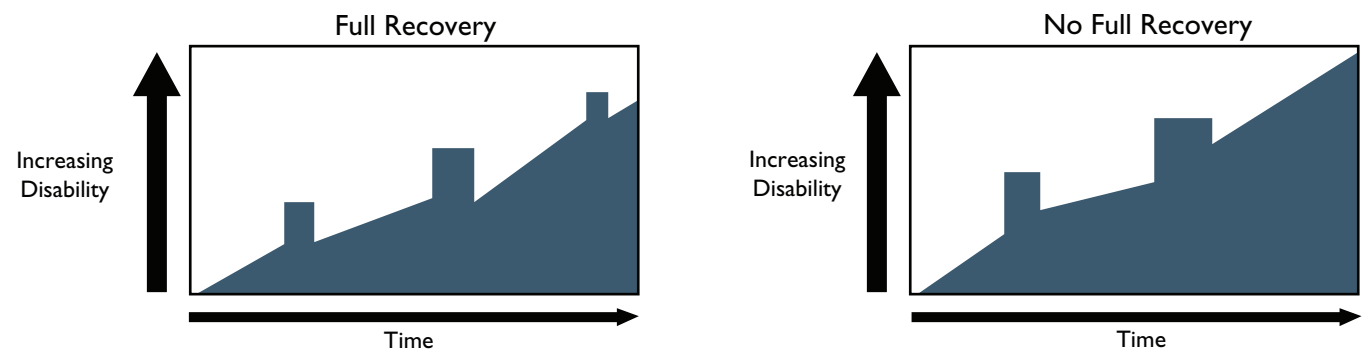
A. Relapsing-remitting



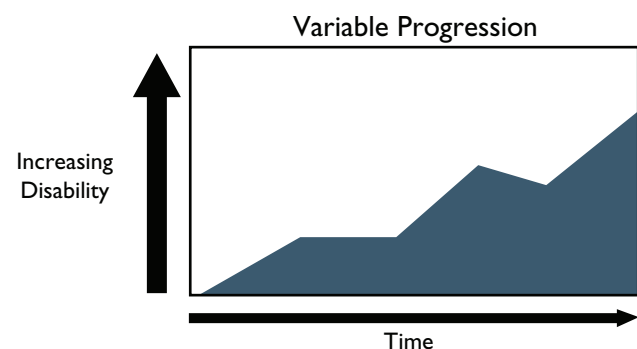
B. Secondary-progressive



C. Progressive-relapsing



D. Primary-progressive



Adapted with permission from Lublin FD, Reingold SC. *Neurology*. 1996;46:907-911.¹⁸

Promoting Adherence to Therapeutic Regimens

Problems with adherence to pharmacologic and non-pharmacologic treatments are well documented in the healthcare literature. Studies of adherence to medication regimens for a variety of chronic diseases typically find mean adherence rates of about 50%, with a wide range of individual results from 0-100%.²¹

Adherence to healthcare regimens presents considerable challenges to chronically ill patients, whose adherence rates in general have been observed to be lower than those with acute illness.²² According to the World Health Organization, patients with chronic disease in developed countries have an average rate of just 50% adherence.^{23,24} In the case of MS, the extent of physical disability and/or cognitive impairment and the complex nature of current treatments make it challenging for even the most motivated patient to adhere to a self-management plan.

THE CONCEPT OF ADHERENCE

The term “adherence” has replaced “compliance” in both the medical and nursing literature and in everyday conversation. The terms “compliance” and “noncompliance” have been described as value-laden, implying the subordinate position of the patient in relation to the healthcare professional.²⁵ In particular, the term “compliance” is incongruent with the essence of the nurse–patient relationship, which has traditionally involved the nurse’s fostering of the patient’s interest and ability to participate in his or her own care. This nurse–patient relationship was exemplified in a conceptual framework developed by Orem.²⁵ Orem’s framework suggests that the degree to which people are able to perform necessary self-care measures determines the degree to which a nurse should be involved in patient care. In other words, if a patient’s ability to meet self-care needs is not adequate, he or she has a self-care deficit. When a self-care deficit exists, nurses must act to help patients meet their therapeutic self-care demands and to promote the patient’s ability to meet demands, within the framework of a genuine interpersonal relationship.²⁵

According to Quigley and Giovenco,²⁶ consistent elements in the various definitions of “compliance” found in the literature include implied power relationships exerted by the healthcare professional over the patient, coercion, and domination. A widely cited definition of “compliance” is that of Haynes and colleagues, who state that compliance is “the extent to which a person’s behavior, in terms of taking medications, following diets or executing other lifestyle changes, coincides with medical or health advice.”²⁷

Because of the negative authoritarian connotations associated with “compliance,” terms such as adherence, therapeutic alliance, consensual regimen, and effective management of therapeutic regimen have emerged.^{25,28}

From the nursing perspective, adherence can best be defined as the active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior that results in a desired preventative or therapeutic outcome. Core elements include partnership, mutually established goals, and a therapeutic alliance.

THEORETICAL PERSPECTIVES

Research into the issue of adherence has focused on explaining how and why patients do or do not adhere to prescribed treatment regimens. Attempts to isolate variables that may influence patient behavior—such as age, gender, and other demographic variables—have not identified a significant correlation between these variables and adherence.²⁸ In contrast, several psychological theories give some insight into adherence and nonadherence.

Self-Efficacy

Self-efficacy or “control,” as defined by Bandura,²⁹ refers to a judgment made by an individual about his or her ability to organize and implement a new, stressful, or unexpected course of action. How individuals perceive this ability is the key to whether a particular task will be accomplished, as perception strongly influences both the expenditure of energy and its duration, especially when an individual is faced with obstacles or unpleasant experiences.³⁰ Accordingly, individuals who persist longer at activities that are perceived to be threatening or negative, such as the preparation and administration of a daily injection, reportedly gain a reinforced and

greater sense of self-efficacy compared with those who give up prematurely and, as a result, retain self-debilitating expectations and fears.^{30,31}

A growing body of evidence suggests that self-efficacy is strongly linked to adherence in a variety of contexts, including continued use of injectable immunomodulatory agents in MS.^{30,31} This is critical, since MS regimens rely upon patients' ability to overcome such complex tasks as preparing and self-administering agents and managing related side effects, even though, as shown in the work by Fraser et al,³² daily therapy does not result in an *immediate* payback but rather the promise of a *future* benefit, ie, fewer relapses. Nevertheless, Fraser and colleagues, in a series of studies involving over 600 MS patients taking glatiramer acetate (Copaxone®), reported that a single unit increase in the Multiple Sclerosis Self-Efficacy Scale (MSSE; an 18-item scale rated 10 to 100, with 10 equating *very uncertain* and 100, *very certain*, indicating how certain individuals are that they will be able to perform specific behaviors) score was associated with an increased likelihood of medication adherence.³⁰⁻³² Patients in the adherent group had significantly greater levels of self-efficacy that persisted for at least 6 months ($P=0.001$).³² For example, individual patients with total MSSE scores of 1800 were 16.4 times likelier to adhere to treatment than individuals with scores of 400.³² When patients were evaluated by MSSE subscales that rated control and function separately, individuals in the adherent group had both a significantly greater belief in their ability to control their MS ($P=0.004$) and in their ability to function with their disease ($P=0.001$) compared with their nonadherent peers.³²

Bandura suggested that successful performance of tasks enhances self-efficacy.³³ With regard to MS patients specifically, education about the preparation and self-administration of injectable immunomodulatory agents, encouragement of hands-on practice in the presence of a nurse or other practitioner, and provision of telephone support can empower individuals to achieve realistic expectations and adhere to their treatment.

Self-efficacy among patients with MS is subject to variables that may include gender and type of MS. In a comparative study of 556 individuals with MS using the MSSE scale, Fraser and Polito reported that women had

a significantly greater belief in their ability to function with MS.³⁴ The study also showed that, in both genders, patients with relapsing-remitting MS (RRMS) reported significantly greater belief in their ability to control their MS and function with it than did those with progressive forms of MS.³⁴ The authors suggested potentially beneficial strategies for self-efficacy including education and support, introduction of role models with MS, physical reconditioning, and referral to a support group.³⁴

Health Belief Model

Many researchers have adapted psychological theories in an effort to help explain adherence. The health belief model, initially developed by a group of social psychologists to explain lack of participation in disease prevention or detention programs, has been expanded to account for patients' adherence to healthcare regimens.³⁵ This model suggests that patients may weigh the advantages and disadvantages of engaging in any action, such as taking a medication.

The health belief model holds that in order to engage in health-related behavior, patients must believe that^{21,36}

- they are susceptible to a particular health problem,
- the problem would lead to serious organic or social problems,
- taking action would reduce their susceptibility to the problem, and
- costs associated with the action are outweighed by its benefits.

Before deciding whether to pursue a health behavior, patients need 2 main types of information: 1) the benefits or potential gains (ie, the extent to which it will reduce the health threat) and 2) the costs (degree of physical, psychosocial, cultural, spiritual, and financial distress associated with a proposed course of action). The results of a recent study of MS patients taking a DMT and the example case below (see Case Study 1) provide examples of how the health belief model may apply to people with MS.

A study by Turner et al³⁷ examined the role of several of these constructs—perceived susceptibility, severity, and benefit—on adherence to DMT among 89 veterans with MS enrolled in a regional VA outpatient clinic.

Six months after an initial telephone interview, adherence was relatively high, with 80% of DMT users achieving 80% adherence. After controlling for disease duration and demographic factors, the investigators found that perceived benefit was the sole health-belief predictor of adherence over time, suggesting that a focus upon the benefits of ongoing DMT may hold promise for enhancing adherence.³⁷

CASE STUDY I

HL is a 35-year-old woman with MS. She had been experiencing urinary urgency and frequency for several months and had been incontinent on two occasions. An initial bladder evaluation demonstrated HL is retaining a postvoid residual volume of 250 mL of urine. Urodynamic studies showed failure to empty because of sphincter dysfunction. The nurse at the MS care center recommended HL learn to self-catheterize. In order to consider this recommendation, HL first had to believe that she might be subject to further episodes of urinary incontinence, retention, and bladder infections; second, she had to acknowledge that not catheterizing could lead to physical discomfort and social embarrassment; and, third, she had to be convinced that self-catheterization would lessen the chance of long-term urinary complications. In summary, in order for HL to decide to learn to self-catheterize, she had to believe that the costs of self-catheterization (disruption of routine, fear and anxiety over procedure, and potential for bladder infection due to technique) were outweighed by the benefit (relief from urinary incontinence and associated social embarrassment). She had to realize that the only way to avoid incontinence and reduce her risk of infections was to self-catheterize regularly.

Other Relevant Psychological Theories

The social learning hypothesis, known as the locus of control theory, states that if people perceive the reinforcement of a behavior as contingent on their own behavior (internal locus of control), they are more likely to repeat the behavior than if the reinforcement is contingent on factors beyond their control (external locus of control).³⁸

One might consider positive health outcomes as the reinforcement for health-promoting behaviors such as

following a treatment regimen. Patients may interpret their health (ie, the reinforcement of health-promoting behavior) as either internally controlled (under their control) or externally controlled (not under their control). For example, a person with MS may fail to adhere to a therapeutic regimen because of an underlying belief that changes in health are not really under his or her own control. Adherence to a therapeutic regimen may be problematic for such a person, since the reinforcement for this behavior (positive health) is thought to be controlled by external forces. On the other hand, persons with an internal locus of control may be more likely to follow a therapeutic regimen, since they perceive their behavior to contribute to their health.

Two particular models of behavior change can facilitate the development of strategies to assist patients with adherence: the *transtheoretical model*³⁹ and the *harm reduction model*.⁴⁰ The transtheoretical model describes the process of change as long-term and dynamic, and incorporates individual variables. Patients move through stages of change, but not always in a linear manner. This allows room for the ups and downs most people experience while attempting to incorporate new self-care strategies into their routine.⁴⁰ The underlying premise of the harm reduction model is that healthcare providers use a nonjudgmental approach when helping patients change behaviors because the individual's dignity and freedom to choose are of prime importance.⁴⁰

Using these models, the stages associated with behavior change are:⁴¹

- precontemplative—aware of the problem, but not planning to change;
- contemplative—ready to change;
- preparation—develops a plan;
- action—progresses toward a goal with support;
- maintenance—goals are reached and sustained;
- relapse—returns to previous behaviors, and feels comfortable that he/she is not being judged.

With its foundational concept that readiness for change is crucial, the transtheoretical model of behavior change can offer a useful tool for reaching treatment goals in MS.⁴² In a study by Berger⁴³ of patients with MS being treated with interferon (IFN) β -1a IM (Avonex®), 4 key

variables accurately predicted 82% of those who discontinued the agent, while correctly identifying 81% of those who were adherent to therapy. These constructs of the transtheoretical model were: “pros” of IFN use, “cons” of IFN use, highest level of education completed, and level of disability.⁴³ Putting theory into practice, Berger compared a software-based phone counseling program based on motivational interviewing and the transtheoretical model of change vs standard care in 366 patients with MS receiving IFN β -1a IM.⁴⁴ (Motivational interviewing, an emerging focus in case management, is an approach to behavior-change counseling that has been shown effective in randomized controlled trials and meta-analyses.⁴⁵) In this study, patients in the intervention group had a significantly lower rate of treatment discontinuation (1.2%) than controls (8.7%).⁴⁴

Implications

Psychological theories have provided researchers with a framework on which to develop “adherence” models and identify key elements in reducing nonadherence. For example, the self-efficacy model highlights the importance of empowering patients to overcome doubts about their ability to achieve challenging tasks or activities when faced with obstacles or adverse experiences. The health belief model highlights the need to present information in a way that convinces the patient that the risk of the illness or health problem is real. The locus of control theory suggests that patients with a strong internal locus of control may be more likely to adhere to treatment regimens, since they believe that adherence may actually make a difference in their health. All theories point to the need for open communication between healthcare professionals and patients, as well as ongoing patient education. The transtheoretical and harm reduction models provide a basic structure upon which healthcare professionals can build a nonjudgmental therapeutic relationship that takes into consideration each individual patient’s desires and needs.

As the healthcare professionals who interact most often with people with MS—either in a hospital, MS center, or home care setting—nurses are strategically placed to help solve the problem of nonadherence. The following sections identify barriers to adherence as they relate to persons with MS, as well as interventions (including

specific ones for DMT adherence) that may enhance patients’ health-related behaviors.

BARRIERS TO ADHERENCE

Nurses must evaluate all aspects of a patient’s situation that may influence adherence, recognizing that an individual’s personality can contribute to the success or failure of the therapeutic interaction. There will be patients who resist any therapeutic intervention or partnership; however, patients’ attitudes and beliefs are dynamic, changing over time. A patient resistant to integrating complicated treatment regimens into his or her life at one time may reassess the situation at a later date. Barriers that can contribute to nonadherence can be loosely grouped into the categories listed in Table 1. Explanations of how these barriers relate to people with MS follow.

TABLE 1.
Barriers That Contribute to Nonadherence

- Communication problems
- Knowledge deficits
- Physical impairments
- Social and cultural variables
- Financial concerns
- Depression and other psychiatric disorders
- Cognitive deficits
- Emotional distress

Communication Problems

The quality of the interaction between patients and healthcare professionals is an important factor. Research has shown that patient satisfaction has a direct effect on adherence.⁴⁶ Dissatisfaction can occur as a result of poor communication on the part of the healthcare provider. Nursing experience suggests that those healthcare professionals who show sensitivity to patients’ verbal and nonverbal communication and who take the time to empathize and understand patients’ feelings facilitate patient adherence, as well as satisfaction.

In many cases patients may not be aware of what is expected of them. Healthcare professionals have their own perceptions of the goals of different therapeutic regimens and, therefore, of what constitutes adherence.

Patients' perceptions may differ radically from those of other patients and from healthcare professionals.

For example, in the case of HL, the patient in Case Study 1, the major goals of bladder management from the nurse's point of view were to maintain renal function, avoid urinary tract infections, and establish normal voiding patterns. Thus, the nurse recommended that HL perform intermittent catheterization at regular intervals throughout the day. HL's major goal, on the other hand, was to avoid incontinence, but she may have been reluctant to catheterize herself regularly. Unless HL had a clear understanding of the importance of regular bladder emptying, she may have chosen not to perform the procedure at the prescribed intervals. She may, in fact, just have done it at those times when it would prove particularly embarrassing to be incontinent.

Expectations play an important part in patients' willingness to adhere to treatment regimens. A patient with unrealistic expectations for a particular medication or treatment regimen is less likely to continue taking it. Thus, it is crucial that the healthcare provider carefully explain not only what a particular treatment does but also what it does not do.

For example, IFN β -1b (Betaseron®) was the first immunomodulator approved for the treatment of RRMS. Phase III clinical trials indicated that the drug reduced the frequency and severity of relapses and decreased the lesion burden seen on MRI.^{47,48} However, although it does reduce the number and intensity of relapses, this agent has not been found to be associated with change in functional status and can be associated with unpleasant side effects.⁴⁹ Before the approval of IFN β -1b, people with MS had been living with a disease that had only supportive treatments. Thus, it is not surprising that the approval of IFN β -1b was accompanied by unprecedented publicity and widespread therapeutic optimism among patients, their families, and the neurological community. In a study of patient expectations of treatment with IFN β -1b, approximately 50% of patients who started therapy had unrealistically optimistic expectations.⁴⁹ Approximately 20% discontinued therapy within 6 months; of these, 64% had overly optimistic expectations. These

findings were further borne out in a survey of 700 MS patients in the North American Research Consortium on MS (NARCOMS) Registry, which demonstrated that 71% of patients taking IFN β -1b discontinued therapy, compared with 40% taking intramuscular (IM) IFN β -1a and 21% of patients taking glatiramer acetate.⁵⁰ Among the various reasons cited for cessation, an increase in symptoms was the most common (21%), followed by a lack of obvious benefit (15%) and flu-like symptoms (14%).⁵⁰

As long-term data on several of the current DMTs become available and with the advent of oral therapies under investigation to treat MS, the role of the healthcare professional in helping patients set realistic expectations of treatments in order to promote adherence continues to be important.

Knowledge Deficits

Patients' lack of knowledge about their symptoms and about treatment regimens can contribute to nonadherence. If patients are not given accurate, easy-to-understand information, they cannot be expected to help in the management of their symptoms. Without all the information necessary to make an informed decision, they may be unable to perform a legitimate evaluation of the benefits of a specific treatment regimen. Knowledge alone does not ensure adherence; even a patient furnished with complete and accurate information may not necessarily understand or integrate it.

Physical Impairments

Some individuals with MS may be physically incapable of taking an active part in their disease management. For example, visual disturbances can interfere with reading instructions and preparing and taking medications. Mobility problems can prevent a patient from accessing clinical services, including rehabilitation centers. Other physical symptoms—such as tremor, fatigue, weakness, and vestibular disturbances—can also impair an individual's capacity to adhere to treatment regimens.

Social and Cultural Variables

A number of social and cultural variables can influence adherence. Social isolation is a major contributor to nonadherence. According to Cameron,⁵¹ the literature

reveals that the stability and support of a patient's family are strongly correlated with adherence.

The stigma associated with a chronic debilitating illness can have a negative impact on patient adherence. Many people with MS may try to hide the existence of their illness from their family (because of fear of alteration of role), from employers (fearing loss of status), and friends (because of fear of rejection). If so, they may be reluctant to adhere to a rigorous management plan calling for self-injection of a medication and participation in physical therapy programs.

Cultural and gender issues also play a role in adherence to management protocols. A woman with MS from a conservative culture may find it extremely difficult to even talk about, let alone perform, intermittent catheterization. A man with MS may be humiliated by his erectile dysfunction and too embarrassed to use any of the devices or drug delivery systems available to relieve the problem.

Financial Concerns

For many patients, limited financial resources preclude a particular treatment regimen. People with MS are often faced with a heavy financial burden. Not only are they expected to take a wide variety of expensive medications, but they frequently need costly equipment such as wheelchairs and transfer devices. At the same time, a patient's income may be restricted because he or she is unable to work due to physical and/or cognitive deficits. In addition, lack of adequate insurance coverage and difficulties navigating the health insurance system can interfere with a patient's capacity to adhere to a comprehensive management plan.

Depression and Other Psychiatric Disorders

People with MS may have concomitant psychiatric disorders. Problems such as borderline personality disorder, bipolar disorder, schizophrenia, and major depressive disorder may affect an individual's willingness or ability to adhere to treatment regimens. Depression is a known risk factor for nonadherence to medical treatment in general; in a meta-analysis of 12 articles published between 1968 and 1998, the odds were 3 times greater that depressed patients would be nonadherent compared with nondepressed patients.⁵² Anxiety and depression

have been reported to diminish adherence in MS.^{24,53} In addition, patients who are substance- or alcohol-dependent frequently do not adhere to their MS therapy.

Cognitive Deficits

Approximately 50% of people with MS experience some degree of cognitive impairment, with some estimates as high as 70%.⁵⁴⁻⁵⁶ Memory loss is the most frequently reported cognitive deficit. Specifically, people with MS have difficulty learning and later recalling new material.⁵⁴⁻⁵⁶ Deficits in information processing speed are also common. A sizable proportion of patients may have visuospatial deficits and/or deficits in executive functions, such as problem solving or planning and sequencing activities.

The implications of these deficits for adherence are obvious—cognitively impaired people with MS will find it difficult to remember to take medications and may have problems carrying out multistep procedures such as self-injection and self-catheterization.

Emotional Distress

Emotional distress associated with a variety of stressors (both MS-related and other life stressors) can impair motivation or ability to adhere to treatment regimens. Heightened emotional distress is commonly reported. The diagnosis of MS carries with it an emotional impact that is lifelong. At various times, patients diagnosed with a chronic illness may experience fear, anger, denial, anxiety, depression, and hopelessness. These emotions may hinder motivation to take medications or perform complicated tasks designed to improve patients' well-being.

ADHERENCE TO DISEASE-MODIFYING THERAPIES

Although the availability of DMT agents has ushered in a new era in pharmacologic management of MS, this class of agents carries with it a distinctive set of adherence challenges. Patients are asked to learn and practice complex self-injection regimens with costly medications that may produce uncomfortable or disturbing short-term side effects, such as flu-like syndrome or injection-site reactions, in order to reap less tangible long-term benefits, such as reduction in relapse rate or delay in progression to disability (but not imme-

diate symptom relief).²⁴ The nurse plays an integral role in initial acceptance and ongoing management of immunomodulatory therapy.

Until recently, few investigators had collected systematic information on long-term adherence rates to DMTs outside the clinical trial setting, or attempted to elucidate reasons for non-adherence. The Global Adherence Project surveyed neurologists and 2,566 patients with MS at 179 sites in 22 countries; in this population, 25.3% of DMT users were nonadherent.⁵⁷ In this study, the rate of adherence was significantly higher for patients receiving IFN β -1a IM than for patients receiving all other DMTs ($P < 0.01$). A literature review by Costello⁵⁸ reported that approximately 60% to 76% of patients with MS were adherent to treatment with IFN β or glatiramer acetate for 2 to 5 years, with the majority of those who discontinue DMT doing so within their first 2 years of treatment.

Predictors and Causes of Nonadherence

Barriers to adherence cited by Costello included problems with injecting, perceived lack of efficacy (often based on unrealistic treatment expectations for symptomatic relief), and adverse effects.⁵⁸ The studies examined by Costello reported that between 14% and 51% of patients discontinued therapy due to adverse events—typically, flu-like symptoms, depression, and injection-site reactions for IFN β users; injection-site reactions, vasodilation, tachycardia, tremor, and depression in glatiramer acetate users; and lipoatrophy in the latter group.⁵⁸ Complacency, treatment fatigue, and deteriorating injection skills were other possible barriers cited.⁵⁸

In a multicenter observational study by Treadaway et al,²⁴ 798 patients with MS were surveyed via the Internet at baseline to identify factors in nonadherence to DMTs, with 708 respondents completing follow-up surveys at months 1 and 2. Rates of nonadherence, defined as missing 1 or more injections, were sustained at 39%, 37%, and 36% at the 3 time points. Among patients who missed injections, the most frequently given reason was simply forgetting to take the medication (offered by 58% of nonadherent respondents). Other reported factors included not feeling like taking the medication (22%), being tired of taking the injections

(16%), injection-site pain (7%), injection-related anxiety (3%), and absence of a helper for administering the medication (4%).²⁴ The survey included users of all 3 IFN β preparations and glatiramer acetate; flu-like side effects were a deterrent in nonadherent IFN β -treated patients, but not in those taking glatiramer acetate.²⁴

This survey did not solicit perceived reasons for forgetting a dose, although the authors mentioned the possible role of cognitive impairment in an MS population.²⁴ In the Global Adherence Project, forgetting was also the most common reason given, cited by 50% of nonadherent respondents.⁵⁷

Predictors of Adherence

Self-efficacy, self-esteem, hope, and perception of benefit have emerged as predictors of adherence.^{31,37,58} In a longitudinal study of 101 individuals with RRMS who were self-injecting IFN β -1a, patients' pretreatment expectations of self-efficacy significantly related to 6-month adherence.⁵³ Adherence correlated with sense of control over MS through treatment, higher levels of hope, and no prior use of other DMTs in a study of glatiramer acetate users.³¹ Treadaway's survey noted that certain patient characteristics were associated with adherence, including older age at disease onset and disease duration of less than 3 years (but not length of time on therapy). Patients undergoing their first treatment with DMT were more likely to be fully adherent than those who had previously used another injection therapy.²⁴

The Toll of Nonadherence

The consequences of nonadherence on the long-term impact of disease-modifying therapy are unclear, but missed doses or discontinued therapy may negatively affect the efficacy of treatment. One study showed that patients with RRMS who discontinued therapy had a significantly higher EDSS score at follow-up than patients who adhered to treatment, with a significantly lower proportion of relapse- and progression-free patients among those who ceased therapy.⁵⁹ In the Global Adherence Project, adherent patients reported better quality of life, less cognitive impairment, and fewer problems with injection-site reactions than nonadherent patients.⁵⁷

NURSING INTERVENTIONS THAT FACILITATE ADHERENCE

As the main conduit for the dissemination of information from other members of the healthcare team to patients, nurses have a great opportunity to enhance patient adherence. Specific ways in which nurses play an important role in facilitating adherence are discussed below and summarized in Table 2.

TABLE 2.
Nursing Strategies That Facilitate Adherence

Fostering the Nurse–Patient Relationship

- Take the time to empathize and sympathize
- Establish a trusting relationship
- Establish a sense of support (availability and accessibility)
- Be sensitive to and provide necessary support for cultural/body image/gender differences

Educating Patients

- Provide understandable information regarding benefits/side effects, risks of therapy
- Give simple, structured instructions
- Provide care partners with instructions
- Encourage use of tape recording, memory notebook, etc.
- Furnish a nondistracting environment
- Offer reinforcement

Enhancing a Patient's Support Network

- Facilitate access to healthcare system
- Facilitate access to home healthcare agencies
- Involve care partners/home care nurses
- Refer to a physical/occupational therapist
- Involve family and friends in care
- Suggest phone contact with other professionals
- Provide community resource material (eg, National Multiple Sclerosis Society)
- Interact with case managers, insurance providers, pharmacies, access programs
- Refer to social worker, physical/occupational therapist, church group, vocational rehabilitation
- Contact pharmaceutical company-funded patient support programs

Setting Realistic Expectations

- Help patients prioritize interventions
- Utilize hopeful approaches
- Offer options
- Present coping strategies (relaxation, deep breathing, visualization, etc)
- Consider concomitant illnesses (eg, psychiatric disorders)

Fostering the Nurse–Patient Relationship

Nurses who specialize in caring for people with MS are crucial to the comprehensive management of these patients. Intimacy is vital to the relationship, which evolves over time. Long-term consistency of the relationship is helpful but cannot always be guaranteed, particularly in settings such as a hospital or outpatient department. However, the nurse and patient can define expectations of the relationship. Before setting mutually agreed-upon goals, it is important that the nurse ask the patient about his or her experience with following treatment plans in the past. This may offer an indication of what goals can be accomplished in the future and, thus, establish a sense of realistic hope.

Trust is an essential element of the nurse–patient relationship. Because of the possible social stigma and lifestyle disruption associated with the disease, a person with MS must know that whatever he or she says will be treated confidentially. The nurse agrees not to discuss the patient's illness with the patient's employers, family members, or friends unless given explicit permission to do so. Trust is enhanced by the nurse's availability and unconditional caring, offered in an environment of acceptance.

Nurses nurture a partnership between themselves and their patients. This partnership often includes families and other caregivers and recognizes patients' motives and priorities. Nurses empower patients and their families to make informed decisions by sharing their expertise and supporting the patient's priorities and decisions.

Educating Patients

It is essential that patients obtain the knowledge necessary to perform recommended self-care behaviors. Given that many patients have some degree of cognitive impairment, educating people with MS can be a challenging experience for nurses. Patients frequently ask the same questions repeatedly or fail to carry out specific procedures correctly. Written or audiovisual instructions that can be taken home and referred to as necessary can be helpful in these situations, as can involving the family or caregiver in assisting the patient. Patients should not be considered capable of performing a particular procedure until they have performed it in the nurse's presence.

Simple, understandable, and complete instructions are critical. For example, people with MS should not be expected to undertake an exercise program without having been explicitly told the type and frequency of exercises to be performed.

People with MS are expected to learn to incorporate complicated, and sometimes intrusive, treatment regimens into their lives. Any way that the nurse can make this easier for patients will help encourage adherence. Learning about the patient's typical daily routine and identifying ways in which treatments can be incorporated into existing activities can facilitate adoption and maintenance of new therapeutic regimens. Providing patients with a written schedule of treatments, physical therapy, and doctor appointments can be helpful in encouraging adherence, as can the use of memory notebooks and reminder calls. Regimens should be simplified and should include as few lifestyle changes as possible. Patients should be made aware of pharmaceutical company-funded patient support programs that provide education materials and advice on immunomodulating agents.

The amount and type of information are not the only factors involved in a patient's ability to comprehend and process. Many nurses find that the environment in which the patient learns the information makes a difference. It may be beneficial to teach patients difficult treatment regimens—such as self-administration of an injectable agent or self-catheterization—in the home. If a patient learns a procedure in the place where it is to be performed regularly, barriers to adherence can be identified and the learning process facilitated. Reinforcement and acknowledgment of success are crucial. When a person with MS successfully manages to adhere to a self-injection regimen or to control bladder symptoms, the nurse reinforces the idea that the efforts are paying off, augmenting the patient's sense of control.

Enhance Patient's Support Networks

Emotional and spiritual support influences patient adherence. Therefore, it is important to include the family in the management plan when appropriate. Should a person with MS have no social support or network on which to rely, the nurse can make a referral to

a support association. The National Multiple Sclerosis Society (www.nationalmssociety.org) and other advocacy groups such as the MS Association of America (www.msassociation.org) and the MS Foundation (www.msfacts.org) can provide valuable support and networking opportunities for people with MS.

MS specialty centers and clinics offer inpatient and outpatient rehabilitation programs, lifestyle change classes, and support groups.⁴⁵ For patients who may face geographic, economic, or logistical barriers to support resources, relatively simple health-promotion interventions such as telephone counseling have shown promise in improving quality of life with MS.⁴⁵ In one randomized, controlled trial of 130 individuals with MS, an in-person motivational interview followed by 5 telephone counseling sessions over 12 weeks was the protocol used to help patients improve a health-promotion area of their choice (exercise, fatigue management, communication and/or social support, stress management, and reducing alcohol or other drug use). The study excluded patients with major depression or disability, and used waitlisted patients as a control group. After 12 weeks, the treatment group reported significantly greater improvement in their target area as well as in fatigue impact and subjective mental-health measures.⁴⁵

Nurses can direct patients to agencies that will allow them to maximize their health insurance opportunities. The increasing use of nursing case managers by managed care organizations can benefit people with MS. These case managers develop contacts and resources within the community that can reduce obstacles to adherence. Case managers can recommend that patients try to obtain expensive medications through subsidized access programs and help them in their decisions regarding the amount and type of equipment needed to facilitate activities of daily living.

Assist Patients to Set Realistic Expectations

Because MS is a disease with no cure, the availability of disease-modifying agents has raised the hopes and expectations of people with MS and their families. Patients frequently have unrealistic expectations of what the new agents, symptomatic medications, and alternative therapies can do for them. They may also have

unrealistic expectations that more traditional treatments, such as physical therapy programs, will restore functional ability. Thus, nurses must give patients all the information they can—positive and negative—about treatment options. Realistic expectations of treatments must be reinforced once treatment regimens have begun and should be revisited during subsequent telephone and face-to-face conversations.

Closely associated with the need to set realistic expectations is the need to provide patients with options whenever possible. For example, patients may adhere to a physical therapy program better if they have a choice of exercises or locales. Some may find it inconvenient to go to a center or outpatient department, preferring in-home physical therapy; others may welcome the opportunity to get out of the house and attend a center for physical therapy.

Patients with concomitant illness may find it more difficult to adhere to multiple regimens or tolerate treatments. The overall MS management plan must take into account concomitant conditions, including psychiatric disturbances, and the compounded negative effects. In such a situation, DMT side effects can be particularly problematic.

DMT-Specific Management Strategies

Treatment with DMTs has become a standard of care in MS, but many patients will discontinue therapy temporarily or permanently at some point during the course of their illness.⁶⁰ In one longitudinal study with a mean follow-up of 2.5 years, more than one-quarter of patients with MS taking a DMT ceased therapy, one-quarter missed doses repeatedly, and almost three-quarters missed at least some doses.⁶¹ In addition to the above-mentioned barriers to adherence, DMTs present particular issues, including injection anxiety, adverse events, and perceived lack of efficacy, that can be ameliorated by the nursing team in partnership with the patient.⁶²

Optimizing adherence to DMTs must begin with the selection of appropriate therapy, followed by effective patient education, not only on the technical procedures related to self-injection, but on realistic expectations for

the outcome of therapy (such as reduced frequency of relapses, reduced number and volume of new MRI lesions, and delay in progression of disability).⁶⁰

Injection-related Issues. Initial and ongoing counseling should respond to the aspects of self-injection that seem likely to impede adherence in an individual patient. Mild to moderate injection anxiety, for example, can be managed by education to allay fears related to injection safety, and also through more intensive tools such as training in relaxation techniques and cognitive reframing (modifying thoughts to make them more accurate and useful).⁵⁸

Adverse Events. The interferon DMTs are commonly associated with injection-site reactions, flu-like symptoms, headache and depression; injection-site reactions such as pain, swelling or redness are more likely with subcutaneous (SC) than IM injections. Adverse effects linked to glatiramer acetate include immediate post-injection reactions (flushing, anxiety, dyspnea for approximately 30 minutes) and injection-site reactions, as well as the possibility of lipoatrophy, the localized loss of fat at an injection site.⁶⁰

Management of injection-site reactions begins with sensitive instruction on self-injection (including correct technique, hygiene, and rotation of injection sites).⁶⁰ The availability of autoinjectors and newer, thinner-gauge needles (30-gauge for IFN β -1b and 29-gauge for glatiramer acetate and IFN β -1a SC) may ease some patients' aversion to self-injection.^{63,64} Pain and swelling at the injection site may be managed with brief local application of ice or warm compresses before and after self-injecting.^{62,65} In a randomized crossover study of 50 patients taking glatiramer acetate therapy, application of a warm compress to the injection site before self-injection significantly lowered the incidence of local injection-site reactions.⁶⁵

Flu-like symptoms associated with IFN β tend to occur within 2–6 hours of the injection and resolve within 24 hours. Counseling should emphasize that symptoms are usually transient. Constructive suggestions may include titrating DMT dosage (starting on 1/4 of a full dose, increasing to half the full dose after 2 weeks,

and reaching full dose at 4 weeks);⁶² timing injections so that symptoms may occur during sleep, or medicating before or after injection with nonsteroidal anti-inflammatory drugs, acetaminophen, or low-dose steroids.^{58,60} Post-injection reactions to glatiramer acetate, with flushing, chest tightness, dyspnea, and anxiety, may last for some 30 minutes after injection; the reactions are not known to have any serious sequelae, and patients should be counseled that they are self-limiting and transient.⁶⁰

Industry-sponsored nursing support programs may also benefit adherence.⁶² According to Schapiro, one such program (the BETA Nurse program for patients taking IFN β -1b) reported that only 2.1% of the more than 10,000 patients enrolled in the program up to that point had reported discontinuation of therapy due to flu-like symptoms, 0.8% due to injection-site reactions, and 1.7% due to perceived lack of efficacy.⁶⁶ The program consisted of initial phone counseling and training with frequent follow-up calls and/or visits, with patients encouraged to use autoinjectors, dose titration, rotation of injection sites, and NSAIDs or other therapy as prescribed to manage adverse events. Similar measures to minimize the impact of adverse effects were used in the BENEFIT study of early IFN β -1b; adherence to study medication was reported as excellent in the placebo-controlled phase of the trial, with 96% of patients choosing to receive open-label treatment in the follow-up study.⁶⁷

CONCLUSION

Patients with MS have a variety of physiological and, in many cases, psychological and cognitive deficits. Adhering to a treatment plan can help stabilize the disease and relieve symptoms to some extent. It is vital for nurses to identify barriers to adherence and to develop strategies that promote adherence. Strategies that enhance self-efficacy, knowledge, communication, and realistic expectations are vital to long-term adherence. Nurses must be aware of potential financial issues, psychological stress, and the availability of social support. Nurses, based upon their knowledge and skills, are in the best position to address adherence issues. Case Study 2 highlights some of the points raised in this section.

CASE STUDY 2

BE is a 42-year-old man recently diagnosed with RRMS. He requested that his neurologist prescribe one of the disease-modifying agents. After discussing the options with BE, the neurologist prescribed glatiramer acetate and asked the MS nurse to talk to BE about the regimen. An appointment was made for BE to return with his care partner for further education. To learn something about the patient's previous experience in adhering to treatments, the nurse asked BE if he had ever taken medication on a regular basis. BE replied that he had been prescribed antibiotics and generally did not complete the course because "he felt better halfway through." The nurse asked BE what his therapeutic expectations of glatiramer acetate were. He said he knew that the drug was not a cure, but hoped that it would help reduce the physical disability he had been experiencing. The nurse explained that glatiramer acetate might reduce the frequency of relapses, but it would not restore him to his prior level of ability. She then explained that BE may experience some mild side effects, such as an injection-site reaction, and that, in rare instances, some patients experience an immediate postinjection reaction, characterized by signs and symptoms that include flushing, palpitations, chest pressure, and difficulty in breathing. She assured BE and his care partner that these side effects, if experienced, were transient. The nurse provided the patient with current information about long-term outcomes with sustained use of glatiramer acetate and emphasized that the implications of sustained use were positive in the study. She suggested that this might help the patient plan for at least 1 year of injections with regular opportunities for individual follow-up. She demonstrated the injection technique and asked BE if he would feel comfortable having to give himself a daily subcutaneous injection. He said that he would try, and after demonstrating the technique again, the nurse asked BE to practice on himself. She also asked the care partner to participate in the training. Once she felt confident that they had mastered the technique, the nurse provided BE and the care partner with written instructions. In keeping with the nurse's philosophy of sustained support, she followed up with weekly telephone calls until she felt that BE was comfortable with the procedure. She continued to call monthly until his checkup at 3 months. Finally, the nurse assured BE and his care partner that she would be available by phone to answer questions and address any

concerns. In addition, the nurse provided the contact information for the industry-supported “helpline” as another mechanism to help sustain long-term adherence.

An open, trusting nurse–patient relationship is critical to long-term adherence. Recent anecdotal evidence from the pharmaceutical industry supports the importance of nursing education and sustained nurse–patient relationships for patients receiving self-injected therapies.

Historically, the nursing profession has espoused the promotion of patient independence and self-care. The dynamic, uncertain, and complex nature of MS presents nurses with unlimited opportunities to provide practical, problem-solving information that will help patients and their families cope with the demands of the illness and its treatments. By encouraging people with MS to participate in the management of their care, nurses empower patients with a sense of control and facilitate psychosocial adaptation to this disease.

Cognitive Impairment: Assessment and Interventions

The symptoms of MS vary from patient to patient and within a patient over the course of the disease. This variability is not limited to the degree of physical dysfunction, but also includes the pattern and severity of cognitive dysfunction. In the majority of people with MS who have cognitive deficits, the impairment is mild to moderate.⁶⁸

Estimates of the prevalence of cognitive impairment among people with MS range from 40% to 70%.^{55,69,70} Cognitive deficits may occur early in the course of the disease in the presence of minimal physical changes, and thus may have little or no correlation with disease severity and duration.^{68,71-75} In up to 20% of patients, cognitive deficits are severe enough to disrupt activities of daily living, family and social relationships, and working ability.⁶⁹ Research suggests that although 60% of people with MS are working when diagnosed, only 30% or less are working after 10 years. Many of those who stopped working reported having done so because of physical and cognitive impairments associated with MS.⁷⁶⁻⁷⁸

Even relatively mild and subtle cognitive deficits may have an impact on patients' day-to-day lives; therefore, assessment of cognitive function should be part of initial and ongoing assessments of people with MS. Time constraints of the neurologist and the nurse generally preclude extensive cognitive screening of all newly diagnosed patients. Furthermore, it is neither practical nor cost-effective to refer all patients for a full neuropsychological evaluation. Accordingly, researchers have identified short, MS-specific screening batteries for use in the clinical setting in these cases. As the healthcare professional with the most regular contact with patients, the nurse plays a pivotal role in recognizing the signs of cognitive problems, identifying the need to refer patients for formal evaluation, and monitoring progress of these deficits and effectiveness of interventions.

THE NATURE OF COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS

In general terms, cognitive impairment refers to adverse changes in the high-level functions carried out by the human brain, including comprehension and use of speech; visual perception and construction; calculation ability; attention; memory; and executive functions such as planning, problem solving, and self monitoring.⁷⁹ Cognitive functions that may be affected in people with MS are listed in Table 3.⁸⁰ Recall memory may be impaired in people with MS, but recognition memory is usually preserved. Attention span and information-processing speed, executive functions, and visuospatial perception may also be affected.^{79,81} However, people with MS perform normally, or with minimal impairment, on tests of general intelligence, language, attention span, and implicit memory.⁷⁹

TABLE 3.
Cognitive Functions Affected in People With Multiple Sclerosis

- Memory (both learning and recall)
- Attention and concentration
- Speed of information processing
- Comprehension of information
- Word finding
- Abstract reasoning
- Executive functions
- Visual perception and constructional ability

RESEARCH PERSPECTIVES

Cognitive function is seldom assessed routinely in clinical practice or clinical trials.⁸² There is a dearth of in-depth studies of cognitive impairment in MS, and a lack of guidelines for its assessment and management.⁸² In the past, the prevalence of MS-related cognitive impairment has often been underestimated, primarily because of the use of insensitive diagnostic procedures such as the 5-minute "bedside mental status" exam.^{83,84} However, some abbreviated batteries for cognitive evaluation have been proven to be rapid, reliable, and sensitive tools to detect MS-related cognitive impairment.⁸⁵⁻⁸⁷ Historically, studies of prevalence using academic medical centers rather than community-based samples may actually result in overestimates, since such centers tend to attract more severely disabled patients.

Using sensitive neuropsychological instruments in representative patient samples suggests that approximately half of the MS population experiences some degree of cognitive impairment.^{54,69,71,88,89} Recent studies suggest that single cognitive testing instruments, predominantly measures of information-processing speed, may actually work better than extensive and lengthy batteries to screen for overall cognitive impairment.⁹⁰

In addition to the prevalence of MS-related cognitive deficits, researchers have investigated the relationships between

- the extent of neuropsychological impairment and indices of neurological disability (eg, EDSS score),
- the duration of illness and severity of cognitive dysfunction,
- the course of MS (ie, chronic progressive vs relapsing-remitting) and cognitive impairment,
- specific MS-related findings on MRI and the type of cognitive deficits.

There have been anecdotal reports of a relationship between menopause and the development of cognitive deficits. More study is still needed to determine the significance of this relationship, and to investigate the relationship between aging and the development of cognitive impairment in people with MS.

Contrary to popular assumptions, people with MS who have minimal sensory and motor impairment are also at risk of cognitive impairment.⁸³ Significant cognitive dysfunction has been detected in approximately half of patients with recently diagnosed MS and/or clinically isolated syndrome suggestive of MS.^{75,91} Studies to date have reported some correlations between the extent of cognitive impairment and indices of disability, such as the EDSS.⁸³ In one study, a group of patients with mild physical disability (mean EDSS score of 2.6) scored significantly worse on tests of memory than did normal controls. Almost 50% of the patients with MS in the study were cognitively impaired.⁷² In an early cluster-analysis of people with MS, one subgroup was cognitively impaired but had minimal neurological disability in other functions (mean EDSS score of 2.2).⁹² In the COGIMUS Study, cognitive impairment was found in about 20% of mildly disabled patients with MS (EDSS

Score 4.0 or lower), and EDSS scores were significantly higher in patients with cognitive impairment than in cognitively unimpaired patients.⁹³

The evidence regarding the correlation between degree of cognitive impairment and disease duration is contradictory. Some researchers have found a significant, albeit low, correlation between these 2 variables,⁶⁸ whereas other researchers have not.^{72,73,89} In a prospective cohort of 44 patients with CIS (n=15) or any type of MS (n=29) for less than 10 years, verbal memory performance was found to deteriorate after 2 years whether patients were stable or active in terms of relapse and disability progression, regardless of cognitive impairment at baseline.⁹⁴ So far, study results suggest that cognitive and neurological deficits do not necessarily develop in parallel, at least in patients still in the early phase of MS.

The relationship between disease course and cognitive impairment is also ambiguous. Some studies have demonstrated that people with primary-progressive MS (PPMS) are significantly more likely than those with RRMS to experience cognitive impairments,^{71,72,95,96} while other studies have not.^{68,84} A small study of patients with PPMS using MRI by Ukkonen found similar cognitive impairment to that in patients with secondary-progressive MS.⁹⁷ In general, patients with PPMS perform worse on memory tests than patients with RRMS.⁹⁸ However, patients with PPMS are often older and have had the disease longer than patients with RRMS.⁹⁸ Those with accumulated disability may also be limited in their testing performance by visual and motor dysfunction.

Research has identified a variety of clinicopathological correlates between MRI parameters and cognitive deficits in MS.^{71,99-104} Nearly all people with MS have abnormal MRI findings, although the overall amount of brain involvement and the sites of lesions vary considerably from patient to patient. MRI findings associated with cognitive deficits may involve changes in white matter lesions, in normal-appearing brain tissue on conventional MRI, in cortical matter, and in deep gray matter.¹⁰⁵

MRI studies have demonstrated modest relationships between lesion load and location and cognitive dysfunction. Correlations have been found between lesions in

the corpus callosum and the speed of information processing, as well as rapid problem solving.¹⁰⁶ Other work by Pozzilli and colleagues showed poor performance on tests of verbal fluency in patients with atrophy of the anterior third of the corpus callosum.¹⁰² Frontal lobe lesions have been thought to affect certain cognitive domains such as conceptual reasoning.¹⁰⁰ Periventricular lesions may be associated with deficits in memory.¹⁰² In a small study of 37 MS patients, periventricular lesions were significantly related to decreased psychomotor speed, and third ventricle width (measure of central atrophy) was a substantial predictive value for cognitive dysfunction.¹⁰⁷ Brain atrophy has also been proposed by Lanz and others as a tool for monitoring disease progress, since axonal injury and loss may be critical aspects of both disability and cognitive impairment.¹⁰⁸

While these and other findings have yet to be strong enough to be relied upon to accurately predict the extent and severity of cognitive deficits for individual patients, more reports continue to elucidate the association between MRI findings and cognitive deficits. In a study of 60 patients with RRMS, Karlinksa reported a correlation between total lesion volume (TLV) and presence of selective and overall cognitive impairment.¹⁰⁹ In one study by Summers, a set of 30 patients with RRMS underwent MRI at baseline and 1 year; then underwent neuropsychological assessment 5 years later; the rate of global brain atrophy in the study's first year accounted for significant variance in overall cognitive performance, memory, and attention/speed of information processing at follow-up.¹¹⁰ Summers also reported on a group of 62 patients with CIS, in whom baseline MRI variables predicted development of cognitive problems as assessed 7 years later.¹¹¹

THE ROLE OF NEUROPSYCHOLOGICAL EVALUATION

Compared with standardized neuropsychological tests, bedside mental status examinations are generally insensitive to the cognitive deficits associated with MS. Thus, cognitive impairment frequently goes undetected by treating neurologists.¹¹² Formal neuropsychological evaluation by a neuropsychologist provides important information regarding cognitive dysfunction. Two widely used and validated test batteries, the Rao Brief Repeatable Neuro-

psychological Battery (BRNB) and the Minimal Assessment of Cognitive Function in MS (MACFIMS) were recently found comparable in sensitivity in a study of 65 patients with MS and 46 controls.¹¹³ Some researchers suggest that in those cases where formal neuropsychological evaluation is not indicated, smaller batteries of sensitive screening tests should be performed.^{69,83,85-87}

The issue of whether to perform neuropsychological evaluation of a person with MS is complicated by the fact that cognitive deficits may be threatening to a patient.⁸³ Newly diagnosed patients may be devastated by the prospect of cognitive dysfunction. On the other hand, those who have had the disease longer and have experienced deficits without understanding their cause may be relieved to know that these problems are a result of their MS.⁸³

The nurse may need to provide information regarding the examination itself, length of testing, and materials that patients need to bring, such as reading glasses. The clinician can assess any special needs or characteristics of the patient, such as an affective disorder; that might alter the test results or necessitate a postponement of the evaluation. It is important for clinicians to realize that the functional impact of particular cognitive deficits identified by such a test may vary, depending on the patient's premorbid level of functioning and coping abilities, employment status and settings, and social support network.⁸³ Neuropsychological evaluation, through either comprehensive testing or screening batteries, is a valuable tool. In addition to clarifying the presence and severity of cognitive impairment in people with MS, it provides information critical to the management of patients. In many instances, families and caregivers incorrectly attribute a patient's cognitive problems to obstinacy, depression, or other forms of emotional disturbance.⁷⁰ Identification of cognitive strengths and weaknesses allows clinicians to give patients and their families a clearer picture of the impact that MS may have on their lives. It also allows all those involved in the care of people with MS to optimize the patient's capacity for living an independent, active life.⁸⁸

COGNITIVE REHABILITATION

Formal treatment options for cognitive deficits are limited.¹¹⁴ Patients with global cognitive impairment,

particularly memory deficits, are unlikely to benefit from standard psychological interventions; therefore, the aim of counseling in these cases is to educate the patient and family about ways to adjust to cognitive deficits.

It is not clear whether medications improve attention or memory deficits,^{115,116} although data suggest that DMTs may help prevent or delay the onset and severity of cognitive impairment related to disease progression.¹¹⁷ In the open-label extension study of a pivotal trial for glatiramer acetate, most patients with RRMS had stable cognitive performance over 10 years of prospective follow-up, possibly reflecting the benefits of the medication on disease burden or progression.¹¹⁸ In a prospective, year-long, open-label study of 16 patients with RRMS, Flechter evaluated the effect of IFN β -1b on cognitive function and clinical course; DMT therapy showed a positive effect on cognitive impairment, independent of EDSS score and disease course.¹¹⁹ Similarly, results from an ongoing study of patients receiving natalizumab (Tysabri®) revealed a significant improvement in cognition, as assessed by the Medical Outcomes Study Cognitive Functioning Scale, after 3 infusions of the agent.¹²⁰

Trials with amantadine, pemoline and modafinil, agents used as off-label treatments against fatigue in MS, have not shown consistent beneficial results on cognition.¹²¹⁻¹²³ Acetylcholinesterase inhibitors used to treat Alzheimer's disease, including donepezil, rivastigmine, and galantamine, have attracted interest for their potential to treat other forms of cognitive impairment, including that experienced by MS patients.¹²⁴ Despite an earlier pilot trial that showed benefit of donepezil on memory in patients with MS,¹²⁵ no benefit was observed in a larger, multicenter trial of 120 patients with MS who received either donepezil or placebo.¹²⁶ Clearly, further study of MS cognitive dysfunction with donepezil as well as other agents currently used to treat cognitive dysfunction associated with Alzheimer's disease is warranted.

O'Brian has stated that cognitive rehabilitation in MS is in its relative infancy, with more research needed to discern effective interventions.¹²⁷ Treatment for cognitive dysfunction in MS is either directed at compensation for deficits, or it is restorative, looking at strategies to

improve performance. Restorative approaches include procedures such as memory drills designed to strengthen memory functions and exercises to improve information processing, speed, and efficiency.¹²⁸ To some extent, direct retraining is based on the assumption that the human brain has a certain amount of "plasticity" and, if properly challenged through systematic, graded practice, may be able to regain some of its losses. Many of the exercises based on the retraining hypothesis have produced improvement on some measures in patients with head injury or MS. However, this approach has been disappointing in its failure to have an impact on performance of everyday activities. Apparently, the brain does not have the ability to recover lost cognitive functions as easily as was originally thought.¹²⁹

During the past decade there has been a gradual shift in emphasis toward compensatory methods, such as the use of organizational strategies, filing systems, notebooks, and other aids. Compensatory methods do not attempt to restore impaired cognitive abilities. It is assumed that these abilities may not in themselves improve, although fluctuations are possible because of the nature of the disease and treatments. Instead, the focus is on how the individual can function more effectively in everyday life.

Most cognitive rehabilitation programs utilize a combination of direct retraining and compensatory measures specifically geared to the needs of the individual patient.¹²⁸⁻¹³² Cognitive rehabilitation is now available to MS patients, and while there is limited research evidence on the value of cognitive rehabilitation in MS, it has shown some potential in early trials. A management program reported by Brissart was designed to improve cognitive deficits through exercises to stimulate preserved functions, and to develop new abilities to compensate for cognitive disabilities; the program, evaluated in 24 patients with MS over 6 months, yielded encouraging results on tests of verbal and visuospatial memory and verbal fluency as well as quality of life.¹³³

IMPACT OF COGNITIVE DEFICITS

Patients in whom cognitive impairment is the major disabling feature have higher unemployment rates.⁷⁰ In

addition, there is anecdotal evidence that these patients have more family instability, suboptimal adherence to treatment regimens, and more chaotic interactions with clinic personnel than do patients with primarily motor deficits.⁶⁸ A report by Kalmar suggests an association between cognitive and functional deficits in patients with MS.¹³⁴

Formal research has shown that cognitive impairment may exert a profound negative effect on daily activities among people with MS.⁷⁰ Impaired memory and attention deficits can make activities such as learning a new task or reading a book difficult or even impossible. Patients may forget appointments, lose objects, and have trouble following the plot of a movie.⁵⁶

Attention and concentration problems caused by MS can be particularly disruptive because daily life often requires completing 2 or more tasks at once. A strong capacity to direct attention is needed to learn new information, perform self-care regimens successfully, and cope with adjustments in daily life.

Many patients report a reduced ability to rapidly process information, particularly when the information is coming quickly from different directions, such as in a busy work environment or hectic household.⁵⁶

Compromised ability to synthesize and prioritize information is common in MS patients, but it may be subtle and not recognized as rapidly as memory problems. It may present as a lapse in judgment.⁵⁶ For example, a football fan with MS who follows the results of games closely in order to predict the outcome of upcoming games may find it difficult to sort the more important from the less important factors in his analyses. Consequently, he may predict an outcome based on irrelevant information.

A particularly embarrassing and hard-to-hide problem is word retrieval, or the “tip-of-the-tongue” phenomenon. Patients get stuck in mid-sentence because they cannot recall a particular word.⁵⁶ Although frustrating to patients and their family members, this problem can be accommodated by substituting another word or describing what is meant.

People with MS sometimes experience problems with visuospatial organization. For example, when asked to assemble a child’s toy, they may have difficulty putting the parts together.⁵⁶

Executive functioning, which involves the ability to adapt to novel situations, generate alternative solutions to problems, and self-regulate behavior, is a critical factor in a person’s capacity to satisfactorily complete daily occupational and domestic activities. This aspect of cognition is often impaired in people with MS.¹³⁵

Any or all of these cognitive dysfunctions can have profound repercussions on the lives of people with MS and may cause major disruptions in school, work, lifestyle, sexual and family functioning, friendships, and activities of daily living.

THE ROLE OF THE NURSE

The failure of healthcare professionals, patients, and patients’ families to recognize or acknowledge the presence of cognitive dysfunction in MS may negatively influence adjustment to the disease and can create additional stress for all involved. The nurse should focus on the patient’s abilities and how to compensate for limitations.

Recognizing Deficits

As the healthcare professional who most frequently interacts with people with MS, the nurse can detect early signs of new or worsening cognitive deficits. He or she should ask the patient and family members (when possible) about cognitive performance in everyday activities and roles. Patients and family members may also spontaneously identify the cognitive deficits. As mentioned above, the decision of whether to refer patients for a full neuropsychological evaluation can be difficult. Table 4 lists some guidelines to assist nurses and other clinicians in this decision.

Nurses frequently initiate a referral to a neuropsychologist and can assist with counseling patients regarding the need for a neuropsychological evaluation. The rationale for a neuropsychological evaluation may include:

- Ensuring accuracy in reporting the status of cognitive abilities to vocational and disability determination agencies.

TABLE 4.
Guidelines for Neuropsychological Evaluation Referral Decisions

	<i>Tests Indicated</i>	<i>Counsel</i>	<i>Tests Not Indicated</i>
Cognitive dysfunction affects capacity to function effectively at work and home	✓		
Patient denies concern about cognitive deficits, and there is no clinical evidence			✓
Patient's employer reports reduced work capacity	✓		
Patient concerned about potential for cognitive dysfunction		✓	
Patient seeks vocational counseling to obtain employment suitable to his/her ability level	✓		
Patient seeks disability benefits	✓		
Patient concerned that cognitive deficits may affect ability to adhere to rehabilitation program	✓		
Clinician wants baseline cognitive assessment prior to initiating immunomodulator therapy	✓		
Family recognizes cognitive problems, but patient denies them		✓	
Patient has noted cognitive impairment, but deficits not likely to be functionally significant, given the patient's low-demand environment			✓
MS of long duration with severe physical disability			✓
Subtle or fluctuating cognitive deficits that may have functional impact	✓		

- Providing appropriate rehabilitation that takes into account cognitive deficits and incorporates compensation strategies.
- Determining the contribution of mood disorder to cognitive dysfunction.
- Assisting in determining baseline cognitive functioning in order to guide treatment planning.
- Creating awareness of cognitive deficits among family, caregivers, and employers.
- Addressing the patient's anxiety about ill-defined cognitive difficulties.

Because the identification of cognitive deficits through formal neuropsychological evaluation can have a great impact on patients and their families, it is important to recognize other factors that may masquerade as, or contribute to, cognitive impairment. People with MS frequently experience stress, depression, and mood swings.

The unpredictability and debilitating nature of the disease, and absence of a cure, can cause emotional distress. Affective disorders, such as depression, may cause secondary difficulties with memory and concentration that may be falsely interpreted as direct results of MS. In some cases, concern about cognitive dysfunction may be enough to produce emotional distress.

Patients may become trapped in a vicious cycle in which anxiety and depression about the disease lead to lapses in memory and concentration, and in turn, the actual existence or threat of cognitive dysfunction leads to anxiety and depression. Nurses can help patients and their families share information that might suggest whether there is an emotional component to cognitive problems.

A key part of cognitive assessment is an investigation of concurrent medications, their dosages, and their possible

impact on cognition. Some medications frequently used in MS have side effects that may lead to, or be mistaken for, cognitive problems. Table 5 lists examples of medications that may affect cognition; it is by no means exhaustive.

TABLE 5.
Drugs That May Affect Cognition

<i>Name/Class of Drug</i>	<i>Use in MS</i>
Amantadine	Fatigue
Antimuscarinics/anticholinergics/antispasmodics	Bladder management
Anticonvulsants (topiramate)	Neurogenic pain
Tricyclic antidepressants	Depression
Anti-inflammatory agents	Pain
Baclofen	Muscle spasticity
Benzodiazepines	Muscle spasticity
Opioids	Pain

Nursing Interventions

Nurses can help patients and their families adjust to cognitive deficits. Much of a nurse's time is spent educating patients on various aspects of their illness. People with MS not only take a number of medications, including disease-modifying and symptomatic agents, but also are frequently required to adhere to physical therapy and complicated bladder and bowel programs. Therefore, the educational role of the nurse who cares for people with MS may be substantial.

Cognitive deficits in people with MS complicate the task of education. Nurses can explore options that will help overcome these difficulties. For example, in cases of memory limitation, patients should be given written and/or audiotaped instructions regarding the administration of various treatments. Repetition and reinforcement of information may be essential. Having a care partner present for educational sessions is a must when cognitive deficits are present. Follow-up after educational sessions is necessary to help with retention and adherence.

Reducing distractions and demands may prove useful for patients with attention/concentration problems. Patients find it easier to retain information if it is taught in a familiar environment, such as the home. Unfamiliar

environments (eg, a medical center) may present distractions and noise as well as increase anxiety.

Safety issues related to cognitive impairment must be addressed. The nurse's role may include assessment of the patient's home environment and support network, and the patient's ability to perform roles such as driving, cooking, and child care. The cognitively impaired person may be at risk for abuse. Referral to protective service agencies may be appropriate. The safety of the environment needs to be evaluated on an ongoing basis. The nurse also needs to be more diligent about the care of other general health issues. Resources for the cognitively impaired person include the National Multiple Sclerosis Society and adult/child protective services.

TABLE 6.
Strategies to Help Cope With Cognitive Deficits

- Make lists (eg, shopping, "to do")
- Use calendars for appointments and reminders for events; develop a consistent daily routine
- Develop a memory notebook to log daily events, reminders, messages from family and friends, driving directions, etc
- Organize the environment so that items used regularly remain in familiar places
- Modify the learning environment for patients' comfort (eg, heat, light, etc)
- Schedule the teaching session for early in the day, and limit it to a short period of time to minimize fatigue
- Conduct conversations in quiet places to minimize distractions
- Repeat information, and write down important points
- Use simple, set-by-step instructions—include the obvious (ie, when giving cooking instructions, include, "Turn off the stove when finished.")
- Follow verbal instructions with written backup, and use visuals (ie, diagrams, pictures) when possible
- Involve care partners in instructions (ie, follow-up phone call to care partner; family at home)
- Teach basic organization skills
- Openly discuss concern about cognitive dysfunction
- Have the care partner monitor the patient for safety
- Keep the patient mentally stimulated (eg, puzzles, word finds, computer games)
- Introduce change slowly, one step at a time
- Refer for formal cognitive rehabilitation

Table 6 lists strategies that have proven helpful in the management of cognitive problems. Nurses should suggest these strategies to patients and their families and work with them to overcome some of the problems presented by cognitive impairment.

Case Study 3 exemplifies the role of the nurse in helping identify signs of cognitive deficits and devising strategies to help patients compensate for these deficits.

CASE STUDY 3

CS is a 35-year-old married woman with a 9-month history of RRMS. She went to see her neurologist because she was experiencing a relapse. Her main symptoms at that time were whole-body paresthesias, right-sided weakness, and severe gait difficulties. The neurologist suggested that she consider beginning therapy with intramuscular interferon β -1a (IFN β -1a). CS told the clinical nurse that she had been experiencing difficulty with her memory and was considering quitting her job as a securities analyst because even when her disease was stable, she was finding it increasingly difficult to concentrate and constantly felt fatigued. She wanted to have a job but was unsure what type of work she would be able to do, given her neurological deficits. The nurse recognized that the memory lapses experienced by the patient could be signs of cognitive impairment and suggested that CS consider formal neuropsychological evaluation. A clear picture of the nature and magnitude of her cognitive deficits would be useful for vocational counseling and would allow the healthcare team to prepare a program to help her adjust to any cognitive problems. In addition, it would be useful to have a baseline assessment of cognitive and physical status in order to monitor the progression of the disease and the effectiveness of IFN β -1a. CS underwent formal neuropsychological testing by a neuropsychologist, the results of which showed that although her basic executive, language, and visuospatial abilities were intact, she demonstrated moderate difficulty in tasks that involved significant attention demands. Memory for complex, non-verbal information was particularly affected. CS was referred for vocational counseling. When teaching CS how to self-administer IFN β -1a, the nurse demonstrated the task, repeated the instructions several times, and provided video and audiotaped instructions for CS to take home. Her husband also received instructions, since he would

possibly have to assist CS with injections from time to time. The nurse also provided written instructions, including a checklist for each step. She emphasized the importance of developing a routine, such as administering the injection at the same time every week. In order to check that CS had retained the instructions and was administering the drug properly, the nurse asked CS to self-inject at her next clinic visit. She also suggested strategies for CS and her husband to organize their home environment to compensate for cognitive deficits. For example, objects should always be returned to their proper locations—the can opener always goes in the top drawer, keys on a key hook by the door. The nurse demonstrated relaxation and meditation techniques that would help improve concentration, and suggested that CS see a cognitive rehabilitation specialist for more formal training in cognitive rehabilitation and stress-management techniques.

CONCLUSION

Cognitive deficits in people with MS can be as debilitating as physical problems. When cognitive problems are suspected, it may be useful to discuss them with the patient and family. Formal neuropsychological evaluation is not necessary for every patient, but in cases where cognitive impairment may impair a patient's capacity to function effectively in the workplace or at home, some form of screening to provide insight into the nature and extent of cognitive deficits is advised.

Further research in the area of cognitive impairment in MS should focus on issues such as the effectiveness of cognitive rehabilitation. In addition, it is important to investigate the interrelationship between MS-related cognitive deficits and the aging process, menopause, and the menstrual cycle. The impact of hormone replacement therapy in people with MS should also be studied. Finally, neuropsychological outcome measurements should be part of clinical trials for new MS treatments, particularly if long-term follow-up trials are undertaken.

Nurses have the opportunity to detect early signs of cognitive impairment, monitor cognitive function, and help patients and their families adjust to the sometimes devastating impact of MS-related cognitive impairment.

Impact of Multiple Sclerosis on Quality of Life

MS—with its unpredictable course and its potential for progressive physical disability and cognitive impairment—can touch nearly every aspect of a patient's life. Physical and cognitive deficits may negatively affect social interaction, recreational activities, educational and vocational attainment, and overall satisfaction with life. The stresses of coping with a chronic illness may lead to difficulties with relatives and friends, resulting in a sense of isolation, depression, and lack of control. The lack of control over one's life circumstances may contribute further to a sense of desolation.

As a key healthcare professional involved in caring for people with MS, the nurse plays a leading role in empowering patients to take control of their lives by arming them with the knowledge to make informed decisions. However, nurses ought not to attempt to influence patient decisions by imposing their own values. By creating an atmosphere of unconditional acceptance, nurses can earn trust and encourage patients to share their expectations, desires, and values. These differ for each patient, and what one may consider poor quality of life, another may consider acceptable.

BACKGROUND

Over the past 3 decades, solicitation of the patient's perspective in assessing the experience and outcomes of medical care has become central to the monitoring and evaluation of healthcare. The outcomes movement has accelerated the development of measures that assess health-related quality of life (HRQOL). These instruments, which assess physical, functional, mental, and social health status, are useful in evaluating the human consequences as distinct from the financial costs or clinical outcomes of interventions.

It is now recognized in the MS community that it is essential to assess HRQOL among MS patients to obtain information on the physical and psychosocial impact of the disease from the patient's perspective.

This aspect of MS research has become particularly important as a result of the availability of disease-modifying agents. The agents were evaluated and approved based on their effects on narrowly defined measures of physical outcome; however, understanding of their broader impact on patients' lives remains incomplete.¹³⁶ Nurses are well aware that many factors beyond the direct effect of medications on the disease process influence the success or failure of these treatments.

Defining Quality of Life

QOL is dynamic, with factors differing across individuals over time. From a philosophical perspective, it can be defined as the degree of congruence between actual life conditions and one's hopes and expectations, which is unique to each person and dynamic in nature.¹³⁷

The concept of HRQOL can be distinguished from the more general, philosophical concept. It is often defined as "the value one places on current abilities and limitations, including the effects of illness and treatment upon physical, emotional, and social well-being."¹³⁸ Table 7 lists definitions of QOL and HRQOL and associated dimensions.^{137,139-148} Dimensions of QOL not directly affected by the disease may affect a patient's capacity to cope with the disease and adhere to or implement treatment plans.

Measurement of Health-Related Quality of Life

Instruments that measure HRQOL take 2 forms—generic and disease-specific. Generic instruments are not directed at a specific medical condition and can be used to compare results across a number of related and unrelated disease states. Among the most widely used of these generic instruments are the Health Status Questionnaire, commonly known as the Short Form (SF)-36 Health SurveyTM, and the Sickness Impact ProfileTM (SIP). Each collects patient-reported information, and both have been widely used in a variety of disease states.^{136,149} Disease-specific instruments are designed to focus on areas of particular relevance to patients with a given condition.¹³⁶ Because of their narrow focus, disease-specific measures generally offer greater precision in assessing the impact of a disease or treatment and are more sensitive to small changes over time.¹³⁶ A number of MS-specific measures have been

TABLE 7.
Definitions and Dimensions of Quality of Life and Health-Related Quality of Life

<i>Definitions</i>	<i>Dimensions</i>
A state of complete physical, mental, and social well-being and not merely the absence of disease and infirmity ¹⁴⁰	Physical, mental, and social well-being ¹⁴⁰
The degree to which one has self-esteem, a purpose in life, and minimal anxiety ¹⁴¹	
The degree of satisfaction with perceived present life circumstances ¹⁴²	
An individual's perceptions of well-being that stem from satisfaction or dissatisfaction with dimensions of life that are important to the individual ¹⁴³	Health and functioning, psychological/spiritual, family, social and economic ¹⁴³
An abstract and complex form representing individual responses to the physical, mental, and social factors that contribute to normal living ¹⁴⁴	
Patients' appraisal of and satisfaction with their current level of functioning compared with what they perceive to be possible or ideal ¹⁴⁵	Physical concerns, functional ability, family well-being, emotional well-being, spirituality, treatment satisfaction, future orientation, sexuality/intimacy, social functioning, occupational functioning ¹⁴⁵
A personal statement of the positivity or negativity of attributes that characterize life ¹⁴⁶	Psychological well-being, physical status, symptom control, nutritional concerns, social concerns, and affective states ¹⁴⁶
The perception of the impact of the disease that is both subjective and culturally bound ¹⁴⁷	Physical, emotional, social, or psychological functions; symptoms of disease or its treatment ¹⁴⁷
A multidimensional construct emphasizing perceptions of both positive and negative aspects of physical, emotional, social, and cognitive functions, as well as the negative aspects of somatic discomfort and other symptoms produced by a disease or its treatment ¹⁴⁸	
The congruence or lack of congruence between actual life conditions and individuals ¹³⁷	

Adapted with permission from King CR et al. *Oncol Nurs Forum*. 1997;24:27-41.¹³⁹

or are being developed. For a summary of the key features of some of these instruments, as well as the SF-36 and SIP, see Table 8.^{136,150-156}

Using generic and disease-specific HRQOL instruments in a clinical setting can provide valuable insight into the QOL of patients. However, regular use can be time-consuming and is more appropriate for research purposes.

IMPACT OF MULTIPLE SCLEROSIS ON QUALITY OF LIFE

In a study designed to demonstrate the impact of multiple-system disease, investigators found that overall, MS

has a much greater impact on QOL than either inflammatory bowel disease or rheumatoid arthritis.¹⁵³

The motor, sensory, visual, bowel, bladder, and cognitive problems associated with MS can disrupt all facets of a patient's life. The disruption associated with these symptoms from MS range from mild to severe and may vary over time according to disease course and available support mechanisms. Symptoms can affect a patient's capacity to work, cause loss of self-esteem, and dramatically erode the lifestyle of patients and their families.

MS is generally diagnosed during early to middle adult-

TABLE 8.
Generic and Disease-Specific Health-Related Quality of Life Instruments^{136,150-156}

<i>Instrument</i>	<i>Description</i>
SF-36 Health Survey ¹⁵⁰	• Generic • Patient-reported data • 8 subscales (physical, social, and role functioning; emotional well-being; mental health; general health perceptions; bodily pain; vitality) • Likert scale • Normative data (can be used to compare HRQOL of study population with that of general and/or other disease population)
SIP ¹³⁶	• Generic • Patient-reported • 136 items in a yes/no format • Subscales include ambulation, bodily care, mobility, eating, work, home, management, socialization and communication
Quality of Life Questionnaire (QOLQ) for MS ^{151,152}	• Disease-specific • Patient-reported data (administered by interviewer) • 24 items on 5 dimensions (5 items on self-selected physical problems, 5 items on mobility, 4 items on fatigue, 3 items on control, and 7 items on emotional upset)
Miller-Farmer QOL Index ¹⁵³	• Disease-specific • Patient-reported data • 41 questions on 4 subscales (functional and economic, social and recreational, affect and life in general, and medical problems)
MS Quality of Life Inventory (MSQLI) ¹⁵⁴	• Disease-specific (developed under the auspices of the Consortium of Multiple Sclerosis Centers) • Includes SF-36 • Patient-reported data, with supplemental objective data (EDSS and cognitive function) • Designed to supplement rather than replace Kurtzke EDSS • Dimensions measured include fatigue, pain, sexual satisfaction, bladder and bowel control, visual impairment, cognitive function, mental health, and social support
MS QOL 54 ¹⁵⁵	• Disease-specific • Patient-reported data • Includes SF-36 supplemented with 18 items (4 on health distress; 4 on sexual function; 1 on satisfaction with sexual function; 2 on overall QOL; 4 on cognitive function; and 1 each for energy, pain, and social function)
Life Situation Survey ¹⁵⁶	• Disease-specific (chronic illnesses, including MS) • Patient-reported data • 20-item scale includes 10 commonly accepted QOL domains (eg, work, leisure, health, love—affection, self-esteem) and 10 additional items specific to chronic illness (eg, stress, mobility, autonomy, energy level, social support, mood/affect, and public support)

hood. The primary developmental goals of this period are the formation of mature interpersonal relationships, choosing or developing a career, and integrating sexuality into a meaningful long-term relationship.¹⁵⁷ Patients may be confronted with considerable alterations in their social environments. In some cases, unmarried patients are forced to return to their family homes, and both patients and their parents and siblings must adapt to this frequently stressful situation.

Couples who may be in the process of starting a family must adapt to a change in circumstances from when the original commitment to the relationship was made.¹⁵⁷ Single patients may find themselves without necessary support. In both situations, feelings of isolation may result.

Symptoms such as gait problems, loss of balance, tremors, and changes in speech and cognition may be interpreted as signs of alcohol intoxication, thus complicating social situations considerably. Other symptoms such as head titubation and a tremulous voice seriously impair a patient's capacity to communicate and be understood.

The impact of MS on a patient's sexual functioning should not be underestimated. Symptoms such as spasticity, urinary incontinence, and fatigue interfere with this aspect of a patient's life. In addition, medications such as anticholinergics, used to manage MS symptoms, as well as medications used to treat other common health problems, can affect sexual functioning.¹⁵⁸ Side effects associated with the β -interferons, such as flu-like syndrome, can also make patients less interested in sexual activity. Alterations in body image can negatively impact a patient's perception of himself or herself as a sexual being.

People with MS may face a restricted range of job opportunities, transportation and architectural barriers, financial disincentives, and limited vocational rehabilitation services. Employer perceptions and self-evaluation of work capacity influence the vocational decisions of people with MS, often negatively, because of inadequate or wrong information.

THE ROLE OF THE NURSE

Monitoring the impact of MS on QOL is a continuous process. The ultimate goal is to help patients maintain

or enhance their QOL. Individuals diagnosed with a chronic disease are confronted with long-term adjustment issues and must constantly strive to maintain a sense of normalcy while managing physical symptoms, performing activities of daily living, and interacting with others.¹⁵⁸ They struggle to retain autonomy and control. Nurses can support this effort.

Nurses who care for people with MS play a pivotal role in facilitating individual and family adjustment to the illness. The impact of MS on emotional status and family relationships often goes unrecognized and untreated. Many patients do not feel comfortable sharing with a physician the concerns they may have about the impact of MS on their social and personal lives. In particular, questions about sexuality and family planning may remain unasked because of embarrassment or lack of knowledge of potential resources.

As educators and conduits of information between patients and other members of the comprehensive care team, nurses have the opportunity to initiate discussions on any number of issues including emotionally sensitive issues that can affect QOL. A trusting therapeutic relationship will foster open communication and the nurse can thus facilitate an environment in which a patient will feel comfortable addressing these issues.

In addressing QOL issues, nurses must be prepared to give individualized attention and advice, employ empathetic listening skills, and approach patient and family concerns creatively. An important first step in helping patients adjust to the limitations of their illness is to create an atmosphere of unconditional acceptance. Reactions to illness and changes in functional abilities will affect individuals differently, and it is critical for nurses to keep their own perceptions of health and illness out of their perceptions of their patients. It may be challenging at times to understand the reaction of patients who, from the nurse's perspective, have a mild disability yet do not cope well with their illness. However, it is the role of the nurse to understand the patient perspective and provide individualized assessments and supportive interventions. The value that patients place on certain aspects of life may change as the disease progresses. "Everybody, well or ill, disabled or not, imag-

ines a boundary of suffering and loss beyond which she or he is certain life will no longer be worth living.”¹⁵⁹ QOL can be regarded as a “movable line” that may shift as a patient’s life circumstances change. Thus, QOL is not necessarily determined by the level of a patient’s disability.

Nurses must be prepared to look beyond the clinical parameters of MS and help patients to adjust, not only in the immediate postdiagnosis period but throughout the patients’ lifetimes. This can include education and referrals that support empowering patients toward self-determination, identification of local support groups, enrollment in patient support programs, contacting of home healthcare agencies, or simply availability when patients—and their families—need to talk. Empowering patients is an integral part of the nurse’s role when dealing with QOL issues.

TREATING SYMPTOMS TO IMPROVE QOL

From a patient’s standpoint, the evaluation and management of neurologic symptoms directly associated with MS exacerbations and progression are urgent priorities in optimizing QOL. The nurse plays a pivotal role in recommending and monitoring symptomatic treatments for MS, including those used to control or alleviate specific symptoms such as fatigue, pain, bladder and bowel problems, depression, and spasticity. Other MS-related symptoms with a negative impact on QOL may include tremor; sexual dysfunction, vertigo, weakness, or difficulty with balance. Effective management of MS symptoms through education, counseling, and rehabilitation—and, when appropriate, pharmacotherapy—can enhance patients’ QOL and ability to function.

The first step in symptom management is evaluation of the causative factors. A particular symptom may be directly associated or worsened by MS, or may relate to a comorbid condition, an adverse effect of medication, or a concurrent illness. Medication for symptom relief (including over-the-counter agents and alternative therapies) must be assessed for any contraindications suggested by MS itself, DMT, or other concomitant medication use. Patients need counseling on realistic expectations for symptom treatment and possible side effects and should be supported in follow-up care.

The Importance of Education

In order to begin coping with the diagnosis and its implications, patients and families must have access to information. Processing information is difficult for people who have been diagnosed with a potentially debilitating disease. Healthcare providers must repeat the information in language that all involved can understand. A systematic approach to providing information needs to be part of the nursing plan for people with MS.

It is clear that MS presents patients with many challenges that may impact their QOL. Patient and family education is extremely important. The more patients know about the disease, the more empowered they are to take control of their lives. Factual information about MS is a basic element in the quest to enhance QOL among people with MS and is crucial to the success of all other initiatives.¹⁶⁰ Knowledge can help support health and minimize the negative features of this unpredictable disease.

As disseminators of this knowledge, nurses can help patients adjust to MS. An understanding of underlying concepts—such as the disease process, symptoms and therapies, prevention of complications, and nonmedical therapies—is the essential first step for patients in learning needed behaviors and coping skills.

Strategies to Maintain Quality of Life

Based on the work of McDaniel and Bach,¹³⁷ the following key dimensions that affect QOL in people with MS were identified. These dimensions encompass a patient’s ability to

- adapt
- communicate
- socialize
- be productive

Although this list is by no means conclusive, it provides a framework for nurses to help patients identify behaviors and develop strategies that will facilitate QOL.

Ability to Adapt

Patients must be able to initiate and respond to changes in their lives. This involves recognizing the need to respond to change; identifying and evaluating options for

change; and setting, reevaluating, and achieving flexible goals. Patients may have to adjust to life changes and limitations in their ability to work, travel, and pursue recreational and social activities. The ability to adapt to change allows patients to continue to function as valuable members of society. Nurses can help patients do this by encouraging them to explore available options. These options may include choices regarding treatment and physical therapy regimens, as well as employment and recreational activities.

Ability to Communicate

It is important for people with MS to be able to express their feelings. The disease carries with it a number of emotional stressors. If patients are unable to communicate adequately, the quality of their lives can be severely eroded and even more stress can be placed on the patient. In addition, many patients do not feel comfortable talking about their physical symptoms, particularly those that may affect their bladder, bowel, and sexual functions.

Nurses can help both patients and their families explore ways to improve communications by first exploring their premorbid communication style. Nurses can share with patients their insights about improving communication. This is important when there are cognitive difficulties, which may affect the speed with which patients formulate thoughts. In some cases, patients and their loved ones may need to be referred to a family counselor, support group, or neuropsychologist.

Ability to Socialize

One of the factors in QOL is the ability to develop and maintain satisfying relationships. This involves identifying those important relationships in patients' lives that may be negatively affected by the disease. It also involves evaluating whether the quality of these important relationships has been affected by the changes imposed by MS. Patients must determine whether changes are needed within these relationships in order to maintain them and must learn to embrace relationships that they value. It is important for people with MS to seek out relationships that are both supportive and reciprocal.

When sexual relationships are affected by MS, nurses can recommend a variety of approaches to limit the

impact on QOL, including medications, assistive devices, audiovisual and written materials, group discussions, couples' sessions, and didactic presentations.

Ability to Be Productive

Because of the wide-ranging physical and cognitive impairments associated with MS, many patients are faced with the prospect of a reduced capacity to work. Early retirement or the necessity to give up a career can cause a serious deterioration in a patient's QOL, not only from a financial perspective but also because of a loss of self-esteem. A referral to an occupational therapist for work-site evaluation is helpful in assessing difficulties in the work environment and identifying adaptive measures that help people achieve the desired or a realistic level of productivity, given the extent and severity of the individual patient's symptoms. It is important to remember that, in some cases, early retirement can improve QOL.

Loss of role, such as that which may be experienced by people with MS who are unable to fulfill the many responsibilities of parenthood, may lead to feelings of failure, uselessness, and loss of self-esteem. Nurses can help patients adjust to the change in their roles. By providing them with information on home assistance services, nurses can assist patients in adapting to and compensating for the consequences of MS.

Case Study 4 exemplifies how MS may affect a patient's QOL and how correct information and support can provide patients with the opportunity to retain some sense of autonomy and not allow the disease to rule their lives.

CASE STUDY 4

VC is a 37-year-old woman who was diagnosed with MS 5 years ago. She was married 2 years prior to diagnosis and was 2 months pregnant at the time she was diagnosed. VC was under the care of a community-based neurologist who had little experience in treating people with MS. Because VC assumed that the disease might have a hereditary component, she elected to have a therapeutic abortion. As time went on, she became increasingly preoccupied with her disease. However, since she did not have access to a specialized MS center, the

information she obtained was not particularly reliable. Because she was afraid of becoming pregnant again and was experiencing intermittent bladder dysfunction, VC refused to have intercourse with her husband. She still very much wanted to have children, so she and her husband eventually proceeded with adopting 2 children. Unfortunately, VC's symptoms prevented her from coping particularly well with the responsibilities of motherhood. She became easily fatigued and, because of gait problems, found it difficult to keep up with her many household and family duties. In addition, VC began forgetting things, which compounded her problems. Her husband knew no more about the disease than his wife, and neither of them was aware that MS could be associated with cognitive deficits. VC's husband became resentful, thinking that his wife was so focused on the symptoms and progress of her disease that she neglected her family responsibilities. In reality, VC was experiencing feelings of isolation and anxiety, because she could no longer perform what were once routine tasks. Because she had no really reliable source of information about the disease, VC assumed that her case was typical and that she could only expect things to get worse. Her self-esteem was gradually eroded, and the increasing strain on the marriage was evident to friends and family. A family member suggested that the couple contact a specialized MS center located in the next state. VC's husband did so and was able to get a referral from the local neurologist. Having built up a belief system concerning the effects and limitations of MS, VC was initially reluctant to pay much attention to the MS nurse at the center. The nurse spent a great deal of time listening to VC's sometimes totally wrong perceptions about the disease. Over a period of months, the nurse was able to gain VC's confidence, providing her with accurate information. Once VC had internalized this information, which in many ways was contrary to her

long-held beliefs, she was able to begin to adapt to her condition in an appropriate manner. She learned to self-catheterize and eventually felt comfortable enough to resume sexual relations with her husband. She joined a support group and saw how other mothers had adjusted to the role of being a mother while coping with MS. The MS center nurse arranged for an assessment of VC's home, and modifications were recommended that would allow VC to compensate for her gait problems. The nurse also recommended a spousal and caregiver support group for VC's husband and strongly encouraged him to accompany VC on her appointments and ask questions he may have about MS and its impact. After several months of counseling and education provided by the MS center nurse, VC and her family were much more equipped to deal with the challenges associated with MS. Although VC still experienced neurological and cognitive problems, she began to learn that the level of her disability need not determine her QOL.

CONCLUSION

T.S. Eliot wrote that "if you don't have the strength to impose your own terms upon life, you must accept the terms it offers you." QOL could be defined as the terms upon which a person is able to live life. Imposing these terms suggests that the person must be empowered as much as possible to take control. Certainly, people with MS may need to feel autonomous to the extent that the severity of their disease and their premorbid personality allows them. By assessing QOL over time, healthcare professionals can learn much about which factors positively influence the QOL of people with MS and use this information to empower patients to take control by giving them options. Thus, patients are given the ultimate control over health-related and life-planning strategies.

Treatment Options and Patient Education Needs

FACTORS INFLUENCING THE TREATMENT DECISION

Until 1993, treatment of MS was symptomatic and episodic. There were no drugs available that actually affected the progress of the disease. With the advent of IFN β -1b (Betaseron[®]), clinicians were able to offer patients a disease-modifying agent and, as a consequence, hope. The subsequent approvals of IM and SC forms of IFN β -1a (Avonex[®] and Rebif[®], respectively), glatiramer acetate (Copaxone[®]), natalizumab (Tysabri[®]), mitoxantrone (Novantrone[®]), and, more recently, another formulation of IFN β -1b (Extavia[®]) have provided clinicians with additional treatment options. Therapies that can be administered orally are currently under investigation and will likely add even more options to the MS treatment armamentarium.

It has become clear that early treatment with an immunomodulator provides the best long-term outcomes, an important point in the care of MS, which is a lifelong disease.¹⁶¹ With the availability of numerous effective agents, how is the treatment decision made? Anecdotal reports indicate that once clinicians have described the drugs and outlined the benefits and disadvantages of each, in most cases, patients make the decision. Because clinicians may defer to the patient's choice, both patient and clinician need a clear understanding of what is known about each agent—in particular, drug efficacy, side effects, and the administration regimen. Nurses must take a patient's history of adherence, cognitive capabilities, and definition of QOL into consideration before initiating educational activities or new protocols. Table 9 summarizes key features of the disease-modifying agents that should be considered in the treatment decision.¹⁶²⁻¹⁶⁹

From the clinician's perspective, the efficacy and safety of the treatment regimen are paramount. Although patients are also interested in these aspects, they are concerned, too, with mode of administration, tolerability,

and impact on QOL. Long-term adherence is key in the success of DMTs, and all the DMTs have been established as efficacious; indeed, clinical and imaging outcomes in head-to-head comparative studies have shown the high-frequency interferons and glatiramer acetate injectable therapies to be more similar than different.¹⁷⁰ Treatment choice should be directed to promote maximum efficacy with tolerable side effects, and lifestyle-related factors may be crucial in selecting a therapy.

Data from randomized clinical trials have demonstrated that each of the disease-modifying agents reduces the frequency and severity of relapses and delays the progression of disability, albeit to varying degrees, and that early treatment may confer added benefit.^{47,48,154,171-184} With good adherence to therapy, long-term efficacy in treating MS is achievable. The following is an overview of clinical trial data supporting the efficacy of available DMTs.

IFN β -1b

Pooled data from randomized, placebo-controlled trials examining the efficacy of low-dose (1.6 MIU) and high-dose (8 MIU) IFN β -1b in RRMS patients demonstrated significant reductions in the frequency and severity of relapses at 2 years and at 5 years.^{47,171} The 5-year pooled analysis investigated MRI lesion burden of disease, showing that IFN β -1b reduced the number and size of lesions seen on MRI.¹⁷¹ In this extension study, the magnitude of the reduction of relapses was similar throughout years 1–5, though the reductions were statistically significant only in years 1 and 2.¹⁷¹ It is not known whether this related to the natural history of the disease or a high dropout rate in both placebo and active treatment groups. In this pivotal trial's 16-year long-term follow-up study, early and sustained exposure to IFN β -1b treatment was strongly associated with reduced risk of negative outcomes including EDSS score 6.0 or higher, wheelchair use, or progression to secondary-progressive MS (SPMS).¹⁸⁵

The rationale for treatment of CIS with IFN β -1b was established by the BENEFIT trial, which randomized 468 patients within 60 days of an isolated demyelinating event to either 0.25 mg IFN β -1b or placebo every other

TABLE 9.
Key Features of the Disease-Modifying Agents¹⁶²⁻¹⁶⁹

Agent (Brand name)	<i>Interferon β-1a</i> (Betaseron [®] , Extavia [®])	<i>Interferon β-1a</i> (Avonex [®])	<i>Subcutaneous</i> <i>Interferon β-1a</i> (Rebif [®])	<i>Glatiramer</i> <i>acetate</i> (Copaxone [®])	<i>Natalizumab</i> (Tysabri [®])	<i>Mitoxantrone</i> (Novantrone [®])
Description	• Recombinant agent, produced in <i>E. coli</i> • Unglycosylated • Amino acid sequence differs from naturally occurring interferon with a serine substituted for the cysteine residue at position 17	• Recombinant agent produced from Chinese hamster ovary cells • Glycosylated • Identical in amino acid content and sequence to human β-interferon	• Recombinant agent produced from Chinese hamster ovary cells • Glycosylated • Identical in amino acid sequence to human β-interferon	• Synthetic polypeptide • Approximates the antigenic structure of myelin basic protein	• Recombinant humanized monoclonal antibody produced in murine myeloma cells	• Synthetic antineoplastic anthracendione
Indication (United States)	Relapsing forms of MS to reduce frequency of relapses, CIS	Relapsing forms of MS to slow accumulation of physical disability and decrease frequency of relapses, CIS	Relapsing forms of MS, to delay accumulation of physical disability and decrease frequency of relapses	RRMS to reduce frequency of relapses, CIS	Relapsing forms of MS to delay accumulation of physical disability and reduce frequency of relapses	SPMS, PRMS, or abnormally worsening RRMS, for reducing neurological disability and frequency of relapses
Dosage/Route/ Administration	0.25 mg/l subcutaneous injection every other day	30 μ g/l intramuscular injection weekly	22 μ g or 44 μ g/l subcutaneous injection 3 times weekly, preferably on same 3 days and at the same time, ie, late afternoon or evening	20 mg/l subcutaneous injection daily	300 mg/IV infusion over 1 hour every 4 weeks	12 mg/m ² (cumulative lifetime dose not to exceed 140 mg/m ²)/ IV infusion administered for 5 to 15 minutes every 3 months
Nursing Considerations	• Injection-site rotation and skin management • Laboratory monitoring – Neutralizing antibodies – Hematological/hepatological abnormalities • Flu-like symptoms, depression, other side effects	• Injection-site rotation and skin management • Laboratory monitoring – Neutralizing antibodies – Hematological/hepatological abnormalities • Flu-like symptoms, depression, other side effects	• Injection-site rotation and skin management • Laboratory monitoring – Neutralizing antibodies – Hematological/hepatological abnormalities • Flu-like syndrome, depression, other side effects	• Injection-site rotation and skin management • Immediate post-injection reaction, lipoatrophy, other side effects	• Only available under TOUCH[®] Prescribing Program • PML, hypersensitivity reactions, signs of liver injury, other side effects	• Cardiotoxicity (increases with cumulative dose): Patients should be monitored for evidence of cardiotoxicity prior to each dose, and total cumulative lifetime dose is not to exceed 140 mg/m² • AML • Other side effects

CIS, clinically isolated syndrome; RRMS, relapsing-remitting MS; SPMS, secondary-progressive MS; PRMS, progressive-relapsing MS; IV, intravenous; PML, progressive multifocal leukoencephalopathy; AML, acute myelogenous leukemia

day.¹⁸⁶ At 2 years, conversion to definite MS was lower among treated patients. Among those in an open-label follow-up phase, patients who received early treatment had a 41% lower risk of progression to MS ($P = 0.0011$) compared with those initially on placebo.¹⁸⁷

IFN β -1a IM

A randomized, placebo-controlled trial of IFN β -1a 30 μ g administered once a week via IM injection for 2 years was shown to delay the time to sustained progression of disability as measured by an increase of ≥ 1.0 unit in EDSS score.¹⁷² In addition, there was a statistically significant reduction in relapses and MRI-evident burden of disease.¹⁷² IFN β -1a IM has also shown benefit for patients with brain lesions on MRI indicative of CIS.¹⁷³ Data from the CHAMPS trial showed a significant delay in the next neurological event, thus delaying the onset of clinically definite MS. Most recently, 10-year data from an open-label extension of CHAMPS showed continued benefit from early treatment in reducing disease progression.¹⁸⁸

IFN β -1a SC

Clinical trials of IFN β -1a SC (and glatiramer acetate, discussed below) were the first studies of immunomodulators to employ a crossover design, switching patients originally randomized to placebo to active treatment in the trial's extension phase. This change followed the establishment of IFN β -1b's efficacy, rendering placebo-based comparisons inappropriate for ethical reasons.

The efficacy of IFN β -1a SC was established through results of an initial 2-year placebo-controlled clinical trial (PRISMS), in which both high (44 μ g) and low (22 μ g) doses of the drug given to patients with RRMS reduced relapse rate, disease progression, burden of disease, and number of active lesions, compared with placebo.¹⁷⁴ In a 2-year blinded extension of the original study, patients who had been randomized to placebo were switched to either high- or low-dose IFN β -1a SC.¹⁷⁵ Results showed that clinical and MRI benefits of IFN β -1a SC were maintained over 4 years in patients always on active treatment, and patients switched to active therapy experienced fewer relapses and exhibited reduced MRI activity and lesion burden than they had during the

placebo period. Efficacy outcomes in patients who had always received active treatment were consistently better than those in patients in the crossover group. A dose-response effect remained evident through the initial and extension phases of the study.

Patients in this trial were retrospectively evaluated for disease activity at approximately 8 years. Of the original patients, 68% returned for 7- to 8-year follow-up. Results supported benefit of IFN β -1a SC over this time period, particularly in patients who received therapy at the highest dose for the entire duration of the study. However, after the fourth year in the study, these patients may have stopped, switched, or resumed therapy with IFN β -1a SC.¹⁷⁶ Thus, "long-term" results reported for this study should be interpreted cautiously, since they may be confounded by actual treatment duration and dosage given.

In patients with CIS, a benefit of early therapy with IFN β -1a SC was demonstrated by the ETOMS trial.¹⁸⁹ A total of 308 patients with a first neurologic event suggestive of MS and abnormal MRI findings were randomized to receive either weekly IFN β -1a SC (22 μ g) or placebo. After 2 years, a significantly lower proportion of actively treated patients had progressed to clinically definite MS; treatment was also associated with lower relapse and MRI activity vs placebo.¹⁸⁹ Though the ETOMS trial's data suggests benefit in CIS patients, IFN β -1a SC is currently not indicated for treatment in patients who have experienced an initial episode suggestive of MS.

Glatiramer Acetate

Glatiramer acetate has been studied extensively and has the longest serially documented record of continuous use in the clinical trial setting. Results of the initial 2-year double-blind, placebo-controlled pivotal trial¹⁷⁷ and an extension study of the double-blind period of up to 11 months¹⁷⁸ demonstrated sustained beneficial effects of glatiramer acetate on relapse rate and on progression of disability. After up to 35 months of double-blind treatment, patients had the option of continuing in an open-label extension study, in which placebo patients were switched to glatiramer acetate therapy.^{179,180} At 8 years, a greater percentage of patients always

on glatiramer acetate demonstrated improvement or stabilization in neurological ability than patients initially on placebo, underscoring the importance of early and sustained treatment in RRMS and the risks associated with delaying therapy.¹⁸¹ After a decade, 62% of patients receiving ongoing therapy with glatiramer acetate had stable or improved EDSS scores, compared to 58% of patients treated for an average of 7 years and 28% of patients who withdrew from the study and returned for evaluation.¹⁹⁰ The lack of placebo comparison diminishes the strength of these efficacy data, as does the lack of information regarding trial dropouts. However, continuing participants have outperformed natural history, indicating that in the group of patients who have continued in the open label following trial, glatiramer acetate has long-term efficacy.^{181,182}

Results of the large randomized, placebo-controlled, 9-month European/Canadian trial demonstrated a significant reduction in the total number of enhancing lesions in glatiramer acetate-treated RRMS patients compared with placebo patients.¹⁸³ In an open-label 9-month extension crossover phase, in which placebo patients began active treatment, the effect of glatiramer acetate on MRI markers of disease was sustained.¹⁹¹ A subanalysis of this cohort also demonstrated that glatiramer acetate treatment significantly reduced the proportion of new MRI-visualized lesions that evolved into persistent hypointense T1 lesions, also known as “black holes.”¹⁹²

In 2009, the indication for glatiramer acetate was extended to individuals with CIS and MRI findings typical of MS, based on the PreCISe study, which randomized 481 such patients to either treatment or placebo for up to 3 years.^{166,193} In the treated group, risk of progression to clinically definite MS was reduced by 45% vs placebo ($P=0.005$), and time for 25% of patients to convert to clinically definite MS was prolonged by 115% (from 336 days to 722 days for placebo and glatiramer acetate groups, respectively).

Natalizumab

Natalizumab, a selective adhesion molecule inhibitor and $\alpha_4\beta_1$ -integrin antagonist, has demonstrated marked efficacy for MS. The drug, a monoclonal antibody

administered by intravenous infusion once every 4 weeks, showed a positive impact on clinical and MRI endpoints in the AFFIRM and SENTINEL studies (the latter in combination with interferon β -1a IM).^{194,195} AFFIRM showed an observed 68% reduction in annual relapse rate compared to placebo and significantly reduced numbers of brain lesions on MRI.¹⁹⁴ SENTINEL also showed positive results, such as a reduction in annual relapse rate of about 54% at years 1 and 2 with natalizumab/IFN β therapy compared to interferon alone.¹⁹⁵

In June 2006, the FDA approved natalizumab's return to market after it was voluntarily withdrawn by its manufacturer after its initial FDA approval following reports of 3 cases of progressive multifocal leukoencephalopathy (PML).¹⁹⁶ One of these cases was in a patient who received natalizumab to treat Crohn's disease. PML is a rare, serious, and frequently fatal demyelinating illness caused by infection with the JC virus and seldom seen in persons with normal immune function. At the time of reintroduction of natalizumab into the market, the risk of developing PML was estimated as 1:1000. As of November 2009, there were 28 reported cases of PML worldwide since its reintroduction to the market. Four of these patients have died.¹⁹⁷ The risk is in keeping with the original risk estimate of 1:1000. It appears that the risk of PML has risen with longer exposure to natalizumab, but it is unknown at this time if the risk will exceed 1:1000. Prescribing must be done through a mandatory registration program known as the TOUCH® Program, to assess and minimize the risk of PML; the drug is now dispensed only at registered infusion centers.

Mitoxantrone

Mitoxantrone is an immunosuppressive, antineoplastic agent approved for use in SPMS, relapsing, or worsening RRMS. It is not approved for primary-progressive disease.¹⁶⁷ In a 2-year clinical trial involving patients with worsening RRMS or SPMS, mitoxantrone treatment resulted in significantly fewer relapses (24.08) vs placebo (76.77), $P=0.0002$.¹⁹⁸ There were also fewer patients with new Gd-enhancing lesions taking mitoxantrone (0%) than with those on placebo (16%), $P=0.02$.

An important caveat associated with mitoxantrone treatment is that it has a dose-dependent cardiotoxic effect: its lifetime cumulative dose in MS patients is 140 mg/m².¹⁶⁷ The drug should only be used in patients with normal cardiac function, and cardiac monitoring is required before each infusion.¹⁶⁷

Head-to-Head Trials

Accumulating data from head-to-head trials has provided a growing body of direct comparative data among DMTs.

The EVIDENCE trial evaluated the efficacy of IFN β -1a IM (30 μ g once weekly) and IFN β -1a SC (44 μ g 3 times weekly) in RRMS patients in a randomized, controlled setting.¹⁹⁹ Results showed that patients who received the higher interferon dose (IFN β -1a SC) were more likely to be relapse-free and also had significantly fewer active lesions at 24 weeks than their counterparts who received the lower-dose, IM formulation. Results for these endpoints at 48 weeks and 16 months continued to favor IFN β -1a SC.²⁰⁰

Another head-to-head trial, INCOMIN, compared IFN β -1a IM (30 μ g once weekly) with IFN β -1b (250 μ g every other day) in patients with RRMS.²⁰¹ At the 2-year point in this prospective, randomized study, a greater percentage of the IFN β -1b patients were relapse-free than were their IFN β -1a IM counterparts, and a significantly greater percentage of IFN β -1b IM patients remained free from new T2 lesions compared with the IFN β -1a IM patients. Differences in efficacy between the 2 drug groups became more pronounced during the second year of the study.²⁰¹

Recently, several randomized clinical trials have compared the efficacy and safety of glatiramer acetate with high-dose IFN β therapy in RRMS. All 3 trials demonstrated comparable efficacy in relapse reduction and other primary endpoints.²⁰² In the REGARD trial, 764 patients were randomized to either IFN β -1a SC or glatiramer acetate for 96 weeks, with no significant difference observed in time to first relapse.²⁰³ A subset of 460 patients given serial MRI scans showed no significant difference for the number and change in volume of active T2 lesions or for the change in volume of Gd-enhancing lesions.²⁰³ Those on IFN β -1a SC

treatment had significantly fewer Gd-enhancing lesions than those on glatiramer acetate (0.24 vs 0.41, respectively; $P=0.0002$).²⁰³

In the open-label, multicenter BEYOND trial, 2,244 patients were randomized to either glatiramer acetate or 1 of 2 doses of IFN β -1b (either the standard 250 μ g or 500 μ g) for 2 years.²⁰⁴ The primary outcome of relapse risk did not significantly differ in any of the 3 pair-wise comparisons; mean annualized relapse rate over 2 years of treatment declined by about 80% in all 3 arms of the trial, and no significant differences were seen among them in MRI activity or EDSS progression.²⁰⁴ Flu-like symptoms were more common in IFN-treated patients ($P<0.0001$), while injection-site reactions were more common in those given glatiramer acetate ($P=0.0005$).²⁰⁴

The BECOME study compared IFN β -1b 250 μ g to daily glatiramer acetate in 75 patients with RRMS, using an optimized MRI protocol to measure a primary outcome of combined active lesions per scan per patient.²⁰⁵ Over a year, the mean number of lesions declined in both treatment groups, with no significant difference between groups.²⁰⁵

Convenience

The mode of administration of the immunomodulators is a lifestyle issue. Once patients have overcome the hurdle of accepting that the majority of the treatment options currently available involve self-injection, they must then decide on dosing route and frequency. After the regimen is begun, patients tend to quickly adapt to the requirements of administration.

Many patients are attracted to a once-weekly injection and do not mind the larger needle associated with the IM route. Others have difficulty with the larger IM needle and opt for the more frequent SC routes. For some, self-injecting every other day or three times a week is preferable to a daily injection, while some patients prefer the daily regimen because they find it less confusing, a particular concern for patients with cognitive impairment.

With the exception of Extavia (which is currently available only as a lyophilized powder that must be

reconstituted with a diluent), all of the immunomodulators are available in prefilled syringes that can be stored at room temperature for certain periods of time, depending on the agent. This may be convenient for patients who travel frequently. The use of an autoinjector that delivers immunomodulators subcutaneously may also offer a more convenient means of administering therapy for some patients.

Emerging Oral Therapies

Several agents to treat MS and its symptoms, some of which hold out the promise of oral disease-modifying therapy, are either under investigation or have recently been approved. Cladribine, fingolimod, laquinimod, and teriflunomide are several promising oral agents, and data from phase II and phase III trials have, thus far, proven them to be safe and effective in the short term.²⁰⁶⁻²⁰⁹ However, data on their long-term safety and efficacy are not yet known. While administering an agent orally instead of via injection would arguably be more convenient for a patient, safety and efficacy are of prime importance in current and future treatment decisions. Though it would seem that adherence would be enhanced with an oral treatment, adherence studies in other disease states have indicated adherence difficulties with oral treatment regimens.

Medications for the treatment of MS symptoms are also of importance to MS patients and their healthcare providers, and like potential disease-modifying therapies, oral formulations of these drugs are of particular interest. One such therapy is dalfampridine (AmpyraTM), which was approved by the FDA in March of 2010 for use to improve walking in people with MS.²¹⁰ Currently, dalfampridine is only distributed through specialty pharmacies, and because dalfampridine can cause seizures and other serious side effects such as renal failure, the FDA approved dalfampridine with a risk evaluation and mitigation strategy (REMS) comprising

a medication guide and communication plan. REMS assessments will be provided to the FDA 18 months, 3 years, and 7 years after the date of the REMS approval.²¹¹

The Nurse's Role in Making the Treatment Choice

The numerous factors that influence a patient's treatment decision make it clear that patients must be equipped with an adequate understanding of the benefits and disadvantages of the immunomodulatory agents. Nurses are in a position to help patients explore which of the agents is most suitable for their life circumstances and expectations. Developing patient skills such as self injection, conveying the importance of early initiation of therapy and adherence, managing side effects, and fostering realistic expectations are within the purview of the nurse. Using key principles of nursing care in MS will facilitate and sustain suitable, individualized treatment choices, including disease-modifying therapy, symptomatic care, and rehabilitative services.

The key to successful treatment of people with MS is balancing the efficacy of the prescribed agent with a patient's capacity or desire to adhere to a treatment regimen, the patient's level of cognitive impairment, and the impact of a treatment regimen on QOL.

The advent of disease-modifying agents during the latter part of the 20th century added to the complexity of MS care and compelled healthcare providers to assess and reassess care patterns based on evidence in addition to clinical experience. The availability of newer agents, including oral therapies, will further add to the complexity. The nurse is a key member of a team of healthcare professionals tending to MS patients and their families. Day-to-day contact, along with knowledge and awareness of critical issues in MS, require the nurse and his or her healthcare team to convey information about prescribed treatments and to promote health and wellness.

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Multiple Sclerosis Resource Guide

Organizations

Consortium of Multiple Sclerosis Centers

The Consortium of Multiple Sclerosis Centers (CMSC) provides networking for all healthcare professionals who specialize in the care of patients with MS. Its activities include an annual educational conference, annual specialty roundtable discussions, and the North American Research Consortium on MS, which conducts multicenter trials, manages a patient registry, and maintains a Web site (www.msccare.org). For more information, contact June Halper, executive director (phone: 201-487-1050, fax: 201-678-2290, e-mail: june.halper@msccare.org).

International Organization of Multiple Sclerosis Nurses

The International Organization of Multiple Sclerosis Nurses (IOMSN) has established standards of nursing care in MS, provides education about MS to the entire healthcare community, and supports MS nursing research. The organization established the MS Nurses International Certification Board to develop and administer the certification examination for MS nurses. For more information call 201-487-1050, fax 201-678-2291, or e-mail info@iomsn.org.

National Multiple Sclerosis Society

The National Multiple Sclerosis Society (NMSS) funds both basic and health-services research. An office of professional education programs maintains a speakers bureau and supports professional education programs in individual chapters. NMSS chapters and branches provide services and information on counseling, equipment, and support programs for people with MS and their families. For more information, call 800-344-4867 or visit www.nationalmssociety.org.

Pharmaceutical Company Support Programs

Ampyra™

Healthcare professionals, patients, and care partners with questions about Ampyra can call 888-881-1918 or visit www.ampyra.com for more information and to sign up to receive updates on the therapy.

BETAPLUS™

BETAPLUS™ provides free comprehensive programs and services for patients taking Betaseron® and their families, as well as other people with MS. Available services include an injection training program, reimbursement services, support groups, and nurse support. For more information, call 800-788-1467 or visit www.betaseron.com/patients/betaplus.

Extavia®

Questions about patient services and the Extavia co-pay assistance program can be answered by calling 866-925-2333. Healthcare professionals with questions about Extavia can call 866-EXTAVIA (398-2842).

MS ActiveSource®

MS ActiveSource® is a free service that provides patients, their care partners, and healthcare professionals with information, assistance, and support to help ensure a positive Avonex® treatment experience. Members are able to create a personal Web profile that provides access to several available tools. For more information, call 800-456-2255 or visit www.msactivesource.com.

MS LifeLines®

MS LifeLines® is an educational tool for people living with MS. People taking Rebif® can also find facts and support for their therapy through this free service, as well as register for events, sign up to receive an information kit, read profiles of other patients, and get tips on living with MS. For more information, call 877-447-3243 or visit www.ms lifelines.com.

Shared Solutions®

Shared Solutions® is a free patient support program available to anyone with MS and anyone who has been touched by MS, including care partners, friends, and family. Patients taking Copaxone® receive additional materials and services related to Copaxone therapy. This program is designed to help patients, their families, and caregivers with counseling, reimbursement issues, self-injection training, and adherence reminders. For more information, call 800-887-8100 or visit www.copaxone.com/supportservices.

Tysabri®

Patients who are interested in learning more about Tysabri or who are currently taking Tysabri can register to learn more about the drug, including the Tysabri TOUCH® Prescribing Program. Patient support services, financial assistance programs, and a mentor program are also available. For more information, call 800-456-2255 or visit www.tysabri.com.



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