

IJMSC Volume 4, Issue 3 October 2002

Editorial

Evidence-Based Medicine



Robert M. Herndon, MD

Robert M. Herndon is Director of the Department of Neurology at the Veterans Affairs Medical Center in Jackson, Mississippi; Professor of Neurology at the University of Mississippi Medical Center; and Editor-in-Chief of the International Journal of MS Care.

The care of persons with multiple sclerosis (MS) is steadily moving from the empirical care typical of most of the last century to increasingly scientific, evidence-based care. A more scientific basis for MS care is dependent on research, particularly that related to clinical trials and outcomes. A fairly recent step in the effort to make MS care more scientific is the development of clinical guidelines for the management of various aspects of the disease.

The creation of guidelines involves the systematic search for, and detailed review of, the relevant literature by experienced professionals. The process includes categorization of the quality of the evidence derived from the research, followed by preparation of a guideline based on the evidence, which is weighed based on the class of the evidence. The end result is a guideline intended to represent "best practice" with regard to the problem in question.

The Consortium of Multiple Sclerosis Centers has been a leader in the development of guidelines for the management of MS. This project has been spearheaded by Deborah Miller, PhD, LISW, of the Cleveland Clinic and has been supported by the Consortium, the Paralyzed Veterans Association, and the Eastern Paralyzed Veterans Association (with some incidental support from other organizations). They put together a council and several teams and have come up with a number of guidelines, including those on disease-modifying therapies, bladder management, and treatment of fatigue. Additional guidelines for spasticity, immunization, and pregnancy are in progress.

There are several important things to remember regarding these guidelines:

1. They are guidelines; they are not gospel. They will not be applicable in all situations and need to be applied with careful clinical judgment.
2. They provide a systematic approach to specific problems, which can be useful even if you don't follow the recommendations precisely.
3. While they are supposed to be as objective as possible, they are written by groups of individuals who have their own biases.
4. The weighing of noncommensurate variables is a matter of judgment by each participant in the process, and this is influenced by individual bias.
5. They are not written in stone; they require periodic updates because of the publication of new studies and as the result of experience in their use. Adequate arrangements for periodic review and updates need to be made.

6. As semi-official documents, these guidelines will undoubtedly be taken as gospel by lawyers. They will be used in any way possible to advance suits against physicians and other allied health professionals.
7. The studies on which the guidelines are based were conducted on highly selected groups of patients. Many patients in routine clinical practice would not meet study criteria, so good clinical judgment is required in the application of the guidelines.

The problem of weighing noncommensurate data is most obvious in the disease-modifying therapy guideline.¹ How do you weigh attack frequency versus differences in disability progression when neither have been compared in trials? How do you treat neutralizing antibodies? Several published studies suggest that patients with neutralizing antibodies do not fare worse than those without, but we know that neutralizing antibodies to interferon in other diseases negates the effects of the drug,² and the studies proposing otherwise really are too small to demonstrate an effect even if the drug was completely neutralized.

Additionally, how do we deal with the evidence on brain atrophy? Do we dismiss the studies because they were done on a "biased" subset of the patients in a larger study, even though that subset completed two years of the study?

One of the biggest problems we face is that the vast majority of clinical trials are carried out by pharmaceutical companies. While the companies' trial designs must follow certain rather strict guidelines, the drug companies often design follow-up and comparison trials specifically to show their own product to advantage when a longer or more rigorously designed trial would produce much more valuable comparative information. Unfortunately, trials are extremely expensive and federal funding agencies do not have the funds to do the prolonged comparison trials that would ultimately show which therapy is optimal.

To continue in the effort to make medicine more scientific, more and better tools are needed. Fortunately, these tools are being developed. Scales such as the Multiple Sclerosis Functional Composite scale are much more accurate and sensitive than previous MS scales. The brain parenchymal fraction measurement of brain atrophy is also quite sensitive and objective. New quality-of-life scales have been, and are being, developed and validated. As members of the CMSC, we can take pride in our role in these developments and in the advancement of MS care.

References

1. Goodin DS, Frohman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology*. 2002;58:169-178.
2. Öberg K, McKenna RM. The incidence and clinical significance of antibodies to interferon- α . In: Reder AT, ed. *Interferon Therapy of Multiple Sclerosis*. New York, NY: Marcel Dekker Inc; 1997:509-521.

Changes in Voiding Patterns in Patients With MS and Extended-Release Oxybutynin

Margie O'Leary, MSN, RN; Janet R. Erickson, BS; Christopher P. Smith, MD; Tracy W. Cannon, MD; Matthew Fraser, PhD; Marlene Boyd, BSN; Rock Heyman, MD; and Michael B. Chancellor, MD

Margie O'Leary, Janet R. Erickson, Christopher P. Smith, Tracy W. Cannon, Matthew Fraser, and Michael B. Chancellor are affiliated with the Department of Urology and Marlene Boyd and Rock Heyman are from the Department of Neurology, all at the University of Pittsburgh School of Medicine.

Abstract

We evaluated the effects and tolerability of extended-release oxybutynin chloride on the voiding and catheterization frequency of multiple sclerosis (MS) patients with neurogenic bladder. This was a 12-week, prospective, dose-titration study of extended-release oxybutynin (oxybutynin XL). MS patients were recruited for this study from the University of Pittsburgh School of Medicine's MS clinic. Entry criteria included a postvoid residual urine volume of less than 200 mL (in noncatheterized subjects). Previous urodynamic testing was not required. Exclusion criteria included individuals with urine results indicating pyuria in the presence of a positive urine culture. These tests were repeated at six and 12 weeks. After a seven-day washout period, patients recorded episodes of voiding or catheterization and incontinence for three consecutive days. Patients received initial daily doses of 10 mg oxybutynin XL in the first week. Doses were increased at weekly or biweekly intervals to a maximum of 30 mg/d. Tolerability information was collected at each follow-up visit. Twenty of the original 23 patients completed the study. The mean age was 46.3 (range, 24 to 61). Fifteen subjects (75%) were women. Subjects reported clinical improvement with decreased urinary frequency and incontinence episodes after dosing was escalated to 30 mg/d. Seventeen patients chose a final effective dosage greater than 10 mg/d, with 13 patients taking at least 20 mg/d at the end of the study. There were no serious adverse events during the course of the study. Extended-release oxybutynin is safe and effective in MS patients with neurogenic bladder. The onset of clinical efficacy occurs within one week, and daily doses up to 30 mg may be indicated and are well tolerated.

Suggested citation: Changes in Voiding Patterns in Patients with MS and Extended-Release Oxybutynin. O'Leary, M et al. *Int J MS Care* [Serial on-line]. 2002;4:(3).

Urinary urgency, frequency, incontinence, and/or infection are common symptoms of patients diagnosed with multiple sclerosis (MS). Loss of normal bladder control can affect significantly an individual's daily activities, enhance fatigue, and negatively influence quality of life (QOL).¹⁻³ It is estimated that at least 90% of people with MS will exhibit symptoms of urinary dysfunction during the course of the disease.⁴

In MS, lesions resulting from demyelination in the brain or spinal cord interrupt the descending and ascending nerve pathways, especially the posterior and lateral columns of the cervical spine, which control micturition.⁵ Detrusor hyperreflexia was the most common diagnosis found in a review of urodynamics patterns observed in MS.⁶ Detrusor hyperreflexia is defined as a sudden increase in bladder pressure, which leads to involuntary contractions of the bladder.⁷

Anticholinergic medications are the most effective agents available today to control overactive bladder symptoms.⁸ They block receptors of the detrusor muscle, thereby decreasing frequency, urgency, and incontinence. Recently, oxybutynin XL has shown efficacy in the treatment of this overactive bladder symptom.⁹

Bladder ultrasound examinations are a noninvasive and painless method of measuring volume of urine within the bladder without performing urethral catheterization, thus eliminating the risk of urinary tract infection or urethral trauma caused by catheterization.¹⁰ Previous research by Chan¹¹ and by Coombes and Millard¹² demonstrated the reliability of the bladder ultrasound scanner.

Bladder diaries are validated, sensitive, and reproducible instruments that are accepted as the gold standard in the assessment of drugs undergoing Food and Drug Administration review for the treatment of urinary incontinence.^{9,13} The three-day diary is recommended by the International Continence Society's committee on standards and clinical trials minimum data. The bladder diary is also endorsed by the World Health Organization's First Consultation on Incontinence as the preferred instrument to measure micturition patterns.

The aim of this study was to assess the effectiveness of oxybutynin XL using diaries, ultrasound, urinalysis, culture, and sensitivity testing as parameters of effectiveness. Another goal was to assess subjective efficacy, safety, and tolerability of this medication during the 12-week treatment period.

Methods

This prospective, open-label trial was undertaken from October 2000 to October 2001 at the University of Pittsburgh Medical Center. Twenty participants completed the study. Subjects were recruited from those who received routine care in the urology outpatient department or through the university's MS clinic. Inclusion criteria specified patients ages 18 and older with clinically definite MS. Exclusion criteria included the addition or change of an antihypertensive medication within the past 90 days, a postvoid residual urine test result of greater than 200 mL (in subjects who did not perform clean intermittent catheterization), and a positive urine culture in the presence of pyuria. Pregnant and/or breast-feeding women were excluded. All subjects gave informed consent for this protocol, which was approved by the University of Pittsburgh's Institutional Review Board. Three subjects withdrew from the study for the following reasons: one was too busy, one was too depressed, and one felt (after three weeks) that the medicine was not effective.

Those who enrolled were prohibited from taking any anticholinergic medication for a minimum of one week. Subjects were required to maintain a three-day baseline diary (after the washout period if previously on anticholinergic medication). The diary included documentation of the number of voids and/or catheterizations in 24 hours, as well as any incidents of incontinence. Laboratory studies prior to therapy included urinalysis, culture, and sensitivity testing. The subjects were initially prescribed a dosage of 10 mg/d oxybutynin XL. The dose was increased in increments of 5 mg until satisfaction was reached, or to a maximum of 30 mg/d. Patients were seen at least once during the study to assess for infection or retention via bladder ultrasound.

Data Analysis

Patient Description

The mean age of the patients who completed the study was 46.3 (range, 24 to 61). Fifteen (75%) of the subjects were women.

Dosages

All patients started with a dosage of 10 mg/d oxybutynin XL. Seventeen of 20 patients (85%) chose a final effective dosage of greater than 10 mg/d. Thirteen patients (65%) were taking at least 20 mg/d at the end of the study. Four patients (20%) who escalated to 30 mg/d chose to continue at that higher dosage. No patient had serious adverse events during the 12-week study, and there was no increase in side effects with increased dosing.

24-Hour Voiding History

The mean number of voids within a 24-hour period was decreased from 9.6 ± 0.4 episodes/24h at baseline to 6.6 ± 0.4 episodes/24h at week 12 ($P < .001$). This demonstrated a statistically significant improvement in daily micturition pattern.

24-Hour Catheterization History

The mean number of catheterizations within a 24-hour period for the five patients who required this additional procedure to empty was decreased from 6.5 ± 1.9 episodes/24h at baseline to 5.0 ± 1.1 ; however, this difference was not statistically significant.

Postvoid Residual Urine

Residuals increased from 64.4 ± 18.8 mL (range, 1 to 211 mL) at baseline to 91 ± 21.3 mL (range, 10 to 251) after 12 weeks. Not only was this apparent increase in mean values statistically insignificant but the mean value was below the generally regarded clinically relevant residual volume of less than 100 mL. There was no subjective or objective evidence of clinically relevant adverse effects relating to residual urine volume. There were no episodes of retention requiring catheterization (in subjects who did not catheterize prior to the study), overflow incontinence, or hematuria.

Nocturia

Frequency of micturition per night decreased from 1.2 ± 0.2 episodes/night at baseline to 0.8 ± 0.2 episodes/night at 12 weeks, and this did reach statistical significance ($P = .0242$). Patients subjectively reported improvements in sleep based on decreases in nocturia.

Daily Incontinence Episodes

The mean number of urge incontinence episodes significantly decreased from 1.2 ± 0.2 per day at baseline to 0.3 ± 0.1 episodes/week after 12 weeks ($P = .0046$).

Infection Rates

We did not see an increase in infection rates during the study. Only two urinary infections in two separate subjects were diagnosed and required antibiotic therapy.

Discussion

MS is a chronic and disabling neurologic illness resulting from demyelination within the central nervous system. Nerve transmission is disrupted and results in a myriad of symptoms. The most distressing symptoms of MS are related to urinary dysfunction and include urgency, frequency, infection, and incontinence.¹⁴ Ninety percent of people diagnosed with MS experience some form of these symptoms during their illness.⁴ Symptoms generally develop slowly during the initial symptomatic relapsing phase of the disease. Behavior is adapted so that in time and as the disease progresses, atypical voiding patterns are evident.

Demyelinating lesions in the brain and spinal cord produce either overactivity or a loss of function within the bladder and sphincter. Urodynamic testing differentiates urinary dysfunction in MS into three distinct categories: detrusor hyperreflexia, detrusor sphincter dyssynergia, and detrusor areflexia.⁵ The first and most common finding in reviews is detrusor hyperreflexia.⁶ This occurs when there is no inhibition of bladder contractions during early filling stages, which is thought to be due to supraspinal lesions.¹⁵ Symptoms include urgency, frequency, nocturia, enuresis, and incontinence. In MS, these symptoms may begin after filling the bladder with a volume as small as 50 mL. In time, the bladder may contract and cannot fill to previous capacity. The average adult bladder holds approximately 400 to 500 mL.⁵ However, in patients with MS, it is common but most unfortunate to have a bladder capacity of only 250 mL. Treatment of this storage dysfunction typically consists of anticholinergic medications.

The next most common category of dysfunction is detrusor hyperreflexia with detrusor sphincter dyssynergia, also known as combined dysfunction. This results when there are lesions in the sacral area that interrupt the coordination between the detrusor reflex and the external sphincter.¹⁵ Double voiding, frequency, urgency, incontinence, infection, hesitancy, nocturia, and enuresis are reported symptoms. Postvoid residual urine volumes are typically greater than 150 to 200 mL. Management consists of the use of anticholinergic medications and clean intermittent catheterization.

Lastly, detrusor areflexia (the inability to empty) is characterized by the absence of detrusor contractions during low pressure filling.¹⁵ Signs of detrusor areflexia include straining to void, poor urinary stream, double voiding, infection, incontinence, and postvoid residual volumes of nearly bladder capacity. Management includes clean intermittent catheterization or surgery in the most difficult cases. Kim et al¹⁶ found no correlation between urinary complaints and urodynamic or magnetic resonance imaging findings.

Nocturia can be a frequent cause of sleep disturbance and strongly associated with repeated awakenings and increased sleep latency.¹⁷⁻¹⁹ Fatigue is another symptom in MS commonly reported as one of the most disabling and validated through the North American Research Consortium on Multiple Sclerosis (NARCOMS) patient database.^{20,21} In a study performed by Clark et al²² in a cohort of MS patients, sleep complaints were noted three times more often than in the general population. Although there is a limited understanding of fatigue in MS, one must assume that urinary frequency, urgency, nocturia, and incontinence would exacerbate this feeling. Management of fatigue is a high priority when managing the health and well-being of MS patients. Several behavioral techniques specific to improving urinary function consist of limiting fluids in the evening, elevating legs above the heart in the afternoon to promote fluid return, and avoiding irritants to the bladder, which include caffeine, alcohol, and artificial sweeteners. Managing urinary urgency and frequency in any way possible may greatly impact sleep quantity and quality and lessen the impact of daily fatigue.

In the past two decades, measurement of symptoms and QOL have become increasingly important when planning any treatment in the field of medicine. In reviews of QOL data and their relation to MS, studies have demonstrated lower QOL scores among MS patients compared to others with chronic illness and to the general population.^{23,24} Aronson²⁵ found that subjects with MS and fatigue have a low concept of health. Even in the general population, loss of bladder control results in significantly reduced freedom in life and well-being.^{1,3} This is compelling evidence for the need to place high priority on management of urinary symptoms in MS patients.

Anticholinergic medications are the most widely used agents for the management of urinary symptoms of overactive bladder and in treating MS patients.^{26,27} Oxybutynin chloride is a potent antimuscarinic agent with pronounced muscle relaxant and local anesthetic activity.^{26,28-30} For the past 30 years oxybutynin has been the most commonly prescribed medication for

overactive bladder and detrusor hyperreflexia.³¹ Several double-blind controlled studies have shown immediate-release oxybutynin's efficacy for detrusor hyperreflexia.^{26,28-30} The overall rates of favorable results (more than 50% symptomatic improvement) were 47% with 3 mg tid and 61% to 86% with 5 mg tid. Side effects were noted in all studies, and severity increased with dosage. The overall incidence of possible side effects was 24.5% for 3 mg tid and 12.5% to 68% for 5 mg tid. Most side effects were related to oxybutynin's antimuscarinic action, with dry mouth as the most common complaint (incidence of 12.2% with 9 mg/d and up to 47.6% with 15 mg/d).

Oxybutynin XL, a once-a-day controlled-release formulation of oxybutynin, was recently developed. Oxybutynin XL uses a push-pull osmotic system (OROS®, ALZA Corporation). A semipermeable membrane surrounds a bilayer core. One compartment contains oxybutynin chloride, and the other is comprised of osmotically active elements. When exposed to water in the gut, the osmotic compartment expands to push the hydrated drug through a tiny laser-drilled hole in the membrane and into the circulation.³¹ This system maintains consistent release of medication for 24 hours and avoids the peaks seen with immediate-release oxybutynin.

Parallel-group, randomized, controlled clinical trials comparing the efficacy and safety of oxybutynin XL with conventional, immediate-release oxybutynin in patients with overactive bladder³²⁻³⁴ demonstrate that the urge urinary incontinence episodes declined log linearly with both formulations. Dose-related dry mouth analysis showed that the probability of dry mouth with an increasing dose was significantly lower with oxybutynin XL than with immediate-release oxybutynin.³⁵

The pharmacokinetics of this delivery system (ie, flat concentration profile) may help to explain less severe dry mouth reported with once-daily oxybutynin versus immediate-release oxybutynin (24.5% vs 46.2%) in a multicenter, randomized double-blind study.³² The latest research also suggests that with oxybutynin XL, most of the drug absorption occurs in the large intestine rather than in the stomach, in contrast to other anticholinergic drugs. This site of drug absorption limits the formation of oxybutynin metabolites (N-desethyl-oxybutynin).^{31,36} Oxybutynin metabolites, rather than oxybutynin chloride, may be responsible for most of the side effects, including dry mouth.³⁵

In our study, the primary outcome parameter, number of voids or catheterizations in 24 hours, significantly improved after oxybutynin XL therapy at the final dose. Moreover, there were decreases in bladder emptying frequency, nocturia episodes, and daily incontinence episodes.

Although the mean number of voids per day is not great (9.6), these patients were concerned enough to seek treatment. Subjects had modified behaviors, including decreasing fluid consumption to avoid problems of urgency and incontinence. It is strongly suspected that these differences would be more significant than they appear if fluid consumption were not a confounding issue.

Conclusion

Oxybutynin XL is a safe and effective therapy in MS patients with neurogenic bladder. The onset of clinical efficacy occurs within one week. Daily doses of up to 30 mg may be indicated and are well tolerated.

There was no difference among treatment groups in the subjects in severity of adverse events. In Study 2, MONYTRON[®] administration for injection was administered once a month. Clinical adverse events most frequently reported in the MONYTRON[®] group included: anorexia (12% of female patients), dyspepsia (12% of patients), nausea (12% of patients) and fatigue (14% of patients). Headache (18% of patients) was the most common adverse event. No laboratory abnormalities occurred in 70% of patients in the MONYTRON[®] group and numerically more frequent than in the control group.

Table 2a
Adverse Events of Any Intensity Occurring in > 1% of Patients* in the MONYTRON[®] Group and Numerically More Frequent Than in the Control Group

Event	Study 2 Percent of Patients	
	MP N = 212	M + MP N = 211
Anorexia ¹	1	53
Dyspepsia	1	33
Nausea	1	29
Fatigue	1	26
Headache ²	1	17
Constipation/abnormal bowel motility pain	1	14
Abdominal pain	1	13
Diarrhea	1	12
Stomatitis	1	11
Headache	1	10
Abdominal pain	1	7

N = MONYTRON[®] MP = methylprednisolone
*Adverse drug reactions/abnormal laboratory test abnormalities
1. Percentage of female patients
2. Percentage of total patients

Table 2b
Laboratory Abnormalities Occurring in > 1% of Patients* in the MONYTRON[®] Group and Numerically More Frequent Than in the Control Group

Event	Study 2 Percent of Patients	
	MP N = 211	M + MP N = 212
ALT ¹ ↑	8	26
AST ¹ ↑	8	26
Gamma-GT ¹ ↑	8	26
Alkaline phosphatase	8	26
Bilirubin ↑	8	26
SGPT ↑	8	26
SGPT ↑	8	26
Bilirubin ↑	8	26

N = MONYTRON[®] MP = methylprednisolone
*Abnormal and increased include 95% confidence interval
1. > 100% only
2. < 100% only
3. < 100% only

Injections and intraperitoneal were reported in the M + MP group (see Table 2b). Microscopic colitis 3 weeks after MONYTRON[®] administration and was sleep paralysis, day and nighttime urinary infections were reported in 1 of 2 patients in the M + MP group and in 2 of 21 patients in the MP group, none of whom received hospitalization. There was no difference among treatment groups in the incidence or severity of adverse events, there were no withdrawals from Study 2 for safety reasons.

General
Allergic reactions - Hypertension, edema, changes, and other have been reported occasionally.
Data bases - Information at the infusion site has been reported, which may result in numbness, swelling, pain, soreness and/or bruise. Discoloration of the skin. Stereotaxic may result in local necrosis with resultant need for debridement and skin grafting. Risk factors have been reported at the site of infusion.
Manufacturing - Sterilization of solutions, including MONYTRON[®], in combination with other active ingredients, has been reported. Multiple vials of solution.
SUSCEPTIBILITY - Nausea and vomiting occurred acutely in most patients and may have originated in reports of anorexia, but were generally mild to moderate and could be controlled through the use of antiemetics. Gastrointestinal occurred within 1 week of therapy.
Gastrointestinal - Nausea and vomiting occurred acutely in most patients and may have originated in reports of anorexia, but were generally mild to moderate and could be controlled through the use of antiemetics. Gastrointestinal occurred within 1 week of therapy.
Cardiovascular - Negative ventricular tachycardia, bradycardia, sinus bradycardia, atrial fibrillation, and asymptomatic second-degree atrioventricular conduction have occurred. See WARNINGS.
Pulmonary - Interstitial pneumonitis has been reported in some patients receiving combination chemotherapy that included MONYTRON[®].
OPHTHALMOLOGY - There is no known specific antidote for MONYTRON[®]. Assistance overseas has been reported. Four patients receiving 40-120 mg IV at a single bolus injection died as a result of acute hypoxemia with infection, hemolytic anemia and antifolate therapy may be required during prolonged periods of severe immunosuppression. Although patients with severe renal failure have received MONYTRON[®], it is unknown if these patients and it is unlikely that the therapeutic effect, if any, would be mitigated by hemodialysis or hemofiltration.
INDICATIONS, ADMINISTRATION, AND DOSAGE
Multiple sclerosis - The recommended dosage of MONYTRON[®] is 12 mg IV at 12-hour intervals for 3 to 11 consecutive intravenous infusions every 2 months. Initiation of IVT (by epidural or IV) is recommended only to administration of the initial dose of MONYTRON[®]. Subsequent IVT infusions are recommended if signs or symptoms of relapse, heart failure, development, or poor to no other response to patients who have received a corticosteroid at a dose of 100 mg IV every 6 hours, should not continue to be administered to multiple sclerosis patients who have received a cumulative intravenous dose of > 1.61 mg IV, or intravenously either IV or IV or a clinically significant reduction in VEE complex blood levels, including plasma, should be monitored after the 12th course of MONYTRON[®] and in the event of signs or symptoms of infection develop. MONYTRON[®] should not be administered to multiple sclerosis patients with neutrophil counts less than 1500 cells/mm³. Liver function should also be monitored prior to each course. MONYTRON[®] therapy in multiple sclerosis patients with abnormal liver function tests is not recommended because MONYTRON[®] clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and thus individualize therapy. Patients with multiple sclerosis who are biologically capable of bearing drug pregnancy, even if they are using oral contraceptives, should have a pregnancy test and the results should be known, before receiving each dose of MONYTRON[®] (see WARNINGS, Pregnancy).

Rev 11/2004
© 2004
MSA 000 14/2004

Manufactured by IMMUNEX CORPORATION, Seattle, WA 98111
By LYDENE PHARMACEUTICALS INC., Geneva, North-River 06064

IMMUNEX
© 2004 Immunex Corporation, Seattle, WA 98111 JAK21-G-IND 1/04

REFERENCES

1. Abrams P, Wein AJ. *The Overactive Bladder: A Widespread and Treatable Condition*. Stockholm, Sweden: Erik Sparre Medical AB; 1998.
2. Liberman JN, Hunt TL, Stewart WF, et al. Health-related quality of life among adults with symptoms of overactive bladder: results from a U.S. community based survey. *Urology*. 2001;57:1044-1050.
3. Wyman JF. Quality of life of older adults with urinary incontinence. *J Am Geriatr Soc*. 1998;46:778-779.
4. Bemelmans BL, Hommes OR, Van Kerrebroeck PE, et al. Evidence for early lower urinary tract dysfunction in clinically silent multiple sclerosis. *J Urol*. 1991;145: 1219-1224.

5. Yang S, Chancellor M. Neurological disorders. In: Cardozo L, Staskin D, eds. Textbook of Female Urology and Urogynaecology. London, England: *ISIS*; 2001:837-855.
6. Hinson JL, Boone TB. Urodynamics and multiple sclerosis. *Urol Clin North Am*. 1996;23:475-481.
7. Chancellor MB, Blaivas JG, eds. *Practical Neurourology: Genitourinary Complications in Neurologic Disease*. Boston, Mass: Butterworth-Heinemann; 1995.
8. Lackner TE. Pharmacologic management of urinary incontinence. *Ann Long-term Care*. 2000;8:29-37.
9. Goldenberg MM. An extended-release formulation of oxybutynin chloride for the treatment of overactive urinary bladder. *Clin Ther*. 1999;21:634-642.
10. Borrie MJ, Campbell K, Arcese ZA, et al. Urinary retention in patients in a geriatric rehabilitation unit: prevalence, risk factors, and validity of bladder scan evaluation. *Rehabil Nurs*. 2001;26:187-191.
11. Chan H. Noninvasive bladder volume measurement. *J Neurosci Nurs*. 1993;25:309-312.
12. Coombes GM, Millard RJ. The accuracy of portable ultrasound scanning in the measurement of residual urine volume. *J Urol*. 1994;152:2083-2085.
13. Gleason DM, Susset J, White C, et al. Evaluation of a new once-daily formulation of oxybutynin for the treatment of urinary urge incontinence. *Urology*. 1999;54:420-423.
14. Betts CD, D'Mellow MT, Fowler CJ. Urinary symptoms and the neurological features of bladder dysfunction in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 1993;56:245-250.
15. Blaivas J, Chaikin D, Chancellor M, et al. A. bladder dysfunction with neurologic disease. In: Mancall E, ed. *Continuum: Lifelong Learning in Neurology*. Baltimore, MD: Lippincott Williams & Wilkins; 1998;79-125.
16. Kim YH, Goodman C, Omessi E, et al. The correlation of urodynamic findings with cranial magnetic resonance imaging findings in multiple sclerosis. *J Urol*. 1998;159:972-976.
17. Leo G, Rao S, Bernardin L. Sleep disturbances in multiple sclerosis [abstract]. *Neurology*. 1991;41(suppl 1):727.
18. Saunders J, Whitham R, Schaumann B. Sleep disturbance, fatigue, and depression in multiple sclerosis [abstract]. *Neurology*. 1991;41(suppl 1):728.
19. Tachibana N, Howard RS, Hirsch NP, et al. Sleep problems in multiple sclerosis. *Eur Neurol*. 1994;34:320-323.
20. Krupp L. Fatigue. In: Burks JS, Johnson KP, eds. *Multiple Sclerosis: Diagnosis, Medical Management, and Rehabilitation*. New York, NY: Demos Medical Publishing; 2000:291.
21. Eastern Paralyzed Veterans Association. Disability due to fatigue and cognitive function as reported by NARCOMS patient registry participants. *MS Q Rep*. 2001;20.
22. Clark CM, Fleming JA, Li D, et al. Sleep disturbance, depression, and lesion site in patients with multiple sclerosis. *Arch Neurol*. 1992;49:641-643.
23. Hermann BP, Vickrey B, Hays RD, et al. A comparison of health-related quality of life in patients with epilepsy, diabetes and multiple sclerosis. *Epilepsy Res*. 1996;25: 113-118.
24. Rudick RA, Miller D, Clough JD, et al. Quality of life in multiple sclerosis: comparison with inflammatory bowel disease and rheumatoid arthritis. *Arch Neurol*. 1992;49:1237-1242.
25. Aronson KJ. Quality of life among persons with multiple sclerosis and their caregivers. *Neurology*. 1997;48:74-80.
26. Gajewski JB, Awad SA. Oxybutynin versus propantheline in patients with multiple sclerosis and detrusor hyperreflexia. *J Urol*. 1986;135:966-968.
27. Yoshimura N, Smith CP, Chancellor MB, de Groat WC. Pharmacologic and potential biologic interventions to restore bladder function after spinal cord injury. *Curr Opin Neurol*. 2000;13:677-681.
28. Andersson KE, Chapple CR. Oxybutynin and the overactive bladder. *World J Urol*. 2001;19:319-323.
29. Thüroff JW, Bunke B, Ebner A, et al. Randomized, double-blind, multicenter trial on treatment of frequency, urgency and incontinence related to detrusor hyperactivity: oxybutynin versus propantheline versus placebo. *J Urol*. 1991;145:813-817.
30. Birns J, Lukkari E, Malone-Lee JG. A randomized controlled trial comparing the efficacy of controlled-release oxybutynin tablets (10 mg once daily) with conventional oxybutynin tablets

(5 mg twice daily) in patients whose symptoms were stabilized on 5 mg twice daily of oxybutynin. *BJU Int.* 2000;85:793-798.

31. Comer AM, Goa KL. Extended-release oxybutynin. *Drugs Aging.* 2000;16:149-157.

32. Anderson RU, Mobley D, Blank B, et al. Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence. OROS Oxybutynin Study Group. *J Urol.* 1999;161:1809-1812.

33. Birns J, Lukkari E, Malone-Lee JG. A randomized controlled trial comparing the efficacy of controlled-release oxybutynin tablets (10 mg once daily) with conventional oxybutynin tablets (5 mg twice daily) in patients whose symptoms were stabilized on 5 mg twice daily of oxybutynin. *BJU Int.* 2000;85:793-798.

34. Versi E, Appell R, Mobley D, et al. Dry mouth with conventional and controlled-release oxybutynin in urinary incontinence. The Ditropan XL Study Group. *Obstet Gynecol.* 2000;95:718-721.

35. Gupta SK, Sathyan G, Lindemulder EA, et al. Quantitative characterization of therapeutic index: application of mixed-effects modeling to evaluate oxybutynin dose-efficacy and dose-side effect relationships. *Clin Pharmacol Ther.* 1999;65:672-684.

36. Sathyan G, Chancellor MB, Gupta SK. Effect of OROS controlled-release delivery on the pharmacokinetics and pharmacodynamics of oxybutynin chloride. *Br J Clin Pharmacol.*

Problems in Clinical Trial Design in Multiple Sclerosis

Jeffrey I. Greenstein, MD

Jeffrey I. Greenstein, MD, is affiliated with the Multiple Sclerosis Institute, Philadelphia, PA

Abstract

Historically, it has been difficult to demonstrate the effectiveness of treatments for multiple sclerosis (MS) because of the variability in the course of the disease, the lack of well-defined, reliable clinical measures, and the pervasiveness of poorly controlled clinical trials. Hence, to interpret the results of clinical trials in MS and make evidence-based decisions regarding treatment for their patients, neurologists should have a basic understanding of appropriate outcome measures and the necessary controls of a well-designed study. This paper reviews the controls required to test the efficacy of agents for the treatment of MS and offers examples of poorly controlled clinical trials to illustrate the problems in interpreting data without such controls. In addition, the outcome measures that should be used to assess the efficacy of treatments on the physical, inflammatory, and cognitive components of the disease are discussed.

Suggested citation: Problems in Clinical Trial Design in Multiple Sclerosis. Greenstein, J. Int J MS Care [Serial on-line]. 2002;4(3).

Multiple sclerosis (MS) often begins as a single acute demyelinating event involving the optic nerve (unilateral optic neuritis), the brainstem or cerebellum (acute brainstem syndromes), or the spinal cord (partial or incomplete transverse myelitis).¹ Four patterns of MS have been described and include the following: relapsing-remitting, primary progressive, secondary progressive, and progressive-relapsing MS.² Relapsing-remitting MS is characterized by well-defined disease relapses followed by periods of full recovery or with residual deficit upon recovery; there is a lack of disease progression during periods between relapses. Secondary progressive MS is characterized by gradual disease progression with or without relapses, minor remissions, and plateaus in a patient whose disease started as relapsing-remitting MS. Primary progressive MS is defined as disease progression from onset, with only occasional plateaus or temporary minor improvements. Progressive-relapsing MS is defined as progressive disease from onset with clear acute relapses, with or without full recovery; periods between relapses are characterized by continuing progression.²

Based on the results of phase III clinical trials, five immunomodulatory agents—interferon beta-1a (IFNβ-1a; Avonex®),³ interferon beta-1a (Rebif®), interferon beta-1b (IFNβ-1b; Betaseron®),⁴ glatiramer acetate (GA; Copaxone®),⁵ and mitoxantrone (Novantrone®)⁶—have become available in the United States for the treatment of relapsing-remitting MS within the past decade. Currently, several studies are ongoing to evaluate new therapies and approved therapies for additional indications within MS.

Conducting clinical trials in MS is challenging due to the wide intra-patient and inter-patient variability in the manifestation of the disease. Reports of therapeutic benefit based on uncontrolled or poorly controlled clinical trials are pervasive in the MS literature. In addition, because of the heterogeneous nature of the disease, clinical outcome measures used to test the efficacy of therapies in MS are prone to serious flaws. Further, clinical trials can answer only a limited number of questions. The design of the trial can influence the extent to which questions can be answered. For example, increasing the number of outcomes can weaken the statistical power of assessments, particularly if one outcome is dependent on another, or if subgroups smaller than the statistical power estimates for the primary outcome are analyzed. Hence, neurologists should critically evaluate the results of these studies with an understanding of the necessary controls that should be employed in clinical trials, as well as appropriate outcome measures. The objectives of this paper are to review appropriate control variables and outcome measures for MS clinical trials.

Important Controls of Phase III Trials

The efficacy of treatments in MS can be proven only by conducting large randomized, double-blind clinical trials with well-defined end points. Phase III trials are conducted following the successful completion of phase I trials in healthy volunteers and suggestion of efficacy in the patient population of interest from phase II trials. Clinical trials should contain a number of controls to prevent extraneous factors from having an effect on the dependent variable and, hence, the outcome of the study. Whenever possible, a well-designed clinical trial should contain all of the following control procedures: blinding (preferably double, but in some circumstances single), randomization, placebo or appropriate treatment control, and determination of baseline disease and end point characteristics. Adequate justification should be provided if any control is omitted.

Blinding

Blinding is an important component of a well-controlled clinical trial. In a double-blind trial, neither the investigator nor the subject knows which treatment the subject is receiving. Blinding a study controls for experimenter and subject biases and increases the probability that these biases will not affect the study results. Therefore, in MS clinical trials, it is important to have a neurologist responsible for assessment and treatment of adverse events and exacerbations (treating neurologist) and a different neurologist responsible for neurologic examinations (examining neurologist). This division of activities reduces the likelihood that the neurologist who is responsible for assessing the primary outcome variable will become unblinded to treatment.

The phase III trials of IFN β -1a, IFN β -1b, and GA for the treatment of relapsing-remitting MS were double-blinded.^{3-5,7} In the phase III trial of mitoxantrone,⁶ Expanded Disability Status Scale (EDSS) evaluations (the primary efficacy end point was the proportion of patients with confirmed progression by an increase of 1 point in the EDSS scale) were performed by trained neurologists who were blinded to study drug. However, assessments of relapses were conducted by treating physicians who were not blinded to treatment.⁶ Unblinded observation could have produced both experimenter and subject bias, which invalidates any effect of the study drug on this outcome measure.⁶

With regard to blinding, one example of a poorly controlled clinical trial is a small, open-label, non-parallel study that compared the efficacy of IFN β -1a, IFN β -1b, and GA for the treatment of relapsing-remitting MS.⁸ The authors reported that both GA and IFN β -1b reduced relapse rate compared to the untreated control group, whereas IFN β -1a had no effect. In addition, the mean

number of relapses during the second six months of therapy was lower in the GA group compared to the those in the untreated control group; however, IFN β -1b and IFN β -1a were reported to have no effect on the mean number of relapses. Mean change in EDSS, a secondary outcome variable, was reduced for IFN β -1b and GA after 12 months, whereas IFN β -1a was reported to have no effect.⁸

The open-label comparison trial⁸ data are questionable for a number of reasons. First, the results of this study contradict the data from randomized, placebo-controlled, double-blind phase III clinical trials of each agent.³⁻⁵ None of the available agents for the treatment of MS have ever been shown to improve EDSS. In addition, in their respective phase III trials, neither GA nor IFN β -1b showed a significant effect on sustained EDSS,^{4,5} whereas IFN β -1a produced a significant reduction (37%) in the risk of sustained disability progression as measured by EDSS.³

Second, there are several limitations and possible biases of this study that make it impossible to draw conclusions regarding efficacy among the three agents. The open comparison study was completely unblinded, with both experimenters and subjects aware of which treatment subjects received.⁸ In fact, patients were reported to have selected one of three therapies or no therapy based on recommendations by an investigating neurologist. Hence, this study contains selection biases, making the validity of any conclusions regarding efficacy questionable.

A trial comparing the efficacy of IFN β -1a (Avonex) 30 μ g once weekly with IFN β -1a (Rebif) 44 μ g subcutaneously three times weekly in patients with relapsing-remitting MS has recently been completed. The primary clinical end point of the study was the proportion of relapse-free patients after 24 weeks of therapy. Although it is important that direct comparison studies are performed among different IFN β preparations, this trial will not provide meaningful results because of its poor study design. Among other design problems, which will be discussed later, patients were not blinded to treatment. Differential reporting of attacks based on differing expectations of treatment could bias the trial outcome. (One potential approach to this comparison would have been the use of a single blind using disability as an end point.) While open-label studies have their place in phase IV research to assess long-term safety and tolerability, they are not valid for evaluating efficacy.

Randomization

In a well-designed clinical trial, subjects are randomly assigned to experimental and control groups using a variety of methods. With random assignment, subjects have an equal chance of being assigned to either the experimental group or the control group. Randomization increases the probability that any effect detected is due to the treatment and not to differences in baseline demographics or disease characteristics between the two groups. Lack of randomization may lead to investigator bias in assigning subjects to treatment groups. All of the phase III clinical trials of currently approved agents for the treatment of MS were randomized.³⁻⁷

An example of a poorly designed clinical trial with regard to randomization and selection bias is the recently reported six-year safety extension study of GA.⁹ In the original phase III trial,⁵ 251 patients were randomly assigned to GA 20 mg (n = 125) or placebo (n = 126). Of 125 patients in the GA group, 101 patients were assigned to "Group A" (patients treated with GA for the entire period) for the open-label phase following the phase III trial (24 dropped out). Of the 24 patients who dropped out, 63% experienced a decrease of 1.5 points or more on EDSS and had no reduction in relapse rate throughout the phase III trial. Therefore, the sickest patients were removed from the open-label study before it began, introducing bias. This study has value as a safety extension study, but it is inappropriate to draw conclusions regarding efficacy from it.

In the unblinded study,⁸ treatment groups were not studied in parallel because there was no external randomization. At the time of study initiation, only IFN β -1a and IFN β -1b were available for the treatment of MS in the United States, and enrollment of patients in the IFN β -1a and IFN β -1b groups was completed several months before any patients were enrolled in the GA group. Once enrollment was completed for the IFN β groups, only those patients who chose GA were allowed to enroll in the study. Hence, another confound of the study is that patients who were enrolled later did not have a choice of therapy.

Placebo Control

When initially evaluating the efficacy of a treatment for MS, it is important to include a placebo control group so that the effect of the drug can be measured in relation to the placebo effect. The phase III clinical trials of approved immunomodulatory agents for the treatment of relapsing-remitting MS included placebo-control groups.³⁻⁷

The unblinded study evaluated the efficacy of three immunomodulatory agents (IFN β -1a, IFN β -1b, and GA) against a "no treatment" group.⁸ This no treatment group comprised patients who decided that they did not want treatment with one of the immunomodulatory agents. Such a group is not a true placebo control, and it is impossible to separate the actual treatment effect of each immunomodulatory agent from the placebo effect. Because the immunomodulatory agents were on the market for varying lengths of time and patients may have had preconceived notions regarding the efficacy of each immunomodulatory agent, the results of the study are biased.

Another example of a poorly designed clinical trial with regard to placebo control is the recently reported six-year safety extension study of the phase III trial of GA.⁹ The authors claim that GA produced a 72% reduction in relapse rate over six years. However, without a placebo group for comparison, this claim is misleading because during a period of years the number and frequency of relapses in MS decrease naturally over time.¹⁰ What the investigators may have observed in these patients is the natural progression from relapsing-remitting MS to secondary progressive MS in patients on GA for a long period of time. In addition, their evaluation of the effect of GA on disability progression is unscientific. The 40.6% of patients treated with GA who worsened by one point or more on EDSS (sustained for more than 90 days) were compared to the 77% progression rate reported in the natural history study by Weinshenker et al.^{9,11} This comparison is invalid because the authors are comparing the treatment group of one study retrospectively to untreated subjects of a completely different study conducted at a different time when disease-modifying therapies were not available. Because there is no placebo control group in the extension study, no efficacy claims can be made.

Baseline Measures

Demographic and disease characteristics that could potentially affect patient responses to therapy should be gathered at baseline, and treatment groups should be compared on baseline characteristics to verify that there are no differences between groups that may bias study results. However, if patients are randomized to treatment groups appropriately, there should be no significant differences in baseline characteristics among groups. In addition, pretreatment (baseline) values of outcome measures should be collected and compared with posttreatment scores to determine if there was a treatment effect.

An example of the importance of collecting baseline data on outcome measures can be demonstrated by examining a recent magnetic resonance imaging (MRI) study.¹² This study evaluated the effects of GA and placebo on brain atrophy as measured by brain parenchymal

volume in a subset of patients with relapsing-remitting MS who were enrolled in the phase III trial.^{5,12} A significantly greater percent reduction from baseline in brain atrophy was observed in GA patients compared with placebo patients ($P = .0078$).¹² However, this result is difficult to interpret because patients were not matched on baseline MRI variables and baseline brain parenchymal volume was not reported, making percent change meaningless if baseline brain parenchymal volume differed between the two treatment groups.

Sample Size

Clinical trials used to make good evidence-based decisions should be of appropriate duration and sample size for the disease being studied. In MS, as in other diseases, the trial duration and the sensitivity of the clinical outcome measure affect the sample size that is required for a clinical trial.¹³ Hence, the statistical rationale for calculating sample size should be clearly stated in the published report. Phase III clinical trials conducted to date have demonstrated significant therapeutic benefits in EDSS between treatment and placebo groups in approximately 150 patients per group in two to three years.¹³

The extension of the IFN β -1b phase III trial highlights the need for an appropriate sample size.¹⁴ This study demonstrated a significant treatment effect on annual exacerbation rate during years 1 and 2, when the sample size was fairly large ($n = 372$ and 331 , respectively). However, despite a relatively constant percent decrease in annual exacerbation rate in the IFN β -1b group, the effect failed to reach significance during years 3, 4, and 5 because the sample size decreased substantially ($n = 286$, 247 , and 166 , respectively). In the GA phase III trial extension,⁹ 251 patients were randomized to the double-blind phase and 152 patients participated in the open-label phase at six years from study entry. In the group of patients who received GA from study onset, relapse rate decreased from 1.49 at baseline to 0.75 at year 1 and 0.23 at year 6. In both the IFN β -1b and GA extension studies, reductions in relapse rates across years may not have been due to clinical effects, but rather due to regression to the mean. In future MS clinical trials, new therapies will likely be compared with IFNs because placebo controls will be considered unethical; and these trials will require larger sample sizes to detect an effect.

Outcome Measures in MS Clinical Trials

Therapies for MS should show activity against three types of efficacy parameters in a well-designed study for efficacy claims: physical disability, MRI measures, and cognition. Although there is not one measure that covers all aspects of MS, a clinical measure that encompasses the major clinical dimensions of arm, leg, and cognitive function (the Multiple Sclerosis Functional Composite) has been developed and results of initial validation studies have been positive.¹⁵⁻¹⁷

Physical Measures

Relapse Rate: Relapse rate is commonly used as the primary outcome measure in clinical trials of MS treatments.^{4,5,7} Relapses are thought to be the clinical manifestation of acute inflammatory focal lesions in the central nervous system.⁸ Although relapse rate is widely used because it is easy to quantify, it should not be used as the sole primary outcome measure for clinical trials. Relapse rates vary as a function of age and duration of disease, with relapses occurring more often in younger patients and decreasing with time from onset of disease.¹⁰ Confavreux et al recently showed that once an EDSS score of 4.0 or greater was reached, disability progression was not affected by either prior or subsequent relapses.¹⁸ These data

suggest that relapse rate alone should not be used as the primary outcome measure in clinical trials because treatments that have a short-term effect on relapses may not affect long-term disability progression.¹⁸ Hence, relapses are symptoms of the apparent clinical effect of the disease on the body and not a true measure of the overall effect of the disease.

Another problem with using relapse rate alone as the primary outcome measure is that there is no consensus among investigators on a single operational definition of relapse, which makes it difficult to compare results among clinical trials. While the phase III trials of IFN β -1b and GA had roughly the same requirement of symptoms defining a relapse, they differed significantly in the minimum duration that symptoms should last before counting the episode as a relapse (48 hours for IFN β -1b, 24 hours for GA). A longer duration provides a more stringent and conservative measure of relapse, and reduces the risk of including transient symptoms and false relapses.

There are several completed and ongoing trials that use relapse rate as the primary outcome measure. For example, relapse rate was the only clinical outcome measure comparing the efficacy of two formulations of IFN β -1a (Rebif versus Avonex). Not only is relapse rate not a good measure for the reasons already discussed, but efficacy was determined after only six months of treatment. Given the heterogeneity that exists in disease symptoms, six months is not long enough to detect any effect of treatment on relapse rate. The open-label study also compared the effects of IFN β -1a, IFN β -1b, and GA on relapse rate as the primary outcome measure.⁸

Disability: Disability status during a period of relative clinical stability is the most desirable single outcome measure in MS.^{10,19} The EDSS is currently one of the most widely used disability measures in MS clinical trials.^{20,21} The EDSS assesses pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and mental function systems. The EDSS is an ordinal scale with scores that range from 0 (normal neurological exam) to 10 (death) and are measured in half-point increments. Scores from 0 to 3.5 reflect the number of functional symptoms scores and the severity of dysfunction for each functional system. Scores above 4.0 are based primarily on the effect of the disease on ambulation.²² The use of a treatment failure end point, such as proportion of patients who experience a predetermined change from baseline EDSS, is the preferred method of analyzing EDSS, especially when inter- and intra-rater variability is taken into account. Investigators should be trained on the administration and scoring of the EDSS to limit such variability. In addition, it is suggested that a buffer (± 0.5 point) be allowed for baseline EDSS scores less than 5.5 without assuming a treatment failure. It is recommended that a 1.0-point worsening from baseline be considered a treatment failure for patients with a baseline EDSS score less than 5.5. For patients with a baseline EDSS score of 5.5 or greater, a 0.5-point worsening should be considered a treatment failure.²³

The use of a survival approach has advantages and disadvantages. The usefulness of this approach depends on the ease of definition of an end point as well as its relevance to the disease process. The ease, sensitivity, and reproducibility of measuring the end points and the use of censoring data also influence the applicability of this method of outcome analysis.

Sustained, rather than unsustained, disability is the preferred method of measuring disease progression. The importance of measuring sustained disability progression is highlighted by a report by Ellison et al, which showed that the longer the disability is required to be sustained, the more likely that change in EDSS will reflect true progression in disability.²⁴ Unsustained disability can be misleading because it takes into account the impact of short-term disability (relapses). If differences exist between the treatment group and the control group in the number of relapses, then the data would be biased. Sustained disability progression (for at least six months) should be analyzed using a Kaplan-Meier analysis, which censors patients who do not reach the disability end point on or before their last scheduled visit. In addition, Kaplan-

Meier analysis considers random attrition from the study population and gives a more accurate estimate of the probability that a patient will worsen.

The open-label study compared the effects of IFN β -1a, IFN β -1b, and GA on change in mean EDSS as one of the secondary end points. However, the evaluation of this end point is not valid for several reasons. First, EDSS scores were not collected in a controlled manner because some EDSS scores were reported by patients over the phone without a visit to the investigating neurologist for verification. Second, mean change in EDSS score is not an appropriate end point because EDSS scores are based on an ordinal scale and parametric statistical methods cannot appropriately be used to analyze this scale.²¹ In this study, mean change in EDSS scores were reviewed using an analysis of variance, a parametric statistical test, making the results of this comparison invalid. Third, the changes reported in EDSS scores were on a narrow scale (a range of 0.2 improvement to 0.2 decline), which have questionable clinical significance.⁸ In addition to this study, mean change in EDSS was a secondary end point in the phase III trials of both GA and mitoxantrone,^{5,6} resulting in questionable validity of the disability findings in these studies.

Inflammatory Measures

MRI measures are commonly used as secondary outcomes in clinical trials of MS treatments. Many phase III trials of immunomodulatory agents have evaluated the number and volume of gadolinium-enhanced T1 lesions,^{3,12,25} number and volume of T2 lesions,^{12,25,26} new or enlarging T2 lesions,^{3,6,25-27} lesion area,⁴ and volume of T1-hypointense lesions.²⁷ Lesions with contrast enhancement on T1-weighted MRI after administration of gadolinium indicate breakdown of the blood-brain barrier and acute inflammatory changes.^{28,29} An 89% reduction in gadolinium-enhanced lesions has been observed in IFN β -1a patients³ who had gadolinium enhancement at baseline (P = .041), an 84% reduction in gadolinium-enhanced lesions has been observed with IFN β -1b (P < .0001),³⁰ and a 29% reduction in lesions has been observed with GA (P = .003).³¹

Lesions can also be identified as an area of high signal on T2-weighted MRI. The number of new or enlarged T2 lesions (T2 lesion load) is thought to provide a measure of past disease activity.³² Of the total lesion load induced by MS in the brain, T1-hypointense lesions are thought to indicate more severe damage,³³⁻³⁵ as T1-hypointense lesions reflect axonal loss, gliosis, and loss of intracellular matrix, in addition to demyelination.

The number and volume of new gadolinium-enhanced lesions appears to have predictive value regarding the short-term course of MS, with higher lesion numbers associated with increased relapse rates, T2 lesion burden, and disability progression.³⁶⁻⁴⁰ However, if MRI measures could be shown to predict the long-term course of MS, they could be used in future MS clinical trials as surrogate outcome measures of disease progression. One study found T1-hypointense lesions, but not T2-hyperintense lesions, to be strongly correlated with progression of disability in secondary progressive MS.³³ Another study found a moderate correlation between T2 lesion load at disease presentation and disability after five years.⁴¹

Brain Atrophy: Three-dimensional measures that are more specific for destructive changes in the brain have recently been evaluated. Rudick et al⁴² performed a post hoc analysis of the effects of IFN β -1a on whole-brain atrophy in patients who participated in the phase III trial. Whole-brain atrophy was measured by brain parenchymal fraction, which is defined as the ratio of brain parenchymal volume to the total volume within the brain surface contour. A total of 140 patients who had MRI scans available from baseline, one year, and two years were included in the post hoc analysis. Results showed that IFN β -1a reduced the rate of brain atrophy by 55% compared with the placebo group during the second year of treatment (P = .03).⁴²

Brain parenchymal volume is another measure of whole-brain atrophy. Ge et al¹² evaluated the effects of GA and placebo on brain parenchymal volume in a cohort of 27 patients with relapsing-remitting MS who were enrolled in the phase III study.^{5,12} Brain parenchymal volume is obtained by subtracting the cerebrospinal fluid volume from the intracranial volume. Results showed a significantly greater percent decrease in brain parenchymal volume from baseline in the placebo group compared with the GA-treated group ($P = .0078$).¹² Brain volume was also measured in 95 secondary progressive MS patients who completed a European trial of IFN β -1b.⁴³ Although clinical results demonstrated a significant delay in disability progression in the IFN β -1b group compared with placebo,⁴⁴ no effect of treatment was observed on brain atrophy.⁴³ Lack of a treatment effect on brain atrophy is likely due to the method utilized to assess atrophy (ie, use of volume rather than brain parenchymal fraction and the evaluation of brain slices rather than whole brain). Unlike brain parenchymal fraction and brain parenchymal volume, slice volume is not normalized, making it susceptible to increased variability among subjects and less sensitive to detect small changes.

Cognitive Measures

Although the clinical presentation and course of MS are heterogeneous,⁴⁵ it is now recognized that cognitive impairment is common in MS, with 43% to 65% of patients exhibiting some neuropsychological dysfunction.⁴⁶ Because of the prevalence of cognitive deficits in MS, evaluation of this feature is an extremely relevant end point for MS studies. The cognitive domains most affected by MS are information processing (distractibility, slowing of mental process, difficulty performing multiple tasks) and verbal and visual memory (forgetfulness, especially delayed recall of recently learned information).⁴⁶ Deficits in visuospatial abilities and executive functions are also common, whereas verbal abilities and attention span are usually spared.⁴⁶ Traditional clinical outcome measures used in MS are insensitive to cognitive changes in the MS population,¹⁹ and none of the currently available neuropsychological measures can detect deficits in all the cognitive domains affected by MS.⁴⁷ Hence, the most prudent approach is to use neuropsychological tests that measure the cognitive domains that are most affected by MS.

Neuropsychological outcomes have been assessed in three trials of disease-modifying agents in patients with relapsing MS. A study of the effects of GA on cognitive function in patients with MS⁴⁸ revealed no statistically significant treatment effects. In a study with IFN β -1b,⁴⁹ one of 13 outcome variables (visual delayed recalled) demonstrated significant improvement following treatment with IFN β -1b 8.0 MIU ($P < .003$). However, this finding is difficult to interpret because no pretreatment neuropsychological baseline scores were reported. In the IFN β -1a phase III trial,^{3,50} IFN β -1a was shown to positively affect measures of cognitive domains that are most vulnerable to MS: information processing and learning/ memory ($P = .011$). In addition, progression of cognitive deterioration was slowed by 47% in patients with multiple sclerosis compared with placebo, based on a commonly used neuropsychological measure (the Paced Auditory Serial Addition Test [PASAT] Processing Rate) ($P = .023$).⁵⁰

Conclusions

There is a need for well-designed clinical trials in MS so that practicing neurologists can make evidence-based decisions regarding treatment for their MS patients. In general, the efficacy of treatments for MS can only be established in large randomized, double-blind clinical trials with well-defined end points. All clinical trials should include sustained disability progression as a primary end point. To evaluate a treatment's effect on all aspects of MS (physical, inflammatory, and cognitive), MRI and neuropsychological end points should be included as well.

With a number of new drugs for the treatment of MS on the horizon, it may become more difficult for neurologists to assess the relative efficacy and safety of these agents against IFNbs, the current standard of care in MS. In the future, it will be considered unethical to conduct placebo-controlled trials because there are effective treatments available. It will therefore be necessary to conduct studies in which both treatment groups receive the standard of care, as in the case of add-on regimens, or the new treatment is evaluated against the standard of care. Some investigators may be tempted to make comparisons between therapies across clinical trials. However, this type of comparison is inappropriate due to important differences in design and patient populations among clinical trials. Although phase IV trials are valid for assessing safety and tolerability, they are not blinded and cannot be used to make efficacy claims. Conclusions regarding efficacy among therapies should be drawn from the results of well-designed, head-to-head comparison studies with well-defined end points, including sustained disability progression.

REFERENCES

1. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain*. 1989;112:133-146.
2. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology*. 1996;46:907-911.
3. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann Neurol*. 1996;39:285-294.
4. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. *Neurology*. 1993;43:655-661.
5. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. *Neurology*. 1995;45:1268-1276.
6. Millefiorini E, Gasperini C, Pozzilli C, et al. Randomized placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. *J Neurol*. 1997;244:153-159.
7. Randomised double-blind placebo-controlled study of interferon b-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. *Lancet*. 1998;352:1498-1504.
8. Khan OA, Tselis AC, Kamholz JA, et al. A prospective, open-label treatment trial to compare the effect of IFN beta-1a (Avonex), IFN beta-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing-remitting multiple sclerosis. *Eur J Neurol*. 2001;8:141-148.
9. Johnson KP, Brooks BR, Ford CC, et al. Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years. Copolymer 1 Multiple Sclerosis Study Group. *Mult Scler*. 2000;6:255-266.
10. Weinshenker BG, Ebers GC. The natural history of multiple sclerosis. *Can J Neurol Sci*. 1987;14:255-261.
1. Weinshenker BG, Rice GP, Noseworthy JH, et al. The natural history of multiple sclerosis: a geographically based study. 3. Multivariate analysis of predictive factors and models of outcome. *Brain*. 1991;114:1045-1056.
12. Ge Y, Grossman RI, Udupa JK, et al. Glatiramer acetate (Copaxone) treatment in relapsing-remitting MS: quantitative MR assessment. *Neurology*. 2000;54:813-817.
13. Rudick R, Antel J, Confavreux C, et al. Clinical outcomes assessment in multiple sclerosis.

Ann Neurol. 1996;40:469-479.

14. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. The IFNB Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. *Neurology.* 1995;45:1277-1285.
15. Cohen JA, Fischer JS, Bolibrush DM, et al. Intrarater and interrater reliability of the MS functional composite outcome measure. *Neurology.* 2000;54:802-806.
16. Cutter GR, Baier ML, Rudick RA, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain.* 1999;122:871-882.
17. Fischer JS, Rudick RA, Cutter GR, Reingold SC. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. *Mult Scler.* 1999;5:244-250.
18. Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. *New Engl J Med.* 2000;343:1430-1438.
19. Whitaker JN, McFarland HF, Rudge P, Reingold SC. Outcomes assessment in multiple sclerosis clinical trials: a critical analysis. *Mult Scler.* 1995;1:37-47.
20. Goodkin DE, Cookfair D, Wende K, et al. Inter- and intrarater scoring agreement using grades 1.0 to 3.5 of the Kurtzke Expanded Disability Status Scale (EDSS). Multiple Sclerosis Collaborative Research Group. *Neurology.* 1992;42:859-863.
21. Wingerchuk DM, Noseworthy JH, Weinshenker BG. Clinical outcome measures and rating scales in multiple sclerosis trials. *Mayo Clin Proc.* 1997;72:1070-1079.
22. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.* 1983;33:1444-1452.
23. Weinshenker BG. Clinical outcome measures for multiple sclerosis. In: Goodkin DE, Rudick RA, eds. *Multiple Sclerosis: Advances in Clinical Trial Design, Treatment, and Future Perspectives.* London, UK: Springer Verlag; 1996:105-122.
24. Ellison GW, Myers LW, Leake BD, et al. Design strategies in multiple sclerosis clinical trials. The Cyclosporine Multiple Sclerosis Study Group. *Ann Neurol.* 1994;36 (suppl):S108-112.
25. Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *N Engl J Med.* 2000;343:898-904.
26. Simon JH, Jacobs LD, Campion M, et al. Magnetic resonance studies of intramuscular interferon b-1a for relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group. *Ann Neurol.* 1998;43:79-87.
27. Simon JH, Lull J, Jacobs LD, et al. A longitudinal study of T1 hypointense lesions in relapsing MS. MSCRG trial of interferon b-1a. The Multiple Sclerosis Collaborative Research Group. *Neurology.* 2000;55:185-192.
28. Katz D, Taubenberger JK, Cannella B, et al. Correlation between magnetic resonance imaging findings and lesion development in chronic, active multiple sclerosis. *Ann Neurol.* 1993;34:661-669.
29. Simon JH. Contrast-enhanced MR imaging in the evaluation of treatment response and prediction of outcome in multiple sclerosis. *J Magn Reson Imaging.* 1997;7:29-37.
30. Stone LA, Frank JA, Albert PS, et al. The effect of interferon-b on blood-brain barrier disruptions demonstrated by contrast-enhanced magnetic resonance imaging in relapsing-remitting multiple sclerosis. *Ann Neurol.* 1995;37:611-619.
31. Comi G, Filippi M, for the Copaxone MRI Study Group (1999). The effect of glatiramer acetate (Copaxone®) on MRI-detected disease activity in patients with relapsing-remitting multiple sclerosis: a multi-center, randomized, double-blind, placebo-controlled study extended by open-label treatment. *Multiple Sclerosis* 5 (Suppl 1): S20.
32. Willoughby EW, Grochowski E, Li DK, et al. Serial magnetic resonance scanning in multiple sclerosis: a second prospective study in relapsing patients. *Ann Neurol.* 1989;25:43-49.
33. Truyen L, van Waesberghe JH, van Walderveen MA, et al. Accumulation of hypointense lesions ("black holes") on T1 spin-echo MRI correlates with disease progression in multiple sclerosis. *Neurology.* 1996;47:1469-1476.
34. van Waesberghe JH, Castelijns JA, Scheltens P, et al. Comparison of four potential MR parameters for severe tissue destruction in multiple sclerosis lesions. *Magn Reson Imaging.*

1997;15:155-162.

35. van Walderveen MA, Kamphorst W, Scheltens P, et al. Histopathologic correlate of hypointense lesions on T1-weighted spin-echo MRI in multiple sclerosis. *Neurology*. 1998;50:1282-1288.

36. Khoury SJ, Guttmann CR, Orav EJ, et al. Longitudinal MRI in multiple sclerosis: correlation between disability and lesion burden. *Neurology*. 1994;44:2120-2124.

37. Molyneux PD, Filippi M, Barkhof F, et al. Correlations between monthly enhanced MRI lesion rate and changes in T2 lesion volume in multiple sclerosis. *Ann Neurol*. 1998;43:332-339.

38. Simon JH, Jacobs LD, Campion MK, et al. A longitudinal study of brain atrophy in relapsing MS. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Neurology*. 1999;53:139-148.

39. Smith ME, Stone LA, Albert PS, et al. Clinical worsening in multiple sclerosis is associated with increased frequency and area of gadopentetate dimeglumine-enhancing magnetic resonance imaging lesions. *Ann Neurol*. 1993;33:480-489.

40. Tubridy N, Coles AJ, Molyneux P, et al. Secondary progressive multiple sclerosis: the relationship between short-term MRI activity and clinical features. *Brain*. 1998;121:225-231.

41. Filippi M, Horsfield MA, Morrissey SP, et al. Quantitative brain MRI lesion load predicts the course of clinically isolated syndromes suggestive of multiple sclerosis. *Neurology*. 1994;44:635-641.

42. Rudick RA, Fisher E, Lee JC, et al. Use of brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS. Multiple Sclerosis Collaborative Research Group. *Neurology*. 1999;53:1698-1704.

43. Molyneux PD, Kappos L, Polman C, et al. The effect of interferon beta-1b treatment on MRI measures of cerebral atrophy in secondary progressive multiple sclerosis. European Study Group on Interferon beta-1b in secondary progressive multiple sclerosis. *Brain*. 2000;123:2256-2263.

44. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on Interferon beta-1b in Secondary Progressive MS. *Lancet*. 1998; 352:1491-1497.

45. Rudick RA, Goodkin DE. Aspects of multiple sclerosis that relate to clinical trial design and treatment. In: Rudick RA, Goodkin DE, eds. *Multiple Sclerosis Therapeutics*. London, UK: Martin Dunitz, Ltd; 1999:3-15.

46. Rao SM, Leo GJ, Bernardin L, Unverzaft F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology*. 1991;41:685-691.

47. Fischer JS. Measures of neuropsychological function. In: Rudick RA, Goodkin DE, eds. *Multiple Sclerosis Therapeutics*. London, UK: Martin Dunitz, Ltd; 1999:31-47.

48. Weinstein A, Schwid SI, Schiffer RB, et al. Neuropsychologic status in multiple sclerosis after treatment with glatiramer. *Arch Neurol*. 1999;56:319-324.

49. Pliskin NH, Hamer DP, Goldstein DS, et al. Improved delayed visual reproduction test performance in multiple sclerosis patients receiving interferon beta-1b. *Neurology*. 1996;47:1463-1468.

50. Fischer JS, Priore RL, Jacobs LD, et al. Neuropsychological effects of interferon beta-1a in relapsing multiple sclerosis. Multiple Sclerosis Collaborative Research Group. *Ann Neurol*. 2000;48:885-892.

Health and Social Profile of Older Adults with MS: Findings From Three Studies

Marcia Finlayson, PhD, OT (C), OTR/L

Marcia Finlayson is an Assistant Professor, Department of Occupational Therapy, College of Applied Health Sciences, University of Illinois at Chicago.

Abstract

Currently in the United States, approximately 45% of people with multiple sclerosis (MS) are older than 55. The majority of these people can expect to live as long as their age peers. This paper provides a health and social profile of 440 older adults with MS (mean age, 64) using data from three separate studies conducted in Canada and the United States. The majority of participants were women, married, living with at least one other person, and reporting that their income was adequate to meet their needs. The most common symptoms reported included fatigue, problems with balance, and weakness. Participants had the most difficulty with doing heavy housework, making a hot meal, managing finances, and bathing. Overall, most participants reported their health as poor. Comparing these findings to existing literature suggests important health differences between younger and older people with MS, and between older adults with and without MS, that may not be sufficiently recognized by existing services.

Suggested citation: Health and Social Profile of Older Adults with MS: Findings from Three Studies. Finlayson, M. Int J MS Care [Serial on-line] 2002;4(3)

Multiple sclerosis (MS) is a chronic, debilitating, neurologic disease that is typically diagnosed in people between the ages of 20 and 40. Prevalence estimates for MS range from 20 to 150 cases per 100,000 people, depending on the population under study and the geographic region of the world.¹⁻³ In the United States, there are approximately 250,000 to 350,000 people who have MS,⁴ and 45% of these (between 112,000 and 158,000) are older than 55.⁵

MS can result in considerable disability, but it does not significantly reduce life expectancy unless the disability associated with the disease is severe.^{3,6} Severe disability occurs in approximately 10% to 15% of all cases of MS.⁵ Therefore, the majority of people with MS can expect to live as long as their age peers. Currently, United States life expectancy estimates range from 74 years for men to 79 years for women.⁷ Together these figures suggest that the majority of individuals who are diagnosed with MS in their early 20s are likely to live with the disease for 50 years or longer. As a result, they will have to cope with normal age-related changes in their life and health as well as having to manage with disability related to MS. Despite this, few researchers have systematically examined the health and social characteristics of older adults with MS.

The MS literature suggests that people with this disease often experience and adapt to changes in their work and social and daily life earlier in their lifetime than the majority of their age peers because of disease symptoms and their consequent disabilities.^{1,8-10} This literature implies two things—first, that older adults with MS may be better prepared for normal age-related changes

than their peers because of experience, and second, that older adults with MS may have different service needs than their age peers because they already possess many skills for adapting to disability. Nevertheless, no evidence exists to support or refute either of these ideas. Within the gerontologic literature, descriptions of the needs and concerns of older adults are common, but it is unclear to what extent this research can be applied to people aging with MS because no general health and social descriptions of older adults with MS are available. Thus, this lack of knowledge limits the ability of researchers and clinicians to select and apply existing gerontologic intervention strategies or to develop new ones to enable people with MS to age-in-place and to continue to participate in family and community life as they age.

This paper is an attempt to fill these gaps in knowledge. Its purpose is to provide a health and social profile of people 55 and older with MS using data from three separate studies conducted in Canada and the United States. The specific objectives of the paper are to describe the social resources available to this population and their health-related characteristics (eg, MS symptoms, activity limitations). This provides a beginning to identifying potential service needs of older adults with MS and areas for future, more focused, research.

Literature Review

In the past, those who had or contracted chronic and disabling conditions early in life were not expected to live into old age. Advances in medical, rehabilitative, and pharmaceutical interventions are enabling these individuals to live well into their retirement years. Research on people who are aging with existing disabilities such as spinal cord injury, polio, and developmental disability suggests that this population has unique health concerns and experiences unique health and functional status issues that may not be well addressed by either aging-related services (eg, geriatric rehabilitation, seniors' programs) or services especially designed for people with their particular diagnosis.¹¹⁻¹³

To date, the vast majority of MS research has come from the basic sciences and has focused on identifying the cause of MS, finding better diagnostic tools, and discovering more effective pharmaceutical management strategies. Recently, there has been more interest in issues related to living with MS: for example, managing fatigue,¹⁴ measuring quality of life,¹⁵ and understanding the stresses of caregiving.¹⁶ These studies enabled health and social service providers who work with people with MS to develop a broader range of potential interventions. Nevertheless, the success of these various studies is raising questions about what lies ahead for people with MS as they age.

Across the major health and gerontological bibliographic databases (ie, MEDLINE, CINAHL, AARP Ageline), only two studies could be located that explicitly examined the topic of aging with MS^{17,18} rather than of being diagnosed with MS at a later age. The first of these two studies described the comorbidities of older adults with MS who were discharged from the hospital.¹⁷ The study found that older adults with MS were more likely than age- and sex-matched peers to have urinary tract infection, pneumonia, septicemia, and cellulitis as their discharge diagnosis, and less likely to have heart attack or failure, angina, cerebrovascular disease, diabetes, or lung disease.

In the second study, a standardized mail-out survey was used to gather information from members of the German Multiple Sclerosis Society.¹⁸ A secondary analysis of 53 participants older than 65 was conducted. Findings showed that half of the sample were living alone and that most (70%) were using a wheelchair. The average length of time with MS was just over 25 years. Forty-seven percent of participants needed help to use the toilet, and 80% needed help to bathe. An alarming 30% of participants reported often or always thinking about suicide.

In other descriptive articles about people with MS, based on needs assessments, only three of the seven indexed studies specified the proportion of participating older adults (range, 17% to

21%), with the actual number of older adults ranging in age from 46 to 91.¹⁹⁻²⁵ None of these studies included age-specific analyses and therefore they provided no insight into the situation or needs of older adults with MS.

Although older adults with MS are rarely studied, older adults with either late-onset and/or relatively stable conditions are the focus of much gerontologic research. The topics popular in gerontological research with these populations appear relevant to people aging with MS. These topics have included, but are not exclusive to, self-care management,^{26,27} long-term care use,^{28,29} aging-in-place,^{30,31} health promotion and disease prevention,^{32,33} and social support and informal caregiving.^{34,35}

Nevertheless, until more is known about aging with MS, the generalizability and applicability of these broader gerontologic findings to this population will remain unclear. Clarity is needed in order to appropriately select, modify, or develop intervention strategies to enable people with MS to age-in-place, to continue to participate in family and community life, and to facilitate the identification of necessary directions for health and social advocacy efforts. As a first step in filling this knowledge gap, a descriptive profile of older adults with MS was developed, specifically focusing on health and social factors.

Methods

This analysis used data from three studies of people with MS, all of which used convenience samples. The first two studies were large mail-out surveys that included people with MS of all ages from two regions in Canada. These studies were conducted in the mid- to late-1990s. The third study was a small mixed-method study conducted in Chicago in 2001 that had an exclusive focus on people with MS who were older than 55. While this latter study is much different in terms of methods and size from the first two studies, its exclusive focus on older adults with MS may have attracted participants who are particularly concerned about aging with MS. As a result, it provides a useful comparison to the first two studies, neither of which focused on older adults. Basic methodologic information about these studies is provided below.

Studies 1 and 2: Both of these studies involved confidential mail-out surveys using the same basic survey instrument and the same cover letter explaining the study and a participant's rights as a research subject. The Manitoba Division of the Multiple Sclerosis Society of Canada conducted Study 1 in 1995. Study 2 was conducted by the Atlantic Division in 1997 and 1998. In both studies, the purpose was to gather information for program planning and social advocacy efforts.^{36,37} The studies were approved, funded, and conducted under the supervision of the respective Boards of Directors.

The original survey tool was developed to meet the information needs of the Manitoba Division. The tool was taken and revised slightly for use in the Atlantic Division. It gathered information on basic demographics, on self-reported general health status, on work and financial situation, and about the MS Society programs and services the respondent was using or had used in the past. All questions in the survey were closed-ended, with response types including dichotomous, multcategory, checklist, and fill-in-the-blank. The survey tool was pretested using focus groups comprising members of the MS Society in Manitoba and was reviewed for style, format, and content by colleagues of this author (the principal investigator for the Manitoba study) and the primary consultant to the Atlantic study.

In Manitoba, the survey was distributed in the spring of 1995 to 720 members known to have MS. A single reminder letter to return the survey was sent two to three weeks after the initial mailing went out. An overall response rate of 65% was achieved, with 142 respondents reporting an age of 55 or older. A description of the sample used in this analysis is presented in the Results section. One staff person completed all data entry into the Number Cruncher Statistical System³⁸ after receiving training from the principal investigator. The principal

investigator completed all data checking and cleaning after the entry was complete and then converted the file into SPSS Version 10.1.4.³⁹

In the Atlantic region, the survey was distributed in the late fall of 1997 to 3,015 members of the Society. No reminder letter was sent out because of financial constraints. An overall response rate of 39% was achieved, with 274 respondents reporting an age of 55 or older. A description of the sample is presented in the Results section of this paper. Professional data entry staff at Dalhousie University in Halifax, Nova Scotia, completed all data entry, checking, and cleaning.

Table 1				
Description of social profile variables, by study				
	Study 1: Manitoba Survey (n = 142)	Study 2: Atlantic Survey (n = 274)	Study 3: Chicago Older Adults study (n = 24)	
Age (mean, standard deviation)	64.3, SD = 8.5	63.7, SD = 6.7	61.8, SD = 6.9	
Sex				
Male	27.5%	32.5%	16.7%	
Female	72.5%	67.5%	83.3%	
Marital Status				
Married	66.7%	72.6%	70.8%	
Widowed	17.0%	12.0%	8.3%	
Separated or Divorced	7.1%	9.9%	12.5%	
Never Married	9.2%	5.5%	8.3%	
Length of Current Marital Status (not including Never Married) (mean, standard deviation)	31.1 years, SD = 14.5	33.2 years, SD = 13.4	28.0 years, SD = 17.0	
Living Arrangements				
Lives alone	24.8%	14.6%	20.8%	
Lives with others	75.2%	85.4%	79.2%	

Study 3: This cross-sectional descriptive study was initiated in the summer of 2001 with the goal of identifying and describing the most common health concerns and service-related issues of people who are aging with MS. The study sample included 24 people with MS at least age 55 and who had MS for 15 years or longer. Participants were recruited through mailings to members of support groups organized by the Greater Illinois Chapter of the National Multiple Sclerosis Society after ethics approval was granted for the study by the Human Subjects Review Board of the University of Illinois at Chicago.

All data collection for the study occurred between July and November 2001. The principal investigator and two trained research assistants completed all of the data collection. The study involved two separate interviews with each participant completed over a maximum of three

weeks. During the first meeting (average length, 1 hour and 45 minutes), the participants were engaged in a qualitative interview focusing on their experiences of aging with MS, their health concerns, and their service needs and issues. Since the qualitative data will not be discussed in this paper, no further elaboration of these data will be presented.

During the second interview (average length, 1 hour and 50 minutes), the following seven of the 10 scales included in the Multiple Sclerosis Quality of Life Inventory⁴⁰ were administered: the SF-36, the Fatigue Impact Scale, the Medical Outcomes Study Pain Effects Scale, the Impact of Visual Impairment Scale, the Perceived Deficits Questionnaire, the Mental Health Inventory, and the Modified Medical Outcomes Social Support Survey. In addition, questions from the social resources, physical health, activities of daily living, and services supplement scales of the Older Adults Resources and Services (OARS) Multidimensional Functional Assessment Questionnaire were administered.⁴¹ Data were entered into SPSS for Windows, Version 10.1.4, then checked and cleaned by the research assistants under the supervision and direction of the principal investigator.

Analysis

For the purposes of this analysis, the questions asked of respondents across the three studies were compared. Forty-four variables relating to the health or social situation of the respondents were identified that either exactly matched in question wording and response coding or matched in question wording with the possibility of response recoding to achieve a match. These variables were recoded as required and merged into a single data set that contained 440 complete records that included information on social situation (marital status, living arrangements, housing type, work status, education, income adequacy) and health status (MS symptoms, activity limitations, use of equipment, self-rated health). All analyses were conducted using SPSS for Windows, Version 10.1.4. Since the majority of variables in the study were dichotomous, nominal, or ordinal, chi-squared tests were used to compare the profiles of participants across the three studies. ANOVA was used to compare variables that were continuous in nature. Because of the small sample size in the Chicago study, some analyses were not possible as the assumptions of the particular test could not be met.

Results

Of the 440 older adults with MS included in this analysis, the average age was 64.0 (SD, 7.3 years). There were no differences in age across the three studies ($P = 0.27$). As expected, the majority of the participants in all studies were female, ranging from 67.5% in the Atlantic survey to 83.3% in the Chicago study. There were no differences in age of participants by sex.

The majority of participants across the three studies were married, and among these the average length of marriage was 37 years (SD, 10 years). Among those who were widowed, the average length of widowhood was 15 years. Those participants who were single were the youngest across the studies (average age, 60.0; SD, 5.4 years) while those who were widowed were the oldest (average age, 69.0; SD, 7.0 years). Consistent with their marital status, the majority were living with at least one other person, although the likelihood of living alone was significantly greater among the participants from the Manitoba study. Not surprisingly, men were less likely to be living alone than women. Table 1 provides the descriptive details of these social profile variables among the participants, by study.

In terms of social status indicators, the majority of participants across all three studies were living in single-family homes (73.6%) that they owned (81.8%). Relatively few were living in a nursing home, but among those who did, their average age was significantly older than those living in other types of housing arrangements. For the most part, the study respondents were well educated, although the Chicago sample was more likely to have postsecondary education than either of the Canadian samples. No relationship between age and educational level was found. The majority across the studies described their current income levels as adequate to

meet their current needs, with no significant differences found by sex or age. Table 2 provides the descriptive details of these social status indicator variables among the participants, by study.

Table 2				
Social status indicators, by study				
		Study 1: Manitoba Survey (n = 142)	Study 2: Atlantic Survey (n = 274)	Study 3: Chicago Older Adults study (n = 24)
Type of housing				
	House	68.3%	77.0%	66.7%
	Apartment	18.3%	10.6%	4.2%
	Condo	2.1%	1.1%	12.5%
	Nursing home	9.2%	5.8%	12.5%
	Other	2.1%	5.5%	4.2%
Home ownership				
	Own	76.0%	84.8%	83.3%
	Rent	19.2%	13.0%	12.5%
	Other arrangement	4.8%	2.2%	4.2%
Education				
	Did not graduate			
	high school	50.7%	44.0%	4.2%
	Graduated high school	17.9%	18.0%	20.8%
	Postsecondary	31.4%	38.0%	75.0%
Adequacy of current income				
	Very well	16.1%	16.1%	37.5%
	Adequate	47.5%	42.2%	45.8%
	With some difficulty	26.3%	28.5%	8.3%
	Not very well	9.3%	9.6%	8.3%
	Totally inadequate	0.8%	3.6%	0.0%

Although data on the type of MS were not gathered for the Chicago study, the Manitoba and Atlantic studies showed that nearly half (46.8%) of these participants had a progressive form of MS. This is consistent with the fact that the average time since MS diagnosis was 18.7 years (SD, 10.7 years). The most common symptoms reported included fatigue (82.6%), problems with balance (81.1%), and weakness (73.3%). The least noted symptom was problems speaking (20.5%). Overall, the average number of symptoms reported was 5.4 (SD, 2.5). The Chicago study population indicated significantly more symptoms than the cohort in either of the two Canadian studies. Spasticity, pain, problems swallowing, and incontinence were all reported significantly more often by those in the Chicago study compared to the other studies. Table 3 summarizes the symptoms reported by participants, by study.

Table 3			
Participants reporting specific MS symptoms, by study			
	Study 1: Manitoba Survey (n = 142)	Study 2: Atlantic Survey (n = 274)	Study 3: Chicago Older Adults study (n = 24)
Fatigue	83.7%	81.3%	91.7%
Problems with balance	76.6%	82.1%	95.8%
Weakness	75.9%	71.1%	83.3%
Pain	40.4%	43.2%	75.0%
Spasticity	40.3%	50.2%	79.0%
Loss of coordination	51.1%	59.3%	62.5%
Tremors	23.4%	24.9%	29.2%
Problems seeing	39.7%	36.3%	50.0%
Problems speaking	17.7%	21.2%	29.2%
Problems swallowing	15.6%	27.8%	37.5%
Incontinence	41.8%	43.6%	70.8%

Mobility impairment was also an important problem among the respondents. Overall, 13.4% were using a walking aid (eg, cane or walker) all of the time but did not ever use a wheelchair or scooter, while 14.1% were completely confined to a wheelchair. A combination of a walking aid and wheelchair was used by 35.8%; 21.7% were ambulatory all of the time without the use of aids. Difficulty with transportation was reported by 34.6% of participants, and no differences were seen across the three studies, even though the Manitoba and Atlantic studies included rural respondents.

Across nine different activities of daily living and instrumental activities of daily living tasks, participants were least likely to be able to do heavy housework independently (81.1%), make a hot meal without assistance (50.2%), manage finances and do banking (40.7%), or bathe without help (40.3%). Only making a hot meal showed a sex bias, with men being more likely to report that they needed assistance even after controlling for age and marital status. Participants had the least difficulty with using the telephone (12.3% needed help) and eating on one's own (15.5% needed help). Details of the activity limitations reported by participants, by study, are shown in Table 4. Note that the table reports percentages of participants who reported that they did not need assistance.

Table 4			
Capacity of respondents to perform ADL and IADL without assistance, by study			
	Study 1: Manitoba Survey (n = 142)	Study 2: Atlantic Survey (n = 274)	Study 3: Chicago Older Adults study (n = 24)
Use telephone	85.8%	88.7%	88.5%
Get to places outside of home	64.2%	65.6%	46.2%
Prepare meals	59.0%	44.5%	63.0%
Do housework	23.1%	15.3%	22.2%
Take medications	73.9%	75.9%	85.2%
Do banking	61.9%	55.8%	85.2%
Eat	85.1%	84.7%	81.5%
Dress and undress	71.6%	63.9%	59.3%
Bathe	61.2%	59.9%	55.6%

ADL, activities of daily living
IADL, instrumental activities of daily living

In all three studies, participants were asked to self-rate their health. In the Manitoba and Atlantic studies, a 5-point scale was used (Excellent, Good, Fair, Poor, Bad) while in the Chicago study a 4-point scale was used (Very Good, Good, Fair, Poor). Across all studies, 4.3% of participants rated their health as excellent or very good, 24.3% rated their health as good, 31.7% reported their health as fair, and 39.8% reported their health as poor or bad. In all studies, the most common response to self-rated health (ie, the mode) was poor health.

Discussion

This health and social profile of older adults with MS provides one of the first descriptive analyses of this population. While the data are not comprehensive and the samples nonrandom, the findings provide insight into this group of people with MS.

The majority of these three groups of older adults with MS are well educated and currently have the economic resources they feel that they need to meet their needs. Most have some level of social support available to them, although it is well recognized in the gerontologic literature that being married and/or living with another person does not necessarily result in social and emotional support.⁴² Given the potential physical and emotional challenges of caring for a person with MS,^{8,16,43} particularly over the lengths of time these respondents had had MS, further exploratory work on the social networks and supports of older adults with MS appears warranted. Such research on the interface between formal and informal caregiving could provide valuable information for MS societies faced with having to provide information and support to both professionals and family members who are affected by MS. Research in this area could assist professionals to develop and deliver family educational events and to prepare and provide family information packages.

The findings of this study showed the prevalence of limitations in eating, dressing, and bathing to be similar to the MS sample in the study by Hoenig et al,⁴⁴ but they are considerably different than the older adults with MS studied by Klewer et al.¹⁸ Participants in the latter study reported greater need for assistance with bathing and eating than the cohort in the current study. While other studies have reported the activity limitations of people with MS,^{1,9} results have been presented as either summary scores or do not have the level of activity detail reported here. A previous article from the full Manitoba study sample shows lower rates of activity limitations than reported here on the older adults only.⁴⁵ These findings demonstrate the need for longitudinal research that can track the development and change in activity limitations among people with MS in order to better understand how age and length of time with MS influence the experience of activity limitations and potential use of services. The activity limitations most reported in this study (ie, doing housework, bathing, preparing meals) correspond to services typically provided through home care programs. It is unknown whether these older adults were receiving adequate assistance with these tasks, but it would also be useful to explore in future research. Of particular concern would be those people with MS who are between 55 and 64 years and are having difficulty managing in their own homes but who are not eligible for older adult services that use 65 or older as a criterion for eligibility.

In terms of MS symptoms, the rates reported in this study are higher for pain, lower for tremors, and similar for fatigue and walking problems compared to the work of Aronson et al.¹ Compared to the work of Black et al,²³ the prevalence of fatigue, balance problems, and pain are higher with this older adult sample compared to their adult sample, but the rates of tremor and problems with speaking are similar. The extent of bladder problems was similar between the Chicago study reported here and the study by Klewer et al.¹⁸ The variations in symptom prevalence across the various studies could be the result of age, years since diagnosis, type and progression of MS, currently utilized treatments, or a number of other factors. The

variability does suggest though that longitudinal studies of changes in the symptom profiles of people with MS as they age would be valuable, both for understanding the disease itself and for developing intervention programs for this population.

Self-rated health of people with MS is not commonly reported in published MS studies, so it is unclear how the rates reported here compare to the general MS population. Compared to studies of older adults, these health self-ratings are lower than what is typically seen in the gerontological literature, even among frail or very old populations. Compared to a community-based sample of 1,406 older adults in Canada, the older adults with MS reported on in this paper were much less likely to report excellent health (4.3%, compared to 17.7%) and much more likely to report poor or bad health (39.8%, compared to 6.0%).⁴⁶ Given the strong evidence in the gerontologic literature about the predictive power of self-rated health for mortality,⁴⁷ the findings of this study raise questions about whether self-rated health has any relationship to mortality among older adults with MS.

As MS research continues to expand the treatment options available to people with MS, it is anticipated that fewer people with the disease will experience the severe disabilities that reduce the life expectancy of some members of this population. Currently, only 10% to 15% of people with MS have disabilities that reduce their life expectancy. As treatment options reduce this number, more and more people with MS will live well into their retirement years. Further research is needed to understand the potentially unique situations of this target group, examine their needs for health and social services and supports, and explore how MS societies and clinics can respond to both the challenges of MS and the normal changes associated with aging. Future research needs to focus on longitudinal designs with representative populations in order to maximize the quality of the data that are obtained.

References

1. Aronson KJ, Goldenberg E, Cleghorn G. Socio-demographic characteristics and health status of persons with multiple sclerosis and their care givers. *MS Manage*. 1996;3:1,6-15.
2. Dean G. World populations in multiple sclerosis. *Neuroepidemiology*. 1994;13:1-7.
3. Weinshenker BG. The natural history of multiple sclerosis. *Neuro Clin*. 1995;13:119-146.
4. Reingold SC. Research directions in multiple sclerosis. *National Multiple Sclerosis Society Web site*. Available at www.nationalmssociety.org/Brochures-Research.asp. Accessed September 9, 2002.
5. Minden SL, Marder WD, Harrold LN, Dor A. *Multiple Sclerosis—A Statistical Portrait: A Compendium of Data on Demographics, Disability, and Health Services Utilization in the United States*. Cambridge, Mass: Abt Associates Inc; 1993.
6. Miller DH, Hornabrook RW, Purdie G. The natural history of multiple sclerosis: a regional study with some longitudinal data. *J Neuro Neurosurg Psychiatry*. 1992;55:341-346.
7. Centers for Disease Control and Prevention. *FASTATS: Life expectancy*. Available at www.cdc.gov/nchs/fastats/lifexpec.cfm. Accessed September 6, 2002.
8. Hakim EA, Bakheit AM, Bryant TN, et al. The social impact of multiple sclerosis—a study of 305 patients and their relatives. *Disabil Rehabil*. 2000;22:288-293.
9. Gulick EE. Symptom and activities of daily living trajectory in multiple sclerosis: a 10-year study. *Nurs Res*. 1998;47:137-146.
10. Dyck I. Hidden geographies: the changing lifeworlds of women with multiple sclerosis. *Soc Sci Med*. 1995;40:307-320.
11. McColl MA. Expectations of health, independence, and quality of life among aging spinal cord-injured adults. *Assist Technol*. 1999;11:130-136.
12. Kemp BJ, Krause JS. Depression and life satisfaction among people ageing with post-polio and spinal cord injury. *Disabil Rehabil*. 1999;21:241-249.

13. Jenkins EL, Hildreth BL, Hildreth G. Elderly persons with mental retardation: an exceptional population with special needs. *Int J Aging Hum Dev.* 1993;37: 69-80.
14. Mathiowetz V, Matuska K, Murphy ME. Efficacy of an energy conservation course for people with multiple sclerosis. *Arch Phys Med Rehabil.* 2001;82: 449-456.
15. Fischer JS, LaRocca NG, Miller DM, et al. Recent developments in the assessment of quality of life in multiple sclerosis (MS). *Mult Scler.* 1999;5:251-259.
16. Gulick EE. Coping among spouses or significant others of persons with multiple sclerosis. *Nurs Res.* 1995;44:220-225.
17. Fleming ST, Blake RL Jr. Patterns of comorbidity in elderly patients with multiple sclerosis. *J Clin Epidemiol.* 1994;47:1127-1132.
18. Klewer J, Pohlau D, Nippert I, et al. Problems reported by elderly patients with multiple sclerosis. *J Neurosci Nurs.* 2001;33:167-171.
19. Somerset M, Campbell R, Sharp DJ, Peters TJ. What do people with MS want and expect from health-care services? *Health Expect.* 2001;4:29-37.
20. Freeman JA, Thompson AJ. Community services in multiple sclerosis: still a matter of chance. *J Neurol Neurosurg Psychiatry.* 2000;69:728-732.
21. Kersten P, McLellan DL, Gross-Paju K, et al. A questionnaire assessment of unmet needs for rehabilitation services and resources for people with multiple sclerosis: results of a pilot survey in five European countries. Needs task group of MARCH (Multiple Sclerosis and Rehabilitation, Care and Health Services Research in Europe). *Clin Rehabil.* 2000;14:42-49.
22. Stolp-Smith KA. Lifetime care needs of individuals with multiple sclerosis. *J Spinal Cord Med.* 1998;21:121-123.
23. Black DA, Grant C, Lapsley HM, Rawson GK. The services and social needs of people with multiple sclerosis in New South Wales, Australia. *J Rehabil.* 1994;60:60-65.
24. Kraft GH, Freal JE, Coryell JK. Disability, disease duration, and rehabilitation service needs in multiple sclerosis: patient perspectives. *Arch Phys Med Rehabil.* 1986;67:164-168.
25. Bennett L, Hamilton R, Neutel CI, et al. Survey of persons with multiple sclerosis in Ottawa, 1974-75. *Can J Public Health.* 1977;68:141-147.
26. Silverman M, Musa D, Kirsch B, Siminoff LA. Self care for chronic illness: older African Americans and whites. *J Cross-Cultural Gerontol.* 1999;14:169-189.
27. Clark NM, Janz NK, Dodge JA, et al. Self-management of heart disease by older adults: assessment of an intervention based on social cognitive theory. *Res Aging.* 1997;19:362-382.
28. Shapiro E, Tate RB. The use and cost of community care services by elders with unimpaired cognitive function, with cognitive impairment/no dementia and with dementia. *Can J Aging.* 1997;16:665-681.
29. Liu K, McBride T, Coughlin T. Risk of entering nursing homes for long versus short stays. *Med Care.* 1994;32:315-327.
30. Anemaet WK, Maffa-Trotter ME. Promoting safety and function through home assessment. *Top Geriatr Rehab.* 1999;15:26-55.
31. Gross B, Caiden M. The implications of aging in place for community-based services for elderly people. *Care Manag J.* 2000;2:21-26.
32. Wallace JI, Buchner DM, Grothaus L, et al. Implementation and effectiveness of a community-based health promotion program for older adults. *J Gerontol Med Sci.* 1998;53A:M310-M306.
33. Kempton A, Van Beurden E, Sladden T, et al. Older people can stay on their feet: final results of a community-based falls prevention programme. *Health Prom Int.* 2000;15:27-33.
34. Aneshensel CS, Pearlin LI, Mullan JT, et al. *Profiles in Caregiving: The Unexpected Career.* San Diego, Calif: Academic Press; 1995.
35. Wallsten SS. Effects of caregiving, gender, and race on the health, mutuality, and social supports of older couples. *J Aging Health.* 2000;12:90-111.
36. Finlayson M, Wiebe J. *Social Action and IFS Survey Report: Manitoba Division.* Toronto, Ontario: Multiple Sclerosis Society of Canada, 1998.
37. Wiebe J, Finlayson M, Payne L. *Social Action and IFS Survey Results: Atlantic Division.* Toronto, Ontario: Multiple Sclerosis Society of Canada, 1998.

38. *Number Cruncher Statistical System*. Kaysville, Utah: NCSS, 1993.
39. *SPSS Version 10.1.4*. Chicago, Ill: SPSS, Inc; 2001.
40. Ritvo PG, Fischer JS, Miller DM, et al. *MSQLI—Multiple Sclerosis Quality of Life Inventory: A User's Manual*. New York, NY: National Multiple Sclerosis Society; 1997.
41. Fillenbaum GG. *Multidimensional Functional Assessment of Older Adults: The Duke Older Americans Resources and Services Procedures*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
42. Pearlin LI, Aneshensel CS, Mullan JT, Whitlatch CJ. Caregiving and its social support. In: Binstock RH, George LK, eds. *Handbook of Aging and the Social Sciences*. San Diego, Calif: Academic Press; 1995:283-302.
43. Aronson KJ. Quality of life among persons with multiple sclerosis and their caregivers. *Neurology*. 1997;48:74-80.
44. Hoenig H, McIntyre L, Hoff J, et al. Disability fingerprints: patterns of disability in spinal cord injury and multiple sclerosis differ. *J Gerontol A Biol Sci Med Sci*. 1999;54:M613-M620.
45. Finlayson M, Winkler Impey M, Nicolle C, Edwards J. Self-care, productivity and leisure limitations of people with multiple sclerosis in Manitoba. *Can J Occup Ther*. 1998;65:299-308.
46. Menec VH, Chipperfield JG. A prospective analysis of the relations between self-rated health and health care utilization among elderly Canadians. *Can J Aging*. 2001;20:293-306.
47. Idler EL, Benyamini Y. Self-rated health and mortality: a review of twenty-seven community studies. *J Health Soc Behav*. 1997;38:21-37.

Abstracts from the International Committee on Database in MS

June 6, 2002
Chicago, Illinois

Abstracts

1. [CUBAN DATABASE SYSTEM IN MULTIPLE SCLEROSIS AND DEMYELINATING DISEASES](#)
2. [WESTERN REGIONAL SURVEY: UPDATE](#)
3. [THE UK NEUROLOGICAL DISABILITY SCALE: RELIABILITY AND RELATION WITH THE NARCOMS PERFORMANCE SCALE](#)
4. [MSDS—MULTIPLE SCLEROSIS DOCUMENTATION SYSTEM](#)
5. [PROFILING FOR NEUROLOGICAL PATIENTS AT BEAUMONT HOSPITAL](#)
6. [COLLECTING CASES: THE FIRST CENTURY OF STUDYING GROUPS OF MS PATIENTS \(1863–1963\)](#)
7. [THE SONYA SLIFKA LONGITUDINAL MULTIPLE SCLEROSIS STUDY](#)
8. [HEALTH OUTCOMES AND COST-EFFECTIVENESS OF DRUGS THAT SLOW MS DISABILITY PROGRESSION: THE IMPORTANCE OF REPRESENTATIVE NATURAL HISTORY DATA](#)

1. CUBAN DATABASE SYSTEM IN MULTIPLE SCLEROSIS AND DEMYELINATING DISEASES

Nelson González-Valdés, MD, J.A. Cabrera-Gómez,* MD, PhD, *Multiple Sclerosis Clinic, Neurological Service, University Hospital Dr Gustavo Aldereguía, Cienfuegos, Cuba

Background: Multiple sclerosis (MS) and neuromyelitis optica syndrome (NMO) are the most commonly diagnosed neurologic disorders of young and middle-aged adults, and one of the leading causes of significant disability in Cuba. The prevalence of clinically definite MS (Poser et al) in Cuba is 4.43/100,000 (95% CI, 4.03 – 4.82), but it may be higher, and probably there are 2,000 MS patients.

Objectives: This study aims to evaluate a new database system for the current national project on clinical, epidemiologic, and immunogenetic studies in MS in the population of Cuba.

Material and Methods: We created a database system for the study of MS and NMO patients that includes demographic data, genealogical history, family history, initial symptoms, current symptoms, neurological examination, evaluative scales (Scripps Rating Neurological Scale, EDSS Kurtzke, Clinical Steps, Ambulatory Index, and 9-Hole Peg Test), a complementary test (evoked potentials), neuropsychological tests, cerebrospinal fluid studies, urodynamic and ultrasound tests for bladder dysfunction, and clinical evaluative forms (Lublin and Reingold). An additional magnetic resonance imaging (MRI) database system was created according to the

recommendations of the International MRI Committee of the CMSC Meeting that was held in Vancouver.

Results: The authors will present the database system during the poster session and the results in the first 200 Cuban MS patients, with clinically definite MS (Poser et al) before 2002 and MS (McDonald et al) after 2002.

Conclusion: This Cuban Database System provides an easy and useful tool for the registry of Cuban MS patients and for possible application to Latin American countries. In addition, this is the first MRI Database Register with the current recommendations for MRI studies in MS.

2. WESTERN REGIONAL SURVEY: UPDATE

James D. Bowen, MD, and George H. Kraft, MD, Rehabilitation Medicine, University of Washington, Seattle

The University of Washington Multiple Sclerosis Rehabilitation Research and Training Center (MS RRTC) was established October 1, 1998. Six areas were established: health promotion, coping, vocational issues, job placement, aging, and demographic research. A comprehensive survey and database were developed that included a large number of questions on all aspects of MS, with a special focus on the six priority areas. The MS Association of King County sent surveys to its members on behalf of the University of Washington MS RRTC. In addition, a variety of other contacts were made. A reminder card and two additional mailings of the survey were used to increase the response rate. Of the 1,453 surveys distributed, valid surveys were returned by 827 subjects for a 57% response rate.

3. THE UK NEUROLOGICAL DISABILITY SCALE: RELIABILITY AND RELATION WITH THE NARCOMS PERFORMANCE SCALE

Dr. Jock Murray, Dalhousie MS Research Unit, Halifax, Nova Scotia, Canada

Background: There are numerous health-related measures available for assessing the type of problems experienced by persons with multiple sclerosis (MS). The UK Neurological Disability Scale¹ has been designed to assess the range of activity limitations encountered in the course of MS without bias toward any particular activity.

Objective: The purpose of this study was to assess the reliability of the Dutch version of the UK Neurological Disability Scale and its relation with the North American Research Committee on Multiple Sclerosis (NARCOMS) performance scale.

Method: Fifty persons with MS, consecutively admitted to a comprehensive rehabilitation program, entered the study after informed consent. Assessments were taken within the first week of admission. In 30 subjects, retests of the UK Neurological Disability Scale were performed at a three-day interval from the first test.

Results: The study included 28 men and 22 women, age 55 ± 10.7 years, with an illness duration of 15.6 ± 9.9 years and a median EDSS of 7 (range, 2 to 8.5). The intra-class correlation coefficients calculated to determine reliability of the scale were 0.96 for intra-rater reliability and 0.92 for inter-rater reliability. The correlation between total scores of UK Neurological Disability Scale and NARCOMS Performance Scale was 0.65 (Pearson correlation coefficient). For subscores, significant correlations were found between mobility and lower limb function ($r = 0.84$), items on hand function ($r = 0.74$), eyesight ($r = 0.72$), fatigue ($r = 0.65$), cognition ($r = 0.50$), and sensory problems and "other" ($r = 0.53$). Bladder and bowel function were moderately related with several NARCOMS subscores, namely bladder-bowel function ($r = 0.45$), hand function ($r = 0.49$), and mobility ($r = 0.38$).

Conclusion: The Dutch version of the UK Neurological Disability Scale is a reliable and valid scale to assess activity limitations for people with MS.

Reference:

1. Sharrack B, Hughes RA. Scale development and Guy's Neurological Disability Scale. *J Neurol.* 1999;246:226.

4. MSDS—MULTIPLE SCLEROSIS DOCUMENTATION SYSTEM

Martin Pette, MD, Universitätsklinikum Carl Gustav Carus, Department of Neurology, University of Dresden, Germany

The Multiple Sclerosis Documentation System (MSDS) is an electronic patient record for the documentation of multiple sclerosis (MS). It can be used in out- and inpatient settings. Based on a structured query language (SQL) server database, the program implements client-server architecture, allowing its application on stand-alone computers as well as on clients in local area networks. MSDS manages data on visiting dates, history, physical examination, blood and cerebrospinal fluid chemistry, evoked potentials, and magnetic resonance imaging. In general, data input is coded, but supplemented by free text fields. Clinical scores covered by the present version of MSDS include the EDSS, the MSFC, the UNDS, and the FAMS. MS diagnosis is specified according to Poser (applied automatically), McDonald, and Lublin and Reingold. Data accuracy and data consistency are supported by internal check mechanisms. Multiple reports (text, tables, and graphics) help to describe the individual disease course, as well as the patient population. Furthermore, MSDS provides a pedigree generator, a biosample database, and a study-protocol editor. A set of paper sheets required for scoring, and also for patient information and education, is supplied by the program. To ensure future data pooling, MSDS automatically keeps a minimal data set of each patient up to date, with the patient's name and birth date replaced by a secure and unique key. There is extensive online help, a print-out manual, and an MSDS homepage. The program has been evaluated at eight German university hospitals and deemed suitable as a basis for the development of a MS documentation standard in Germany. Supported by public funding, 14 German institutions specializing in the care of MS patients (12 university hospitals) have started the use of MSDS as of the beginning of 2002.

5. PROFILING FOR NEUROLOGICAL PATIENTS AT BEAUMONT HOSPITAL

Aileen Barrett, Head of Physiotherapy Department, Beaumont Hospital, Dublin, Ireland

Background: The purpose of this project is to profile the level of disability of patients with multiple sclerosis (MS). As a group of health professionals we collected our own specific information on the type and level of disability, assessment of needs, type of intervention, and resultant outcome. No measure was used to determine the patients' perception of their health status. Therefore, there was no overall picture of the level of disability or the needs of this patient population with resultant difficulties in establishing multidisciplinary care pathways and in-service planning.

Methodology: A customized database was written to collect, collate, and analyze the data for the purpose of this study. This database was available to (and used by) all of the disciplines involved in this project. The population included patients with a definite diagnosis of MS attending rehabilitation services within the agreed time frame of one year starting March 1, 2001. The different categories of disability measured are mobility, cognitive status, nutrition, social independence, function, communication, and swallowing. The EuroQol is used as a measure of quality of life. The measures used have been tested for validity and reliability.

Results: The information from the data analyzed will enable us to determine the level and type

of disability in this population and the patients' perception of their quality of life.

Discussion: This project is the first venture of its kind in Ireland. It will profile this patient population with regard to their needs and their type and level of disability and will contribute to improved management of patients with MS and better service planning. This is an initial step towards measuring the benefits of intervention in a patient population.

6. COLLECTING CASES: THE FIRST CENTURY OF STUDYING GROUPS OF MS PATIENTS (1863–1963)

T. Jock Murray, MD , Dalhousie MS Research Unit, Halifax, Nova Scotia, Canada

As this symposium explores current and future database/registry methods for multiple sclerosis (MS), it is interesting to reflect on how patient populations were collected, grouped, and studied in the past. This paper will examine how the earliest investigators collected cases to develop the profile and characteristics of the clinical and pathological features, the clinical types, the course of the disease, and later the geographic patterns and familial relationships. I will relate how Leyden, Rindfleisch, Vulpian, and Charcot initially collected cases to define the disease in the 1860s. Later case series were studied to determine how they could be further classified, whether according to anatomical region of involvement or by the temporal sequence of their attacks and disability. Large case series were collected in the great clinics of Paris, Berlin, Vienna, London, and Edinburgh in such different ways that it resulted in different profiles, resulting in controversies on issues of gender, geographic distribution, familial cases, and prognosis. For example, until the 20th century it was uncertain whether the disease was more common in men, more common in women, or equal in the sexes. Some found life expectancy to be as short as eight years, others more than 30 years. In this century, case collection initially did not alter substantially, but different features were sought and further questions asked. After World War II, more stringent methods were applied to the way populations were studied as part of the search for geographic patterns of the disease. In recent decades the methodology for defining populations of MS patients and studying representative groups has been further developed, and this will be the topic of the symposium.

7. THE SONYA SLIFKA LONGITUDINAL MULTIPLE SCLEROSIS STUDY

Sarah Minden, MD, Abt Associates Inc., Cambridge, MA

The Sonya Slifka Longitudinal Multiple Sclerosis Study is a research-focused, prospective cohort study supported by the National Multiple Sclerosis Society. It is designed to examine the role of therapeutic, socioeconomic, genetic, and immunologic factors in disease course, outcomes, and quality of life. Baseline and six-month follow-up data were collected from 2,166 patients including demographics, disease course, disease activity, functional status, quality of life, use of disease-modifying agents, health services utilization, and access to care. Baseline data on physician practice characteristics and on patients' clinical status were collected from 731 participants' physicians. Blood specimens for serial immunologic studies and genetic analysis have been drawn from 150 newly diagnosed patients. Baseline and six-month data will be presented. Preliminary analysis of baseline data shows that 78% of the sample are female and 92% Caucasian. The mean age is 48 years with a mean duration of multiple sclerosis (MS) of 10 years. Fifty-two percent are not employed. Sixty-six percent are currently married and 18% are divorced or separated. Ninety-six percent have completed at least a high school education. Sixty-two percent have relapsing-remitting MS, 22% secondary progressive MS, 12% primary progressive MS, and 4% progressive-relapsing MS. Forty-five percent report having mild MS that does not cause visible problems with walking. Twenty-nine percent of the sample report needing a mobility aid; 15% report using a wheelchair. Fifty-six percent of the sample are

currently taking one of the FDA-approved MS disease-modifying drugs. In the past 12 months, 10% needed prescription medications but could not obtain them; 12% needed MS-related care but were not able to get it; 5% needed general medical care but could not get it; 2% needed mental health care but were not able to get it. The presenters will also discuss development of the survey instruments, data collection procedures, and the status of the project.

8. HEALTH OUTCOMES AND COST-EFFECTIVENESS OF DRUGS THAT SLOW MS DISABILITY PROGRESSION: THE IMPORTANCE OF REPRESENTATIVE NATURAL HISTORY DATA

Murray G. Brown, PhD, Department of Community Health and Epidemiology, Dalhousie University, Halifax, Nova Scotia, Canada; Co-authors: John D. Fisk, Departments of Psychology, Psychiatry and Medicine, Paul Veugelers, Department of Community Health and Epidemiology, T. Jock Murray, Department of Medicine, Ingrida S. Sketris, College of Pharmacy, Chris Skedgel, Department of Community Health and Epidemiology, Dalhousie University

Introduction: The efficacy and effectiveness (e&e) of drugs that slow multiple sclerosis disability progression (MSDP) are measured by increased time to disability end points, or reduced probabilities of progression. The validity, generalizability, and robustness (VGR) of e&e estimates reflect the comparability, representativeness and size of treatment and control groups, study duration, and repeat observations. The VGR of e&e estimates determine, in large part, the VGR of health technology assessment (HTA) results for health outcomes (E), cost consequences (C), and cost-effectiveness (C/E) ratios.

Hypothesis: HTA results are sensitive to which MSDP natural history (NH) data are used, holding all other factors constant.

Methods: The sensitivity of HTA results to source of MSDP NH data is simulated. Outcomes are measured by Disability-Years-Avoided (DYA), Quality-Adjusted-Life-Years (QALY) gained, and % Disease Burden Avoided (DBA). Variables modeled: MSDP (EDSS) NH by MS subtype; onset or prevalence perspective; efficacy/effectiveness; treatment eligibility/termination criteria; compliance; treatment start by years since onset; treatment duration; within-disability-stage progression; posttreatment regression; net cost perspective (public, private, societal); discount rate. Source of MSDP NH data is also treated as a variable in the present analysis.

Results: HTA results (DYA, QALY, DBA, C, C/DYA, and C/QALY) are codetermined by many variables, but fundamentally by the speed and patterns of MSDP NH data entered in the model. Discussion models are efficient tools for simulating health and economic outcomes for MS drugs that slow MSDP, when complete direct evidence is unavailable and may never become available. HTA model results are very sensitive to differences in the speed and pattern of MSDP NH data. The VGR of HTA results for drugs that slow MSDP depend crucially, therefore, upon the collection and availability of valid, reliable, and representative natural history data.