

A

bstracts - Platform

Platforms



MS Disease Mechanisms and Modifying Therapy

1:00 - 1:20 pm	P01	Evaluation of Safety And Tolerability of Mitoxantrone in the Continuation of the Worsening Multiple Sclerosis (RENEW) Study
1:20 - 1:40 pm	P02	Safety, Tolerability, and Immunogenicity of Natalizumab: 2-Year Results from AFFIRM
1:40 - 2:00 pm	P03	The Efficacy of Natalizumab on Clinical and MRI Measures in MS: 2-Year Results From AFFIRM
2:00 - 2:20 pm	P04	The Potential for Remyelination in Multiple Sclerosis
2:20 - 2:40 pm	P05	SENTINEL: A Randomized Controlled Trial of Natalizumab and Interferon
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Psychosocial Issue in MS

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1:40 - 2:00 pm	P09	A Qualitative Investigation of Predictors of Adjustment in Older Individuals with MS
2:00 - 2:20 pm	P10	Coping Strategies Both Positively and Negatively Predict Quality of Life, Anxiety, and Depression in Patients with MS-Related Pain
2:20 - 2:40 pm	P11	MS Mothers' ADL Functioning During the First Postpartum Year
2:40 - 3:00 pm	P12	Effectiveness of a Home-Based Gynecologic and Breast Cancer Screening Program for Women With MS

Rehabilitation and Symptom Management in MS

1:00 - 1:20 pm	P13	Effects of Virtual Reality Cues on Gait in Multiple Sclerosis Patients
1:20 - 1:40 pm	P14	Impact of Attention on Memory Functioning in MS: An Exploratory Study
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2:00 - 2:20 pm	P16	Evolution of a Responder Analysis for Evaluation of Fampridine in MS
2:20 - 2:40 pm	P17	The Impact of Cognitive Impairments on the Daily Lives of Persons with MS
2:40 - 3:00 pm	P18	A Randomized Trial Of AVP-923 for Treatment of Pain in Multiple Sclerosis

**(P01) EVALUATION OF SAFETY AND TOLERABILITY OF MITOXANTRONE IN THE IN
CONTINUATION OF THE WORSENING MULTIPLE SCLEROSIS (RENEW) STUDY**

Background: The long term safety of mitoxantrone therapy was evaluated in patients with RRMS, PRMS and SPMS in the multicenter, open-label RENEW study.

Objectives: To continue to monitor clinical relapses and evaluate and monitor serious adverse events (AE) on cardiac function, hemolytic toxicity, and cumulative dose data of mitoxantrone therapy in the RENEW study.

Methods: 509 patients with worsening RRMS, PRMS, or SPMS who initiated mitoxantrone (12mg/m²) within 3 months of IRB approval were included. Exclusion criteria were patients with PPMS; history of congestive heart failure (CHF); left ventricular ejection fraction (LVEF) <50%; previous treatment with mitoxantrone, other anthracenediones or anthracyclines were excluded.

Results: Data was collected from April 2001 to January 2004 for 505 patients. The mean cumulative dose was 59.7 mg/m² (8.0-131.8 mg/m²) and the mean treatment duration was 1.2 years (0.0-2.8 years) Discontinuation of treatment occurred in 253/505 (35%) patients due to physician decision, 32% patients requested to be removed from treatment and 15% removed for other reasons. Of the 88 patients who discontinued treatment because of physician decision, reasons given were disease stabilization (29), AE (13), and disease worsening (9). Of the 82 patients who discontinued treatment because of patient request, reasons were lack of efficacy (28); AE (8); lack of efficacy and worsening of disease (5). In the previous and current reporting periods a total of five patients died, two possibly related to mitoxantrone treatment. A total of 67 patients experienced 89 serious AE: 55 treatment unrelated, 21 possibly related, 11 probably related, and 2 events definitely related but not unexpected. LVEF <50% has occurred in 6 patients and no cases of therapy-related leukemia were reported. Updated safety data will be discussed.

Conclusions: The results support the favorable benefit-risk profile of mitoxantrone as it continues to demonstrate generally manageable side effects in patients. Continued observation of patients in the study will provide important longer-term safety and tolerability data for mitoxantrone use in clinical practice.

Study supported by: Serono, Inc (Speaker's bureau, investigator, and consultant for Serono, Pfizer, Teva Neuroscience, Biogen IDEC. Investigator for Neurocrine Biosciences, Opexa, and Merck. Employees of Serono, Inc.)

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**(P02) SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF NATALIZUMAB:
2-YEAR RESULTS FROM AFFIRM**

Objective: To determine the safety, tolerability, and immunogenicity of natalizumab over 2 years of treatment in patients with relapsing multiple sclerosis (MS).

Background: A 2-year phase III clinical trial (the AFFIRM study) was initiated to evaluate the efficacy and safety of natalizumab in MS patients. One-year data from AFFIRM (based on a median follow-up time of 20 months) showed that natalizumab was safe and well tolerated.

Study Design: AFFIRM is a randomized, double-blind, placebo-controlled, multicenter phase III clinical trial in patients with relapsing MS. Eligible patients were randomized 2:1 to receive monthly intravenous infusions of either natalizumab 300 mg or placebo for up to 116 weeks. Safety and tolerability were determined through the assessment of the incidence and severity of AEs, hematology/blood chemistry, and urinalysis. Anti-natalizumab antibodies were measured using a screening enzyme-linked immunosorbent assay (ELISA) on blood samples obtained from patients at baseline and every 12 weeks. Persistent positive patients were defined as patients who had detectable antibodies at two or more time points within 42 days.

Results: The 2-year analysis of safety includes 2,076 patient-years of observation and 1,338 patient-years of natalizumab exposure. Common AEs associated with monotherapy use of natalizumab included headache (35.1% vs. 30.8%), fatigue (26.8% vs. 20.8%), and arthralgia (18.7% vs. 14.4%). There were similar proportions of patients with serious AEs in the natalizumab and placebo groups (19% and 24%, respectively). The incidence of infections was similar between treatment groups; the incidence of serious infections was 2.6% vs. 3.2%, placebo vs. natalizumab. Serious hypersensitivity reactions occurred in 1.3% of natalizumab patients. Thirty-seven patients (6%) were persistently positive for antibodies. Persistently positive patients experienced a loss of natalizumab efficacy and an increase in infusion-related reactions.

Conclusions: Natalizumab in AFFIRM was generally safe and well tolerated.

Study supported by: Biogen Idec, Inc. and Elan Pharmaceuticals, Inc. (Profs. Kappos and Miller have received research support from Biogen Idec. Prof. Polman, Dr. O'Connor, and Dr. Phillips have received consulting fees and honoraria for speaking from Biogen Idec. Profs. Havrdova and Hutchinson have received consulting fees for serving on an advisory board for Biogen Idec. Dr. Lublin and Prof. Giovannoni have received consulting fees, honoraria for speaking, and research support from Biogen Idec. Prof. Wajgt has nothing to disclose. Ms. Lynn, Dr. Panzara, Dr. Toal, and Dr. Sandrock are employees of Biogen Idec, Inc.)

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**(P03) THE EFFICACY OF NATALIZUMAB ON CLINICAL AND MRI MEASURES IN MS:
2-YEAR RESULTS FROM AFFIRM**

Objective: To report the effect of natalizumab on the 2-year pre-specified efficacy endpoints of the AFFIRM study.

Background: Natalizumab is the first $\alpha 4$ -integrin antagonist in the new class of selective adhesion molecule inhibitors for the treatment of multiple sclerosis (MS). One-year data from the AFFIRM study showed that natalizumab significantly reduced annualized relapse rate by 68% ($P < 0.0001$), the number of new or enlarging T2-hyperintense lesions by 80% ($P < 0.0001$), and the number of gadolinium-enhancing lesions by 92% ($P < 0.0001$) compared with placebo.

Study Design: AFFIRM is a randomized, double-blind, placebo-controlled, multicenter phase III trial of natalizumab in relapsing MS. Patients received natalizumab 300 mg or placebo intravenously every 4 weeks for up to 116 weeks. The 2-year primary efficacy endpoint was disability progression as measured by Expanded Disability Status Scale. Secondary efficacy endpoints were relapse rate, T2-hyperintense lesion volume, number of new T1-hypointense lesions, and disability progression as measured by the Multiple Sclerosis Functional Composite (MSFC).

Results: Of 942 patients enrolled, only 9% dropped out with 91% completing the study. Natalizumab significantly reduced the risk of sustained disability progression by 42% over 2 years compared with placebo (Hazard Ratio=0.58, 95% CI: 0.43, 0.77; $P = 0.0002$). In addition, natalizumab had a significant effect on all secondary endpoints. The effect of natalizumab on annualized relapse rate was sustained over the second year of treatment and consistent with the 1-year results; natalizumab reduced annualized relapse rate by 68% (0.23 natalizumab vs. 0.73 placebo; $P < 0.0001$) over 2 years. Natalizumab significantly reduced T2-hyperintense lesion volume (median percent change = 9.4% decrease on natalizumab vs. 8.8% increase on placebo; $P < 0.0001$), the mean number of new T1-hypointense lesions (1.1 natalizumab vs. 4.6 placebo; $P < 0.0001$), and disability progression as measured by the MSFC ($P < 0.0001$) compared with placebo.

Conclusions: Natalizumab significantly reduces the risk of disability progression in patients with relapsing MS.

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(P04) THE POTENTIAL FOR REMYELINATION IN MULTIPLE SCLEROSIS

Remyelination in MS is typically limited and short-lived. Since remyelination is the purview of oligodendrocytes and since oligodendrocytes have been shown to express a wide variety of immune system molecules, it is possible that the defective response in MS is immune-gene related. The zone separating totally demyelinated from normal-appearing white matter in MS is extremely narrow (<50 μ m), which may suggest that regulatory mechanisms exist - on one side curtailing outward progression of lesion, and on the other, inward repair by oligodendrocytes. This presentation will review cellular and molecular events at the margins of different lesions and will present the MS lesion as a dynamic, moving target. Oligodendrocytes in developing lesions are severely depleted and display several cytokine receptors (some pro-apoptotic), but little or no apoptosis. As lesions age, oligodendrocytes at the lesion margin sometimes display dramatic increases in number and may express survival molecules. We have recently shown this oligodendroglial hyperplasia to be associated with upregulated levels of the chemokine receptor, CXCR2, an immune system molecule implicated in oligodendrocyte migration and positioning. Neighboring hypertrophic astrocytes expressed high levels of CXCL1, a ligand for CXCR2, suggesting functional relationships between astrocyte-produced chemokine and CXCR2-expressing oligodendrocytes which also displayed evidence of proliferation. Another pathway examined involved the developmental molecule, Jagged1, and its receptor, Notch1, the latter expressed by oligodendrocyte precursors. Jagged1 in MS occurred in hypertrophic astrocytes in association with Notch1-expressing oligodendrocytes. Jagged/Notch pathway activation was confirmed by the presence of the downstream bHLH molecule, Hes5, an inhibitor of oligodendrocyte maturation. Therefore, chemokine pathways may facilitate oligodendrocyte recruitment, while Jagged/Notch activation leads to inhibition of oligodendroglial maturation, a feature perhaps underlying the failure of remyelination in MS. Thus, limited remyelination in MS may represent the cumulative effect of both immune and developmental pathways and therapies targeting their modulation may lead to enhanced repair mechanisms.

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(P05) SENTINEL: A RANDOMIZED CONTROLLED TRIAL OF NATALIZUMAB AND INTERFERON β -1A IN MS

Objective: To determine if the addition of natalizumab to interferon beta (IFN β)-1a (Avonex) is more effective than IFN β -1a alone in patients with relapsing MS.

Background: Despite IFN β therapy, many patients continue to experience disease activity, requiring the need for additional treatment options. Natalizumab is the first α 4-integrin antagonist in the new class of selective adhesion molecule (SAM) inhibitors for MS. In preliminary studies, natalizumab appeared well tolerated alone and when added to IFN β -1a.

Study Design: SENTINEL is a randomized, double-blind, placebo-controlled, multicenter phase III clinical trial. Patients with relapsing MS, a baseline Expanded Disability Status Scale score of 0.0-5.0, treatment with IFN β -1a for at least 12 months, and at least 1 relapse during IFN β -1a treatment in the 12 months prior to randomization were eligible. Patients were randomized to receive monthly intravenous infusions of 300 mg natalizumab or placebo in addition to standard therapy with IFN β -1a (30 mcg intramuscularly once weekly) for up to 116 weeks. At 1 year, the primary efficacy endpoint was relapse rate and secondary efficacy endpoints were number of new or enlarging T2-hyperintense lesions, number of gadolinium-enhancing (Gd+) lesions, and proportion of relapse-free patients.

Results: A total of 1171 patients were evaluated. Compared with IFN β -1a alone, the addition of natalizumab to IFN β -1a reduced the annualized relapse rate by 53% (IFN β -1a plus Natalizumab vs. IFN β -1a plus Placebo; 0.38 vs. 0.82, $P < 0.0001$). The addition of natalizumab reduced the mean number of new or enlarging T2 lesions by 76% (0.5 vs. 2.1, $P < 0.0001$) and the mean number of Gd+ lesions by 88% (0.1 vs. 0.8, $P < 0.0001$). The proportion of relapse-free patients was increased from 46% with IFN β -1a alone to 67% with add-on therapy ($P < 0.0001$).

Conclusions: In patients with relapsing MS who experienced disease activity during IFN β -1a monotherapy, the addition of natalizumab to IFN β -1a was significantly more effective than IFN β -1a alone.

Study supported by: Biogen Idec, Inc. and Elan Pharmaceuticals, Inc. (Drs. Weinstock-Guttman, Stuart, Calabresi, Galetta, Rudick, Lublin, Wynn, and Prof. Confavreux have received consulting fees, honoraria for speaking, and research support from Biogen Idec. Prof. Radue has nothing to disclose. Ms. Lynn, Dr. Panzara, and Dr. Sandrock are employees of Biogen Idec, Inc.)

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**(P06) SAFETY AND TOLERABILITY OF NATALIZUMAB ADDED TO INTERFERON β -1A:
RESULTS FROM SENTINEL**

Objectives: To determine the safety, tolerability, and immunogenicity of natalizumab when added to interferon beta (IFN β)-1a (Avonex).

Background: Natalizumab is the first A4-integrin antagonist in the new class of selective adhesion molecule (SAM) inhibitors for the treatment of MS. An exploratory study showed that natalizumab was well tolerated when added to IFN β -1a.

Study Design: SENTINEL is an ongoing, randomized, double-blind, placebo-controlled, multicenter phase III clinical trial in patients with relapsing MS who experienced at least 1 relapse during IFN β -1a treatment in the 12 months prior to randomization. Patients were randomized 1:1 to receive monthly intravenous infusions of natalizumab 300 mg or placebo, in addition to their standard weekly regimen of intramuscular IFN β -1a 30 mcg, for up to 116 weeks. Safety was assessed through the incidence and severity of adverse events, hematology/blood chemistry, and urinalysis. Throughout the study, patients underwent testing for anti-natalizumab antibodies using an enzyme-linked immunosorbent assay every 12 weeks and were tested for IFN β -1a neutralizing antibodies every 6 months. Persistent positive patients were defined as patients who had detectable antibodies at two or more time points within 42 days.

Results: A total of 1171 patients received treatment with either IFN β -1a plus Natalizumab (n=589) or IFN β -1a plus Placebo (n=582); safety analyses are based on a median follow-up of 19 months. Common adverse events that occurred at least 2% higher in the IFN β -1a plus Natalizumab group included nasopharyngitis (31.9% vs. 29.6%), depression (18.2% vs. 14.3%), and insomnia (16.1% vs. 13.4%). Serious hypersensitivity reactions occurred in less than 1% of patients. Thirty-seven patients (6%) were persistent positive for anti-natalizumab antibodies. The effects of antibodies on clinical efficacy and safety will be presented.

Conclusions: Natalizumab appears safe and well tolerated when used in combination with IFN β -1a (Avonex) in patients with relapsing MS.

Study supported by: Biogen Idec, Inc. and Elan Pharmaceutical Inc. (Drs. Weinstock-Guttman, Stuart, Calabresi, Galetta, Rudick, Lublin, Wynn and Prof. Confavreux have received consulting fees, honoraria for speaking, and research support from Biogen Idec. Prof. Radue has nothing to disclose. Ms. Lynn, Dr. Panzara, and Dr. Sandrock are employees of Biogen Idec, Inc.)

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**(P07) SUBGROUPS OF INDIVIDUALS LIVING WITH MULTIPLE SCLEROSIS:
IMPLICATIONS FOR INTERVENTION**

Three research questions were investigated: Can reliable subgroups in a population of individuals with MS be identified? Can membership in these groups be predicted by levels of disability? Do characteristics of these subgroups suggest different interventions? MS symptoms vary by time and by individual. MS symptoms' variability, pattern and impact on functioning suggest different subgroups exist in the population. We used latent variable analysis to examine how disease history, symptoms, health care, health status, depression, coping, and use of immunomodulating therapies (IMT) clustered in a sample of 550 individuals with MS from Eastern Washington State. Variables in the model described physical, cognitive, and social aspects of functioning. The four-subgroup model had the best fit. Group 1 (n=159) had an average MS duration of 12 years, Group 2 (n=102) 14 years, and Group 3 (n=143) 20 years. The membership in the three groups could be predicted by the disease severity, e.g., the longer the duration, the higher the EDSS score, and the more symptoms subgroup members endorsed. All three groups endorsed good coping with MS, low levels of depression, and good perceived social support. Group 4 (n=138, duration = 10 years) did not follow this pattern, reporting the shortest MS duration, but the highest levels of pain, fatigue, heat sensitivity and depression. Their overall quality of life, coping with MS, and participation in important activities was also the poorest. The largest proportion of the individuals in this subgroup (62%) reported using IMT. In general, Group 4 seemed to be considerably more distressed than could be predicted by EDSS scores or duration. Preliminary findings suggest that early interventions should be aimed at reducing depression, anxiety, improving coping skills, and increasing social support. Many other complex research questions in MS could be addressed by using latent variable modeling.

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(P08) USING THE LENS OF RELATIONAL AUTONOMY TO TACKLE ETHICAL CONFLICTS.

Health care professionals are faced with the challenge of providing services in an environment of competing value systems while treating individuals with MS. Personal, professional, institutional, patient and caregiver values can conflict with one another and create ethical dilemmas, most notably around the concept of respect for persons or the principle of autonomy. Ten health care professionals representing multiple disciplines actively involved in the treatment of individuals with MS were interviewed in depth and the data were analyzed using qualitative techniques. A central theme identified was that health care providers struggle with how to best respect a patient's right to make a "bad" choice and fulfill their obligation to provide good medical services. The tensions that exist relate to the provider's interpretation of autonomy as an individual's right to make a choice free from coercion as an independent moral agent. This traditional ideal of an autonomous individual acting independently is inappropriate when considering the situation of patients, especially those with disabilities or in need of any assistance. We argue that a more appropriate definition of autonomy examines the patient in the context of important relationships that already exist and focuses on fostering a healthy relationship between the patient and the health care team. Through case examples, we will present ethical dilemmas that arise in the context of treating patients with MS and analyze the strengths and weaknesses of using relational autonomy as a strategy to address ethical dilemmas in clinical practice. If the delivery of health services is examined through the lens of relational autonomy, it becomes more a question of responsibility than rights. Providers have a responsibility to examine each person's care and acknowledge the important relationships involved. By doing so we replace this ideal of independence with an ideal of providing the best care.

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**(P09) A QUALITATIVE INVESTIGATION OF PREDICTORS OF ADJUSTMENT
IN OLDER INDIVIDUALS WITH MS**

Few studies have examined psychosocial characteristics in the older MS population. These generally find quality of life to be as good as or better than that of younger individuals; however, proposed predictors of adjustment account for little variance in outcome. The present study was designed to identify predictors of adjustment in older individuals with MS.

The Perceptions of Aging Interview was developed to explore two lines of inquiry: MS: Perception of Aging, based on themes in the literature on adjustment in MS, and Life Strengths, adapted from Kivnick's Life Strengths Inventory. This portion identifies strengths and resources participants draw on in relation to: hope and faith, determination, independence and control, purposefulness and pleasure, competence, values and sense of self, love and friendship, productivity, and wisdom.

Consecutive participants from a larger study of aging and MS were invited to participate until the point of saturation. Thirteen individuals with a mean age of 68.3 completed telephone interviews.

Interviews were transcribed and content analyzed. First, codes were created to reflect responses. Second level coding involved grouping codes into categories and themes. HyperResearch software was used to test hypotheses.

Participants were well-adjusted and viewed MS and aging as intertwined. They reported their health and overall self-perceptions were equivalent to or better than those of their peers. Several factors positively influenced these evaluations in a majority of participants: mobility/independence (92%), mastery in a given area (69%), cognitive function (69%), having no comorbid conditions (69%), involvement in life (92%), acceptance coping (69%), cognitive reframing/reprioritizing (100%), pacing and planning (69%), selective optimization with compensation (69%), social support (92%), religion (69%), intellectual pursuits (77%), and generativity (61.5%).

This study identified several predictors of adjustment that have not been examined previously in the literature. Many of these predictors are modifiable through clinical intervention, and should be examined in future research.

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(P10) COPING STRATEGIES BOTH POSITIVELY AND NEGATIVELY PREDICT QUALITY OF LIFE, ANXIETY, AND DEPRESSION IN PATIENTS WITH MS-RELATED PAIN

Previous studies have demonstrated that how patients cope with pain can affect their quality of life and mental health. The purpose of the present study was to determine whether quality of life in terms of perceived physical functioning and reported levels of anxiety and depression were affected by pain and coping strategies. 65 patients diagnosed with MS completed several questionnaires including the type and frequency of pain they experienced. Additionally, they completed questionnaires about quality of life, anxiety, depression, and coping strategies to manage pain. Three separate multiple regressions were performed, loading age, gender, length of time since diagnosis, type of pain experienced (chronic/acute), and coping strategies as predictors and level of Physical Functioning, depression, and anxiety as criteria. Results demonstrated that type of pain and coping strategies significantly predicted Physical Functioning ($F = 3.016$, $p = .003$). Specifically, chronic pain and Catastrophizing predicted lower levels of Physical Functioning ($t = -2.391$, $p = .021$; $t = -2.194$, $p = .033$). Coping strategies also significantly predicted anxiety level, ($F = 3.048$, $p = .003$), specifically, patients who used more Coping Self-Statements subsequently reported lower anxiety levels ($t = -2.235$, $p = .029$). Finally, coping strategies significantly predicted levels of depression, ($F = 2.036$, $p = .043$). Catastrophizing predicted higher reported levels of depression ($t = 2.573$, $p = .014$). The results of this study demonstrate that pain is only one aspect of multiple sclerosis that can affect quality of life and mental health. The way in which patients cope with pain appears to play an important role in how they perceive their level of functioning as well as levels of anxiety and depression. In conclusion, helping patients develop positive coping strategies, such as coping self-statements, may in turn improve both their perceived quality of life and mental health.

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(P11) MS MOTHERS' ADL FUNCTIONING DURING THE FIRST POSTPARTUM YEAR

Research Problem: Studies have shown that many mothers in the general population have not yet fully resumed their usual levels of everyday activities at six months postpartum. ADL functioning may be further compromised among mothers with MS as a result of MS relapse. Identification of specific areas of ADL functioning deficits among mothers with MS over the postpartum year can provide caretakers and health providers with information from which appropriate interventions can be sought. The purpose of this longitudinal study was to compare ADL functioning of mothers with MS who experienced a relapse with those who did not at 3-month intervals throughout the first postpartum year.

Method: Pregnant women with MS or those who had recently given birth were recruited across North America (N=174). The women completed the 15-item ADL Scale for Persons with MS at 1, 3, 6, 9, and 12 months following birth of their baby or babies together with a health questionnaire that included the experience of MS relapse. MS relapse was confirmed by the participants' neurologist or by medical record review. Independent t-tests were used to determine if differences existed between mothers who experienced relapse with those that were relapse-free in two categories of ADL functioning (Personal care & Communication, Intimacy & Socializing). Mann Whitney U tests were used to determine if specific ADL items within the two ADL categories showed statistically significant differences between the groups.

Results: As expected increased deficits in ADL functioning occurred in the relapse compared to the non-relapse group mostly during the birth to 3 and 10-12 postpartum months. Significantly poorer (all $p < .05$) Personal & Communication functions included 'getting in and out of the tub or shower', 'turning from side to side while lying', 'working buttons/zippers/laces', 'walking inside the house', 'getting to and from their present method of travel', 'using a telephone', and reading printed material'. Significantly poorer (all $p < .05$) Intimacy & Socializing functions included 'participating in social and recreational activities' and 'confiding in someone'.

Conclusion: Mothers with MS are vulnerable to relapse and continuing or re-occurring ADL functional deficits during the year following birth of their baby/babies. Consideration needs to be given to possible ways that may prevent relapse and promote a higher level of ADL functioning.

Study supported by: Rutgers, The State University of New Jersey, Research Council (partial support)

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(P12) EFFECTIVENESS OF A HOME-BASED GYNECOLOGIC AND BREAST CANCER SCREENING PROGRAM FOR WOMEN WITH MS

Background – Studies document that disabled women participate less in health screening activities than nondisabled women due to: transportation, insurance, physical and attitudinal barriers, lack of energy, increased care needs and lack of knowledge regarding health needs.

Objective- To evaluate the effectiveness of providing an in-home program for gynecological screening in women with MS.

Methods- In conjunction with the Allegheny District Chapter NMSS and Magee Women’s Hospital, a home based program providing gynecological and breast screening was instituted in Western Pennsylvania in 2002. Cervical and breast exams were performed in the home.

Results- After a 6 months planning phase, recruitment of 150 women over 2 years occurred through self or health professional. One hundred and five women were examined in the home by a nurse midwife and referred to Magee Hospital for mammography and dexa scan testing. Previous exams ranged from 1-30 years, (mean length 7 years). After screening, women required further diagnostics studies, surgery or treatments that were coordinated through a Magee clinic specializing in disability care. Any problems observed in the home requiring intervention were made to the appropriate health professional or local chapter staff and these issues included: mental and /or physical health, domestic violence, financial, insurance, and long term care needs.

Conclusion- The program was well received by participants. Many women had not had physical exams of breast and cervix since onset of disability. Women seen in the home felt that their breast and gynecological health needs were met in a comfortable and convenient fashion according to surveys. Men and women not practicing routine screening measures need to be identified by health professionals as they are being evaluated in other settings and encouraged to practice screening behaviors. Convenient and cost effective programs for people with disabilities must be identified and developed.

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(P13) EFFECTS OF VIRTUAL REALITY CUES ON GAIT IN MULTIPLE SCLEROSIS PATIENTS

We have studied the effects of visual cues, provided through a portable visual-feedback virtual reality apparatus, on the walking abilities of Multiple Sclerosis (MS) patients. On-line (display-on) and residual short-term therapeutic effects on the walking speed and the stride length were measured in sixteen randomly selected MS patients. Patients with ambulation index (reference walking speed) below the median showed an average on-line speed improvement of 13.46%, while improvement in patients with ambulation index above the median was 1.47%. The average short-term therapeutic improvement in the walking speed was 24.49% in patients with ambulation index below the median and 9.09% in patients with ambulation index above the median. Similar results were obtained for improvement in stride length. These results seem particularly significant when compared to the results obtained for the controls, who showed no improvement at all.

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**(P14) IMPACT OF ATTENTION ON MEMORY FUNCTIONING IN MS:
AN EXPLORATORY STUDY**

Introduction:

Attention and memory are often affected in patients with MS-related cognitive impairment. Although MS can independently influence functioning in either of these domains, it is possible that, in some patients, perceived memory deficits may actually reflect the impact of decreased attention on the ability to encode and retrieve information. This would have implications for treatment, as therapies aimed at improving attention could, in fact, lead to the amelioration of memory complaints in such patients.

Methods:

Objective attention and memory data were obtained from patients ($n = 43$) with clinically definite diagnoses of relapsing-remitting or secondary-progressive MS. Data from correlation matrices between attention and memory measures guided the determination of variables entered into a number of stepwise multiple regressions. The regression analyses were conducted to test the hypothesis that, in MS patients, performance on attention measures predicts memory functioning.

Results:

Correlation analysis revealed statistically significant ($p < .01$) correlations of moderate to high magnitude ($r = .40$ to $.71$) between measures of attention and memory. Regression analyses revealed statistically significant ($p < .05$) findings when attention scores were used to predict memory performance. Depending on the measures entered into the multiple regressions, the proportion of variance (r^2) in memory accounted for by performance on attention measures ranged from $.221$ to $.535$.

Discussion:

As hypothesized, findings suggest a substantial contribution of attention to memory functioning. Thus, for some MS patients with complaints of memory loss, the primary problem may be attention difficulties that are negatively impacting memory. Specifically, poor attention can interfere with one's ability to learn, and later recall, new information. For such individuals, treatment and compensatory strategies aimed at maximizing attention will likely reduce the perception of memory problems. Limitations of this study and future research directions are discussed.

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**(P15) EFFICACY OF PAROXETINE IN TREATING MAJOR DEPRESSIVE DISORDER
IN PERSONS WITH MS**

The literature on pharmacotherapy for depression in MS is extremely limited and largely anecdotal. To address this gap, we conducted a double-blind, randomized, placebo-controlled clinical trial of one commonly used SSRI, paroxetine, for the treatment of depression in persons with MS. Forty-two persons with MS and a diagnosis of Major Depressive Disorder and/or Dysthymia were randomly assigned to one of two parallel, 12-week treatment arms: paroxetine or placebo. A psychiatrist met with each participant to confirm psychiatric diagnoses, prescribe the study medications, and monitor side effects and dosing. The primary outcome measure was the Hamilton Depression Rating Scale (HAM-D). Secondary outcomes included fatigue, perceived cognitive deficits, pain, and self-reported quality of life. Measures were administered at pre-treatment, Week 6, and posttreatment. Intent-to-treat analyses revealed that both the treatment and the control groups improved from pre-treatment to post-treatment. The treatment group improved more than the control group on most measures, but few differences were statistically significant. For the primary outcome, 55% of participants in treatment had at least a 50% reduction in the HAM-D score, compared with 40% in the control group; this was not statistically significant. Controlling for age, gender, EDSS score, ABC drugs, and treatment adherence did not affect the significance of any results. Among subjects who completed the study, 79% of treatment subjects met the primary outcome criterion of a 50% reduction in Ham-D, compared with 42% of controls ($p=0.073$). Significant improvements in quality of life and fatigue were also found in the active treatment completers relative to controls. Our results indicate that, when using intent-to-treat analyses, paroxetine was not effective in treating depression relative to placebo. However, when examining only study completers, we found that a greater proportion of the treatment group improved. Explanations for and implications of these findings will be discussed.

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(P16)EVOLUTION OF A RESPONDER ANALYSIS FOR EVALUATION OF FAMPRIDINE IN MS

A double-blind, placebo-controlled, parallel-group trial of Fampridine-SR was performed at 24 centers. A total of 206 subjects with MS were randomized to one of four cohorts: Fampridine-SR 10, 15, 20mg bid or placebo. In total, 195 subjects from all 4 groups completed the trial. A 2-week placebo run-in was followed by a 2-week dose escalation, 12-week stable treatment period, 1-week down-titration, and follow up 2 weeks later. The prospective primary efficacy variable was average percent change from baseline in walking speed during the stable dose period, using the Timed 25 Foot Walk. There was a significant effect for all dose groups compared to placebo at the first visit after up-titration. There was a trend toward increased walking speed during the entire stable dose period but the significance of this different declined over time against a wide background variability of walking speed that was partly independent of treatment. To address this variability, we examined post hoc whether a responder analysis, based on consistency of improvement during treatment, would provide a more sensitive and representative measure of treatment effect. A "responder" was defined as a subject with walking speed during at least three of the four on-drug visits that was faster than the maximum speed measured during the five off-drug visits (four pre-treatment, one at follow-up). The responder rate was significantly higher in all three active dose groups (35, 36 and 39%) compared to placebo (9%, $p < 0.002$ for each dose group). Response status was not significantly related to baseline demographics, including type or severity of MS. Adverse events were consistent with previous experience. The responder analysis appears to provide a more sensitive approach to measuring the effects of fampridine on ambulatory function.

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**(P17) THE IMPACT OF COGNITIVE IMPAIRMENTS ON THE DAILY LIVES
OF PERSONS WITH MS**

The estimated prevalence of cognitive impairments among persons with multiple sclerosis (MS) varies from 43% to 72% and includes reduced memory, limited attention and concentration, slowed information processing speed, and decreased learning and utilization of executive functions. The current knowledge regarding cognitive impairments in MS is based almost exclusively on the results of studies examining performance on neuropsychological tests. While these test results can describe the nature and severity of cognitive impairments, they yield incomplete information about the severity of disability and functional limitations that can result from cognitive impairments. Therefore, the overarching purpose of this study was to describe the impact of cognitive impairments on functional performance and disability among persons with MS as seen from their perspective.

Four individuals with different life roles were recruited for the study. Participants' ages ranged from 46 to 60 years old, and have been diagnosed with MS between 10 and 27 years. Data collection included 3 in-depth qualitative interviews with each participant, completed over a three-month period, in addition to the administration of the Perceived Deficits Questionnaire, completion of Cognitive Experience Forms, and a background form.

Participants were found to experience a wide range of cognitive impairments including changes in memory, attention, concentration, problem solving, and ability to multi-task. The data gathered from the face-to-face interviews indicated that the cognitive impairments had a significant impact on participants' ability to function in daily activities in their life roles. Activities impacted by cognitive impairments included managing a household, working, socializing, and participating in desired activities. Participants described incorporating various compensatory strategies to help alleviate some of the burden caused by cognitive impairments, for example, modifying the home, utilizing social supports, and changing their attitudes and priorities. Cognitive impairments are impacting participants' quality of life by preventing them from successfully engaging in meaningful activities.

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(P18) A RANDOMIZED TRIAL OF AVP-923 FOR TREATMENT OF PAIN IN MULTIPLE SCLEROSIS

Objective: To evaluate the efficacy of dextromethorphan/quinidine (DM/Q; AVP-923) for treating pain in multiple sclerosis (MS).

Background: 40% of MS patients report disabling pain. Dextromethorphan may alleviate neuropathic pain by decreasing glutamatergic signaling. Previous studies suggest efficacy but are inconsistent, possibly due to variations in DM plasma levels resulting from phenotypic differences in patients' metabolism. AVP-923 is a combination of dextromethorphan hydrobromide (30 mg) and quinidine sulfate (30 mg). Quinidine inhibits the first-pass metabolism of DM thereby increasing its systemic availability.

Methods: A multicenter (22), randomized (n=150), double-blind, placebo-controlled trial was conducted to assess the safety and efficacy of AVP-923 in the treatment of pseudobulbar affect in MS. Mean change from baseline in the pain intensity rating scale (PIRS) score was a secondary endpoint. Adult patients with MS (mean duration ~10 years) and pseudobulbar affect (~10% prevalence in MS) were included. No entry criteria were specified for pain, and patients used concomitant analgesics. Effects of AVP-923 given twice daily for 12 weeks were compared to placebo. Patients completed the PIRS at Days 1, 15, 29, 57, and 85. Participants indicated the amount of pain experienced within the previous 24 hours using a 5-point scale. Efficacy and safety were evaluated in randomized subjects who took study medication (n=76 AVP-923, n=74 placebo).

Results: Baseline PIRS scores were similar in the AVP-923 (1.4 ± 1.02 , mean \pm SD) and placebo (1.4 ± 0.99) groups, indicating mild/moderate pain. Both groups similarly and frequently used analgesics (fentanyl, gabapentin, lidocaine, oxycodone, tramadol, Vicodin®, OTC drugs). Treatment with AVP-923 resulted in twice as great a mean decrease in PIRS score (0.4 ± 0.09 , adjusted mean \pm SE) than placebo (0.2 ± 0.09) ($P=0.0271$). Adverse events (AEs) were mostly mild or moderate; AE-related discontinuation was 14.5% AVP-923, 10.8% placebo.

Conclusions: Placebo-controlled trial results indicate efficacy of AVP-923 in diminishing pain intensity in MS although pain was not the primary endpoint.

Study supported by: Avanir

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