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# Demyelinating Disorders 3

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## WFN15-1044
## Demyelinating Disorders 3
## Antibody-mediated oligodendrocyte remyelination protects axons and restores axonal transport in progressive demyelinating disease

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**Background**: The precise mechanisms by which axonal injury occurs in multiple sclerosis are unclear; one hypothesis is absence or failure of remyelination, suggesting that promoting remyelination may protect axons from death.
**Objective**: The objective of the present work is to investigate whether promoting remyelination protects axons and restores transport function.
**Methods**: Remyelination was induced in Theiler's virus-infected SJL/J mice using an oligodendrocyte/myelin-specific recombinant human monoclonal IgM, rHIgM22. As an indirect measure of spinal cord integrity, brainstem magnetic resonance spectroscopy was performed across treatment groups. At the completion of the experiment, spinal cord morphology (inflammation, demyelination, remyelination and mid-thoracic axon density) was assessed in detail. Retrograde labeling studies were performed on the spinal cord to provide direct evidence that remyelination protected axons.
**Results**: Brainstem *N*-acetyl aspartate concentrations were increased at 5 weeks post-treatment with rHIgM22, which remained stable out to 10 weeks. Spinal cord morphology studies revealed enhanced remyelination in the rHIgM22-treated group compared to isotype control antibody- or saline-treated groups. Importantly, rHIgM22-mediated remyelination appeared to protect small- and medium-caliber mid-thoracic spinal cord axons from damage despite similar demyelination and inflammation across experimental groups. The most direct confirmation of remyelination-mediated protection of descending neurons was an improvement in retrograde labeling. Treatment with rHIgM22 significantly increased the number of retrograde labeled neurons in the brainstem, indicating that preserved axons are functionally competent.
**Conclusion**: Our work provides direct evidence that remyelination preserves spinal cord axons, and protects molecular axon trafficking in a chronic murine demyelination model of human multiple sclerosis.

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## WFN15-1055
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## Walking, quality of life, and safety with prolonged-release fampridine treatment in clinical practice: Interim results of the liberate study

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**Background**: Impaired walking is common in multiple sclerosis (MS) and negatively impacts patients' lives.
**Objective**: To collect long-term, real-life data in MS patients treated with prolonged-release (PR) fampridine (dalfampridine extended-release in the United States) in clinical practice.
**Methods**: LIBERATE is an observational, ongoing study enrolling patients initiating treatment with PR-fampridine 10 mg twice daily in routine clinical practice. Endpoints include patient-perceived impact of MS measured by the Multiple Sclerosis Impact Scale-29 physical subscale (MSIS-29 PHYS) and physician-assessed Clinical Global Impression of Improvement (CGI-I) of walking ability. Safety was also assessed. Patient and/or institutional review board approval was obtained, as necessary. Interim results from France and Germany are reported.
**Results:** As of July 2014, 1803 patients enrolled in Germany and France of whom 1155 were dosed and completed 6-month follow up (n = 820 remained on-treatment; n = 335 had discontinued treatment but remained on study as patients "off-treatment"). A greater (mean [SD]) improvement in the MSIS-29 PHYS score from baseline to month 6 was observed among patients on-treatment (−8.57 [16.92]; n = 633) versus patients off-treatment (−2.59 [16.85]; n = 238). CGI-I scores improved in 70.1%, remained stable in 22.5%, and worsened in 7.4% of patients on-treatment (n = 582) at Month 6, versus 12.0%, 66.1% and 21.9% of patients off-treatment (n = 192), respectively. The most common adverse events were insomnia (n = 94 [5.2%]), vertigo (n = 64 [3.5%]) and headache (n = 62 [3.4%]).
**Conclusions**: PR-fampridine was well tolerated and was associated with improved MSIS-29 PHYS scores and walking ability from baseline over 6 months in clinical practice in Germany and France.

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**WFN15-1056**
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**Relapse rates and work productivity among patients receiving disease modifying therapy (dmt) for multiple sclerosis (ms)**

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**Background:** Real-world studies suggest that natalizumab results in lower relapse rate versus other MS DMTs and improves work productivity.
**Objective:** To compare relapse rates and work productivity using Work Productivity and Impairment (WPAI) questionnaire between MS patients treated by platform therapies, oral therapies or natalizumab.
**Methods:** RRMS patients receiving natalizumab, platform or oral therapies for greater than 12 months were identified from the 2015 Adelphi MS Disease Specific Programme, a global (U.S., U.K., Spain, Italy, France and Germany) cross-sectional study that obtained patient consent/approval. Average treatment effects (ATEs) for 1113 patients (156 natalizumab, 711 platform, 246 oral) were estimated and adjusted utilizing a propensity score generated from age, gender, EDSS score at current treatment initiation, line-of-therapy, BMI, duration of current treatment, time since MS diagnosis, and number of comorbid conditions. Physician-reported relapses in the previous 12 months and work productivity were compared across treatments.
**Results:** Relapse and WPAI data were available for 934 (122 natalizumab, 617 platform, 195 oral) and 222 (34 natalizumab, 137 platform, 51 oral) patients, respectively. Natalizumab patients suffered fewer relapses than platform (ATE = −0.21 vs. 0.48, $p = 0.020$) and oral therapy patients (ATE = −0.14 vs. 0.45, $p = 0.075$). Patients receiving natalizumab reported significantly less presenteeism, i.e., attending work while sick) than those receiving platform (ATE = −10.16% vs. 19.26%, $p = 0.001$) or oral therapies (ATE = −8.28% vs. 22.65%, $p = 0.0018$). Treatment was not associated with less overall work impairment.
**Conclusion:** Treatment with natalizumab compared to platform or oral therapies was associated with a lower relapse rate and a significant reduction in impairment at work or presenteeism.

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**WFN15-1231**
**Demyelinating Disorders 3**
**Epidemiology of multiple sclerosis in Brazil**

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**Background:** Multiple Sclerosis (MS) is an autoimmune chronic disease, characterized by demyelinating of central nervous system. Local studies showed a prevalence around 12.5 to 27.2/100,000 habitants, and literature has evidenced it to be more common in women (71.4% to 76.8%) and Caucasians (77% to 85.7%), both between 35.4 and 37.3 years.
**Objectives:** Analyze the epidemiology of MS in Brazil, the shape of distribution through federal unities (FU) and compare the prevalence in men and women.
**Materials and methods:** We used secondary information of hospital admissions from DATASUS, since 2008 to 2012, in a form of quotient: number of admissions over FU's population, multiplied by 100,000, in each year, for both genders.
**Results:** It was observed a rise of prevalence in the direction North–South. Rio Grande do Sul, alternating with Santa Catarina and Distrito Federal that presented the highest rate (0.9 higher than the national rate, which showed the biggest values in 2011). The lowest numbers were found in Alagoas and Paraíba. The major prevalence occurred in women, about 2.23 times the value of the men, according to the local studies aforementioned, with 95% of reliability.
**Conclusion:** From 2008 to 2012, there was a national increase in the prevalence, and an association between the genetic and the concentration of Caucasians was noticed, which may justify the rate at South region, although the link with women is not understood yet.

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**WFN15-1232**
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**Multiple sclerosis and peripheral nerve demyelination**

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**Objective:** There are a number of case reports describing multiple sclerosis (MS) patients associated with demyelinating neuropathy, but its frequency in the whole MS population is unknown. In a study published in 2008, nerve conduction abnormalities suggestive of demyelinating neuropathy were found in 3 of the consecutive 60 relapsing remitting MS (RRMS) patients.
**Methods:** We present a 40 year old female diagnosed with RRMS 10 years ago. She had been using copaxone for the last 8 years with favorable prognosis. Even though she had discontinued the drug due to pregnancies she did not experience any attack following the birth of two children. As she started complaining of paresthesias in the lower extremities, she was evaluated with nerve conduction studies revealing severe sensory motor neuropathy. Investigations for a cause of neuropathy revealed no abnormal findings. As her complaints persisted along with worsening of ENG findings, sural nerve biopsy was performed revealing severe denervating neuropathy along with reinnervation, and findings suggestive of tomaculous neuropathy. She was questioned again to rule out a hereditary neuropathy, but she denied any family members to have similar complaints. Genetic analysis revealed deletion on chromosome 17p11.2-12. Her neurologic examination did not worsen in the following 1.5 years, and paresthesias improved following administration of pregabalin.
**Conclusion:** Approximately 5% of MS patients develop demyelinating neuropathy. The association could result from a common pathogenesis possibly due to epitope spreading during the long course of MS. Association of chronic inflammatory demyelinating polyneuropathy with MS is not frequent, but needs to be recognized as a treatable condition.

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**Demyelinating Disorders 3**
**Brain lesions in Venezuelans NMOSD patients**

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**Background:** Neuromyelitis optica (NMO) inflammatory demyelinating disease of central nervous system (CNS), selectively affects optic nerve and spinal cord. NMO was considered a disease without brain involvement. Since the discovered of NMO IgG/Anti Aquaporin 4 the concept of NMO broaden to NMO Spectrum Disease, brain lesions are frequently associated with clinical and BMRI, with characteristic configuration and location.
**Objective:** Demonstrate and describe the presence of brain lesions BMRI in NMOSD patients at Maracaibo University Hospital in Venezuela.
**Material and methods:** A retrospective study was conducted in patients diagnosed with NMOSD at Maracaibo University Hospital to document brain lesions in BRMI. We reviewed files of 95 patients over a two year period in April 2013–2015.
**Results:** 95 patients were seen at the Department of Demyelinating diseases in Maracaibo University Hospital in Venezuela. 70 patients with Multiple Sclerosis and 25 with NMOSD, which constitutes a relative frequency of 26%. Of these 25 NMOSD patients, 18 (72%) showed brain lesions, distributed as follows: Nonspecific lesions, punctate or patchy — 6 patients, extensive large irregular cerebral hemispheres — 8 patients, corpus callosum linear lesions — 5 patients, hypothalamus lesions — 2 patients, thalamus lesions — 3 patients, periventricular lesions — 4 patients, III and IV ventricle lesions — 7 patients, cerebellum lesions — 5 patients , optic lesions — 1 patient and pyramidal tracts lesions — 2 patients.
**Conclusion:** In Venezuela we observed a high relative frequency on the NMOSD which is 26% — one of the highest percentages in America. They showed a high amount of brain lesions in 72%.

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**Alteration of the intestinal microbiota by short-time antibiosis protects mice from CNS-specific autoimmunity**

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Environmental factors are suspected to trigger Multiple sclerosis (MS) in people with genetic disease susceptibility. Although little is known about the nature of the environmental trigger(s), emerging evidence from animal models of MS suggests that the gut flora is critically required for disease development. Antibiotics can rapidly alter gut microbial signatures. Thus, we evaluated the effect of antibiotic interventions on CNS autoimmunity using a transgenic mouse model of opticospinal experimental autoimmune encephalomyelitis (EAE; OSE mouse). OSE mice harbor myelin oligodendrocyte glycoprotein (MOG)-specific T as well as B cells. Approximately 50% of untreated OSE mice develop spontaneous EAE. In contrast, 4 week-old mice treated for 2 weeks with an antibiotic cocktail remain fully protected from the disease. Analysis by 16s RNA sequencing revealed that antibiotic treatment had profound impact on the composition of the intestinal microbiota. Interestingly, changes in the intestinal microbiota were accompanied by a reduction of the Interleukin-22 serum level.

Work to identify the mechanisms how antibiotic treatment and hence, alteration of the intestinal microbiota can dampen the autoaggressive immune response is underway. In summary, these findings demonstrate that alteration of gut bacteria can have a profound impact on CNS-specific autoimmunity.

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