Neurology RESEARCH REVIEW™

SUPPLEMENT: MULTIPLE SCLEROSIS

Making Education Easy

Issue 89 – 2025

In this issue:

Abbreviations used in this issue

AQP4 = aquaporin-4
EDSS = Expanded Disability Status Scale
JCV = John Cunningham virus
MRI = magnetic resonance imaging
MS = multiple sclerosis
NMOSD = neuromyelitis optica spectrum disorder
PIRA = progression independent of relapse activity
pwMS = people with MS
RRMS = relapsing-remitting MS

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MULTIPLE SCLEROSIS AUCKLAND

Welcome to the latest issue of Neurology Research Review, focusing specifically on MS.

In this issue, Swedish investigators report the impact of progression independent of relapse activity (PIRA) on quality of life in people with RRMS, a review of postmarketing data confirms an association between fumaric acid ester drugs and serious gastrointestinal adverse events, analysis of a multicentre cohort evaluates the significance of trigeminal neuralgia within the disease course of MS, and Japanese investigators report the utility of satralizumab for relapse prevention in patients with NMOSD. Also in this issue, a local study looks at the prevalence of MS in NZ.

We hope you find these and the other selected studies interesting, and welcome your feedback.

Kind regards,

Dr Jennifer Pereira
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Quality of life is decreased in persons with relapsing-remitting multiple sclerosis experiencing progression independent of relapse activity

Authors: Lindberg S et al.

Summary: This prospective observational study in Sweden investigated the impact of progression independent of relapse activity (PIRA) on quality of life in patients with RRMS. A total of 125 newly diagnosed individuals with RRMS were assessed over 5 years using the EuroQoL-5-Dimension-3-level (EQ-5D-3L), EQ-visual analogue scale (EQ-VAS) and 29-item MS-Impact-Scale (MSIS-29). Patients were grouped according to whether they had PIRA (worsening EDSS independent of relapses) or not. At 5 years, 19.2% of patients had PIRA. Linear mixed-effects models showed that non-PIRA patients had better quality of life than PIRA patients over the 5-year study period (EQ-5D-3L: $p<0.001$; EQ-VAS: $p<0.001$; MSIS-29-PHYS: $p<0.001$; and MSIS-29-PSYCH: $p<0.001$).

Comment: As novel therapies for the treatment of PIRA become available, identifying those patients who will benefit and as early as possible will be an important part of our clinical practice. Our current strategy is to look for progressive neurological symptoms and signs despite high-efficacy disease-modifying therapy and analyse MRI scans for slowly expanding lesions (SELs) or magnetic rim lesions (MRLs). The most promising treatment for PIRA is tolebrutinib – a Bruton tyrosine kinase inhibitor administered as a daily pill which can cross the blood-brain barrier and target smouldering immunological disease. Studies such as this quality of life study identify other measures that will likely also be useful.

Reference: Mult Scler. 2025;31(5):548–57

Abstract

Severe gastrointestinal adverse reactions including perforation, ulceration, hemorrhage, and obstruction: A fumaric acid ester class new safety risk

Authors: Kim T et al.

Summary: This study reviewed the FDA Adverse Events Reporting System database and published medical literature to identify cases of serious gastrointestinal (GI) events in patients taking fumarate acid ester (FAE) drugs for the treatment of MS. Forty-nine cases of GI adverse reactions (perforation, ulceration, haemorrhage, and obstruction) causally associated with FAE drugs were identified. Most of them occurred within 4 months of drug initiation and required hospitalisation. Ten cases required red blood cell transfusions, nine required surgical intervention, and two patients died.

Comment: In NZ, dimethyl fumarate (Tecfidera®) is funded by PHARMAC. It is administered as a twice-daily tablet. Due to the known side effects of flushing and GI upset, patients starting this drug are advised to start with 120mg once daily in a "Tecfidera® Sandwich" which means – eat food, take tablet, eat more food – to minimise these side effects. The dose is slowly increased to 240mg twice daily. In clinical practice as per the clinical trials, most patients will tolerate dimethyl fumarate well when this strategy is followed. Given the potential for serious harm detailed in this study (GI perforation, ulceration, haemorrhage and obstruction), 75% of which occurred within the first 4 months of starting treatment, consider further investigations when significant GI symptoms are reported and an early switch to an alternative treatment is advised.

Reference: Mult Scler. 2025;31(5):578–86

Abstract

To read previous issues of Neurology Research Review **CLICK HERE**

Trigeminal neuralgia within the disease course of MS: Diagnostic and therapeutic implications from a multicenter cohort

Authors: Laakso SM et al.

Summary: This study examined the diagnostic and therapeutic implications of trigeminal neuralgia in pwMS. Of 171 pwMS at three international sites, 0.9–1.9% were diagnosed with trigeminal neuralgia. It was the first potential demyelinating symptom in 9.9% of patients, but in most (86%) of them it occurred after their MS diagnosis (median 13–16 years). One-fifth of patients had a clinical relapse within 6 months of trigeminal neuralgia onset.

Comment: In a stretched public healthcare system where MRI imaging is a precious resource and the most common cause of trigeminal neuralgia is neurovascular compression, this article acts as a reminder that MRI imaging should be undertaken to identify those with trigeminal neuralgia as a presenting symptom of MS. Fifteen percent of patients in this study experienced trigeminal neuralgia prior to a formal diagnosis of MS and 20% of pwMS had a relapse within 6 months of trigeminal neuralgia.

Reference: Mult Scler. 2025;31(5):607–11
Abstract

Hypnosis and mindfulness audio recordings for reducing fatigue in individuals with multiple sclerosis

Authors: Jensen MP et al.

Summary: This randomised controlled trial evaluated the impact of therapeutic hypnosis and mindfulness meditation on fatigue in pwMS. 333 pwMS and fatigue were randomised 1:1:1 to receive access to therapeutic hypnosis audio recordings, access to mindfulness meditation audio recordings, or no access to recordings (treatment as usual) for 28 weeks. Individuals that were assigned to the hypnosis or mindfulness meditation groups reported significantly greater reductions in fatigue impact, sleep disturbance, and depressive symptom severity than controls after 4 weeks. These improvements were maintained at 16 and 28 weeks after treatment assignment.

Comment: Fatigue is a disabling symptom in MS. It is the most common reason that pwMS reduce working hours or stop paid employment. Management of fatigue remains a common topic of discussion in MS clinics. Here is another non-medical strategy to suggest to your patients that may offer some symptomatic improvement – the authors are considering developing software to enable the delivery of the recordings used in this trial to pwMS via smartphones.

Reference: Mult Scler. 2025; published online Apr 17
Abstract

The team at Research Review want to take this opportunity to thank Dr Jennifer Pereira for her valuable contributions to Neurology Research Review over the years. We wish her well with future plans.

INDEPENDENT COMMENTARY BY
Dr Jennifer Pereira BHB, MBChB, FRACP, MD

After undergraduate training in medicine at the University of Auckland, Jennifer trained in neurology at Auckland City Hospital. Postgraduate training consisted of an MS research fellowship, with the Therapeutic Immunology Group in the Department of Clinical Neurosciences, University of Cambridge (UK). **For full bio CLICK HERE.**

Effectiveness of satralizumab in a real-world clinical setting in Japan: Interleukin-6 receptor inhibition in neuromyelitis optica spectrum disorder: A six-month interim analysis of a multicenter medical chart review

Authors: Fujihara K et al.

Summary: This real-world study evaluated the efficacy of satralizumab for relapse prevention in AQP4-positive patients with NMOSD. The medical charts of 124 patients with NMOSD (mean age 51.1 years, 93.5% female; mean disease duration 7 years) who initiated satralizumab at one of 25 sites in Japan were reviewed. 120 patients (96.6%) were relapse-free at 26 weeks. The annualised relapse rate was 0.069 at week 26 compared with 0.445 in the year prior to satralizumab initiation. Treatment with satralizumab permitted dose reduction of concomitant oral glucocorticosteroids and immunosuppressants over 26 weeks.

Comment: In NZ, rituximab is available for the treatment of NMOSD if patients meet criteria required in a Special Authority. They must have a severe relapse or a relapse despite mycophenolate and prednisone. Access to funded satralizumab would need to be through a named patient application (NPPA) and this treatment would be appropriate for those failing rituximab. This would occur rarely; relapse rates in the small clinical trials of rituximab for AQP4-positive NMOSD were analysed in a 2022 meta-analysis and showed 70–90% of patients will be relapse free on rituximab.

Reference: Mult Scler Relat Disord. 2025;98:106384
Abstract

High-dose vitamin D in clinically isolated syndrome typical of multiple sclerosis: The D-Lay MS randomized clinical trial

Authors: Thouvenot E et al., for the D-Lay MS Investigators

Summary: The D-Lay MS trial investigated the effects of high-dose cholecalciferol on disease activity in patients with clinically isolated syndrome (CIS) typical of MS. At 36 MS centres in France, 316 untreated patients aged 18–55 years with CIS duration <90 days and serum vitamin D levels <100 nmol/L were randomised 1:1 to receive oral cholecalciferol 100,000 IU or placebo every 2 weeks for 24 months. The primary outcome was disease activity, defined as occurrence of a relapse and/or MRI activity (new and/or contrast-enhancing lesions) over 24 months of follow-up. Disease activity was observed in 60.3% of patients in the vitamin D group and 74.1% in the placebo group at 24 months (hazard ratio 0.66, 95% CI 0.50–0.87; p=0.004), and median time to disease activity was longer in the vitamin D group (432 vs 224 days; p=0.003).

Comment: Low vitamin D has a role in immune regulation, and it is via this mechanism that low vitamin D acts as a risk factor for the development of MS. It has been postulated that vitamin D supplementation might be beneficial to pwMS. In an earlier attempt to answer this question, the PrevANZ study published in *Brain* in 2024 was undertaken in Australia and NZ and found no reduction in MS disease activity with daily dosing of vitamin D – either 1000, 5000 or 10,000 IU over the 48 weeks of the study. The major differences between the PrevANZ and the D-Lay study reported here, are that the D-Lay study used a dosing of 100,000 IU every fortnight, and those enrolled in the PrevANZ study were not vitamin D deficient – whereas the D-Lay study recruited only pwMS with low vitamin D levels. The current recommendations stand: replace vitamin D to the normal range and start disease-modifying therapy in those with RRMS.

Reference: JAMA 2025;333(16):1413–22
Abstract

Long-term disability trajectories in multiple sclerosis: A group-based trajectory analysis of the AusLong cohort

Authors: Zarghami A et al., for the AusLong Investigator Group

Summary: This analysis of the AusLong cohort evaluated long-term disability trajectories in pwMS. Data for 263 pwMS over a 10-year follow-up period were analysed. Three distinct disability trajectories based on EDSS were identified: no/minimal, moderate and severe. Patients with a no/minimal disability trajectory had no significant progression of EDSS over 10 years, while those with a moderate or severe disability trajectory had disability worsening (median time to reach EDSS 4 was 9 and 7 years in the respective groups). Older individuals and those with more relapses in the first 5 years after clinical diagnosis or a higher number of comorbidities at baseline were more likely to have a worse disability trajectory. Neither baseline MRI nor anatomical site of initial symptoms had a significant impact on long-term outcomes.

Comment: Data on disability trajectories in pwMS can inform clinical decisions, particularly the use of high-efficacy therapies in high-risk subgroups. Although these treatments carry risks – such as infusion reactions, opportunistic infections, and reduced vaccine efficacy – patients with risk factors like older age, frequent early relapses, and multiple comorbidities are both more susceptible to complications and more likely to experience disability progression. In such cases, the potential benefits of high-efficacy therapy may outweigh the risks.

Reference: J Neurol Neurosurg Psychiatry 2025;96(5):424–34
Abstract

Low natalizumab trough concentrations are associated with reduced seroconversion of the John Cunningham virus in natalizumab-treated patients with multiple sclerosis

Authors: Gelissen LMY et al.

Summary: Natalizumab-treated pwMS who are JCV seropositive are at increased risk for progressive multifocal leukoencephalopathy (PML). This study assessed whether lower natalizumab trough concentrations are associated with less JCV seroconversion than higher natalizumab trough concentrations. Two cohorts of patients treated with intravenous natalizumab in the Netherlands were combined to assess JCV seroconversion rates during periods of high (≥15 µg/mL) and low (<15 µg/mL) natalizumab trough concentrations. Overall, 357 patients from 21 hospitals in the Netherlands were included. The annual JCV seroconversion rate was 8.4% during periods of high natalizumab trough concentrations compared with 4.8% during periods of low trough concentrations (p=0.0035).

Comment: Most infusion centres in NZ are administering natalizumab using an extended dosing regimen to reduce the PML risk. Approximately 50% of pwMS will be JCV-negative prior to starting treatment. For those who are JCV-negative the quoted risk of seroconversion is 4–10% per annum. Remaining JCV-negative in NZ is advantageous as we only have two high efficacy agents available, natalizumab and ocrelizumab. Natalizumab trough levels are known to be high in those with low BMI. It may be that in the future we take a personalised approach as is being studied in a further trial called SUPER-NEXT in which enrolled patients start with a dosing interval of 6 weeks and then the dosing interval is increased based on trough levels.

Reference: J Neurol Neurosurg Psychiatry 2025; published online Mar 25
Abstract

Subcutaneous ocrelizumab in patients with multiple sclerosis: Results of the phase 3 OCARINA II study

Authors: Newsome SD et al.

Summary: The OCARINA II trial compared ocrelizumab drug exposure after subcutaneous (SC) versus intravenous (IV) administration. A total of 236 ocrelizumab-naïve patients aged 18–65 years with relapsing and primary progressive MS and an EDSS score of 0–6.5 were randomised 1:1 to initially receive a single ocrelizumab IV dose (administered as two 300mg infusions, 2 weeks apart) or a single ocrelizumab SC dose (920mg injection on Day 1). At week 24, patients who received the initial ocrelizumab IV dose switched to ocrelizumab SC 920mg every 24 weeks until week 96; patients who received the initial ocrelizumab SC dose remained on SC ocrelizumab every 24 weeks until week 96. The primary end-point was ocrelizumab area under the serum concentration-time curve from day 1 to week 12 (AUC_{W1-12}). The study demonstrated that ocrelizumab SC 920mg was non-inferior to ocrelizumab IV 600mg for the primary end-point (geometric mean ratio 1.29) and also for AUC_{W1-24} (geometric mean ratio 1.27).

Comment: SC ocrelizumab has recently been approved by Medsafe, and we await the outcome of ongoing PHARMAC negotiations regarding funding. Its availability will significantly ease the burden on overstretched infusion centres, reducing administration time from several hours to a 10-min SC injection. Notably, the initial dosing – traditionally administered as two 300mg IV infusions on Day 1 and Day 15 – can now be given as a single subcutaneous dose on Day 1, alleviating pressure on limited infusion slots.

Reference: Neurology 2025;104(9):e213574
Abstract

Identifying multiple sclerosis in linked administrative health data in Aotearoa New Zealand

Authors: Boven N et al.

Summary: This study used linked administrative health records to update the findings of the 2006 NZ National MS Prevalence study. MS cases were identified from hospital records, pharmaceutical dispensing records, needs assessments for older adults, and disability support records between Jan 1988 and Jun 2022. A total of 7890 people (73% female) with MS were identified, and the crude national prevalence was estimated to be 96.6 per 100,000 in 2022 compared with 72.4 per 100,000 in 2006. Age-adjusted prevalence (per 100,000) was highest for Europeans (124.7), followed by Middle Eastern/Latin American/African (85.5), Māori (41.8), Asian (16.8) and Pacific peoples (11.1).

Comment: This study of MS prevalence in NZ suggests, as has been identified globally, that the prevalence of MS is increasing with time (providing the data are accurate) from 72 per 100,000 in 2006 to 96 per 100,000 in 2022. This trend is thought to be due to increased diagnostic accuracy and awareness, longer life expectancy and lifestyle factors such as reduced sun exposure and other MS risk factors.

Reference: N Z Med J. 2025;138(1612):71–82
Abstract