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REVIEW

Primary progressive multiple sclerosis: progress and challenges

Claire M Rice,¹ David Cottrell,² Alastair Wilkins,³ Neil J Scolding⁴

¹University of Bristol Institute of Clinical Neurosciences, Frenchay Hospital, Bristol, UK

²Department of Neurology, North Bristol Trust, Frenchay Hospital, Bristol, UK

³Department Neurology, University of Bristol, Frenchay Hospital, Bristol, UK

⁴Neurology Department, University of Bristol, Institute of Clinical Neurosciences, Frenchay Hospital, Bristol, UK

Correspondence to

Professor Neil J Scolding, Neurology Department, University of Bristol, Institute of Clinical Neurosciences, Frenchay Hospital, Bristol BS16 1LE, UK; n.j.scolding@bristol.ac.uk

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ABSTRACT

Primary progressive multiple sclerosis (MS) has long been recognised as presenting great difficulties to our management of what is increasingly a treatable neurological disease. Here we review some basic and clinical aspects of primary progressive MS, and describe how the disorder in fact offers powerful insights and opportunities for better understanding multiple sclerosis, and from a practical perspective an invaluable clinical substrate for studying and treating progressive disability in MS. Difficult hurdles remain, however, and these too are reviewed.

INTRODUCTION

From its first historical depictions, multiple sclerosis has always been described and diagnosed by its clinical semiology, its particular and peculiar clinical pattern and course. And intrinsic to this defining description, it was explicitly recognised from the first that two types of clinical processes could occur: the acute and almost eponymous relapse, and chronic, persistent progressive disease. As the decades passed, so the labels applied to different patterns of clinical course increased—relapsing-remitting, relapsing-progressive, primary progressive, secondary progressive, progressive-relapsing, benign, fulminant and so on—but all are permutations and combinations of the two first-noted clinical phenomena, the acute relapse and progression. Most patients—85–90% present with the former, the remainder with progression-onset disease: primary progressive multiple sclerosis (MS).

CLINICAL FEATURES AND DIAGNOSIS

It is curious, and rather little emphasised (at least in the last 50 years^{1–2}) that the clinical features of primary progressive multiple sclerosis (PPMS) are so often very different from those of acute MS relapses. The latter include optic neuritis (usually unilateral) in approximately 25% of cases, brainstem events (around 45%) and partial spinal cord syndromes, often exclusively sensory, often involving sphincter and/or sexual dysfunction. By contrast, primary progressive MS most commonly presents with a spinal syndrome, a spastic paraparesis usually with no clear sensory level (80–85% cases). Some 10–15% present with progressive cerebellar ataxia, and a smaller number with cognitive, other brainstem or visual symptoms (2–4%).^{3–4} Interestingly, PPMS appears to exhibit only the slightest gender bias (1.1–1.3 to 1) unlike the 3:1 female to male predominance of MS overall^{3–4}; the mean age of onset is greater (~40 vs ~30—rather similar to the average age of onset of

secondary progression in those with relapse onset disease), and it is almost never seen (or at least recognised) in childhood.

With regard to clinical course, in the London Ontario Cohort, PPMS patients required unilateral assistance to walk (disability status score (DSS) 6) some 8 years after presentation, and became wheelchair-bound (DSS 8) after 18 years.³ Age of onset, gender or clinical presentation onset did not appear to influence the rate of progression. However, the rate of initial decline (from onset to DSS 3) was of some value as a prognostic indicator, correlating with an accelerated time to expanded disability status scale (EDSS) 8. Early imprinting of the disease process in PPMS therefore seems to occur (as it does in those with frequent relapses in the early years of relapsing-remitting disease).

The similarities between the clinicoanatomical features of primary and secondary progressive MS might have long ago suggested similar pathological substrates for any form of progression, just as these clinicoanatomical differences between primary progressive and relapse onset disease have implied dissimilar pathophysiology, but it was only when axon loss was rediscovered in the 1990s by Trapp's group in the US and Ferguson's in the UK that these distinctions became more appreciated. The almost non-overlapping nature of the differential diagnosis of these two presentations of MS has, however always been apparent (see table 1).

The investigation of suspected PPMS arguably needs to be more rigorous than that of its relapsing-remitting counterpart. Often, a confident diagnosis is far more difficult to achieve: PPMS can commonly be a diagnosis of exclusion, and the passage of time is often an important element. The required investigations can largely be deduced from the list of mimics in table 1 (which includes infective and other inflammatory conditions largely as a matter of completeness: few show the slow, relentless clinical course of PPMS).

It is worth adding that, in the diagnosis of MS, MRI scanning of the spinal cord can occasionally be far more informative than that of the brain, non-specific lesions being all but non-existent in the cord. It should also be noted that the pattern of MR change seen in PPMS is not objectively distinguishable from that of relapsing-remitting multiple sclerosis (RRMS). Similarly, spinal fluid examination, an essential part of the investigation of possible PPMS (whereas some now regard it as optional in relapsing-remitting (RR) disease), in containing oligoclonal bands in some 80–90% cases, shows no features that distinguish primary progressive (PP) from RR MS. (That said, the

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Table 1 The differential diagnosis of primary progressive multiple sclerosis

Primary progressive MS	Differential diagnosis
Degenerative	
MND	Infective/Inflammatory
Structural (c. spine/Chiari)	HIV
Hereditary	Syphilis
HSP—SCAs	Prions
Leukodystrophies (AMN, Krabbe's), PKU	Vasculitis, sarcoid, lupus
Metabolic	Schistosomiasis, Brucellosis
Vitamins B12, E	Neoplastic (paraneoplasia)
Copper	Idiopathic/cryptic
Hypothyroidism	
Toxic—phenytoin, lathyrisim, nitric oxide	
Alcohol	

AMN, adrenomyeloneuropathy; HSP, hereditary spastic paraplegia; MND, motor neuron disease; NO, nitric oxide; PKU, phenylketonuria; SCA, spinocerebellar ataxia.

cellular reaction not uncommonly seen in acute relapses is very unusual in PPMS.) Reaching a diagnosis of PPMS when oligoclonal bands are unequivocally negative is difficult, but measuring evoked potentials, particularly assessing multiple pathways, can be extremely helpful.

The emergence of 'diagnostic criteria' in MS can be particularly useful for standardisation in clinical trials and in epidemiological studies (a justification easier to sustain had they not required repeated revision and updating), but it should be stressed that for PPMS, such criteria are not evidence-based and await validation.

ONE DISEASE OR TWO?

The similarities mentioned above—in clinical features (compared with secondary progressive disease), spinal fluid and MR findings, begin to address the question some have posed of whether PP and relapse onset MS are one and the same disease—or whether, in parallel with neuromyelitis optica, for example, primary progressive disease will come to be seen as a distinct disorder. The consensus at present is against the latter⁵: that primary progressive disease is but one phenotypic manifestation of MS, not radically different from relapse-onset disease. In addition to these similarities (see box 1), the facts that 6–10% PPMS patients develop relapses at some point in their disease course, and that in families that include multiple members with MS, both phenotypes are seen (indeed this may be true in identical twins, each with MS) also point towards this

Box 1 RR and PPMS—one disease or two?

- ▶ MRI—not objectively distinguishable
- ▶ CSF banding—not objectively distinguishable
- ▶ Evoked potentials—not objectively distinguishable
- ▶ Genetics—not distinguishable
- ▶ Neuropathology—not distinguishable
- ▶ Clinical features—not distinct from secondary progressive multiple sclerosis

RR, relapsing-remitting, PPMS, primary progressive multiple sclerosis; CSF, cerebrospinal fluid.

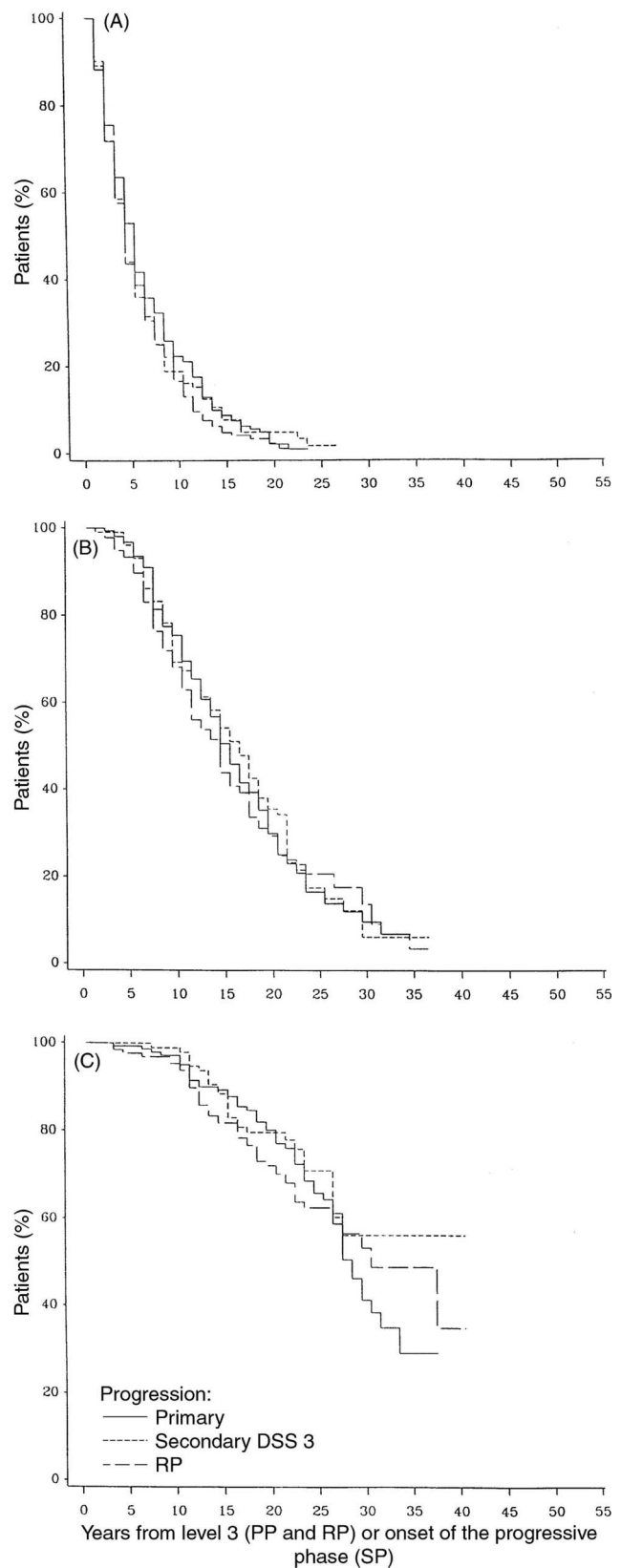


Figure 1 The figure shows the distribution of time taken to progress from DSS 3 to DSS 6 (A), 8 (B) and 10 (C) in SPMS patients compared with that for the time taken from the onset of MS to DSS 10 in PP and RP patients. DSS, disability status score; PP, primary progressive; RP, relapsing-progressive; SP, secondary progressive; SPMS, secondary progressive multiple sclerosis. Reproduced with permission from Kremenchutzky M, *et al. Brain* 1999;122:1941–50.

being one disease, not two. Finally, the natural history of disability progression in PPMS appears virtually identical to that of secondary progressive disease when compared from onset of the progressive phase (figure 1A–C).^{3 6}

MANAGEMENT

The (generally accepted) pathobiological identity of PPMS with relapse onset disease has implications for therapy. At present, there are no useful disease-modifying treatments for secondary progressive MS; nothing reverses, stops or even appears significantly to slow progressive disability once established, and we can safely infer that the same applies to PPMS. Conversely, we might also conclude that, if we wish to find treatments that alter the course of progression, we might do best to test putative therapies in patients with PPMS, since the (near) absence of relapses creates a far more reliable substrate for assessing their impact, freed from the distracting and misleading ‘noise’ of relapse activity. Few would doubt that any agent helping in PPMS would be similarly effective in secondary progression.

Sadly, there are no such treatments at present, but this by no means amounts to therapeutic impotence. A wide variety of symptomatic drugs and interventions, beyond the scope of this article but excellently reviewed elsewhere^{7 8} can be of major benefit in patients with progressive MS—whether for pain, fatigue, depression, bladder incontinence, impotence, spasticity or tonic spasms. The first symptomatic drugs to improve mobility are beginning to emerge, if of limited efficacy,⁹ while treatments to help ataxia, tremor and nystagmus remain very poor.

FUTURE THERAPEUTIC APPROACHES FOR PPMS

There are two aspects of ‘disease modification’ in relation to progressive MS: preventing or delaying the onset of progression, and modifying its course once it is established. The former relates to relapse-onset disease (although the appearance of MRI changes an extraordinary 10 years prior to clinical presentation of PPMS¹⁰ implies a preclinical phase that could represent an important therapeutic opportunity). In RRMS, it seems likely, though is as yet unproven, that as more effective relapse-preventing immunotherapies emerge, these will be confirmed to delay the onset of secondary progression.^{11–13} Indeed, since this transition (‘RR to SP’) determines the long-term prognosis of an individual presenting with relapses far more accurately than relapse rate or new MRI activity, making the onset of secondary progression a primary outcome measure for trials of RR patients might represent a significant advance in trial design.

Slowing, let alone halting, progression remains a serious challenge. There is a consensus that current immunotherapies do not significantly influence the course of progression once established in relapse onset disease.^{11 14} Valuable efforts have been made to study their effect in PPMS, but where this has been done, again no impact has emerged.^{15–18}

While the question of whether progression in multiple sclerosis is principally a neurodegenerative disorder, or whether that degeneration is still driven by a ‘smouldering’ low-grade inflammatory process sequestered within the central nervous system (CNS)¹⁹ has not entirely been resolved, the therapeutic impetus appears to have shifted in recent years towards exploring non-immune neuroprotective strategies in progressive MS—not least because of the lack of effect of immune approaches. A phase 2 trial of lamotrigine²⁰ has proved negative, but a comparable trial of phenytoin is planned and one of topiramate is already underway (<http://clinicaltrials.gov/ct2/show/NCT00217295>), there being much interest and a persuasive evidence base

suggesting that sodium channel blockade can reduce axonal injury in experimental allergic encephalomyelitis (EAE).^{21 23}

There is, similarly, a wealth of evidence that cannabinoids are neuroprotective in cell culture paradigms and MS disease models.^{24 26} The first successfully executed multicentre randomised controlled trial of cannabis in MS²⁷ primarily explored its symptomatic effects on spasticity, but a later subgroup analysis raised the possibility of a clinically relevant neuroprotective effect, and a large phase 3 trial of cannabinoids has now been completed. While this showed no benefit in primary outcome disability measures (http://www.ctu.mrc.ac.uk/news_and_press_releases/news_archive/cupid_30052012.aspx), subgroup analyses suggested promise in individuals less disabled at onset.

Riluzole, licensed for amyotrophic lateral sclerosis (ALS) and which inhibits glutamate transmission, is currently being trialled in patients with MS (<http://clinicaltrials.gov/ct2/show/NCT00501943>), not least since excitotoxicity and oxidative stress are increasingly considered important therapeutic targets.²⁸

This is plainly in effect a completely new field, and such trials have offered powerful validation of the methodology in ‘disability progression trials’, while the increasing interest also shown by the pharmaceutical industry in developing treatments for progressive disease is a further encouraging sign.

Growth factors

Neurotrophins have also been to a great extent considered as neuroprotective agents in progressive MS. This is partly because there is good evidence that myelin and oligodendrocyte-derived growth factors support axons, and that their loss contributes to axon loss,^{29 33} and partly because of the promiscuous protective effects of such agents irrespective of the mechanism of injury—a bonus when the precise mediators of axon and neuron damage remain to be defined. However, and notwithstanding our rapidly expanding knowledge of the *biology* of neurotrophins, the search for therapeutically useful neurotrophic factors has a rather long and dispiriting history. Clinical trials in disorders ranging from stroke and motor neuron disease to sensory neuropathy have all failed, the agents invariably proving either intolerable or ineffective. A single early phase clinical trial of insulin-like growth factor (IGF)-1 in MS was similarly unfruitful.³⁴

STEM CELL THERAPIES

The original rationale of developing stem cell therapies was not so much to stop progression as to reverse disability by repairing damage, and the means of achieving this was by replacing oligodendrocytes by injecting their precursors. But substantial changes in our understanding of tissue damage in chronic MS have in effect shifted the paradigm of cell therapy. The realisation that proliferative oligodendrocyte progenitors exist in the adult human brain,³⁵ and that significant numbers of these cells appear in MS lesions,^{36 38} undermined the rationale of adding more cells. The apparent presence of endogenous neural progenitors or stem cells³⁹ adds further doubt to this approach. That spontaneous remyelination is in fact rather more widespread than originally perceived—and this quite specifically includes PPMS⁴⁰—also calls into question a strategy based solely on increasing remyelination. But in addition, in secondary but particularly primary progressive MS, the relationship of demyelinated lesions to accumulating disability is highly questionable. It is generally now accepted that so-called ‘normal-appearing’ tissue in the MS brain and spinal cord is not normal, and that diffuse tissue damage particularly affecting neurons and

axons plays the major pathophysiological role in progression—so that targeted injection of cells into specific lesions, even if it did lead to successful local myelin repair, would probably have little if any effect on progressive disability.

These significant advances in our understanding of multiple sclerosis have not so much outstripped advances in stem cell biology as they have altered the way we think about cell therapy. Additionally and importantly, they have focused attention on the underlying molecular mechanisms of remyelination failure,⁴¹ a better appreciation of which may well yield pharmacological approaches to promoting remyelination, and with this axonal stabilisation.^{42–43} ‘Traditional’ pharmacotherapeutic interventions to promote remyelination, using the circulation to distribute any effective agent throughout the brain and spinal cord, plainly are better suited to the diffuse damage that we now know underlies progression, in a way that injecting cells into discrete lesions does not. Of the underlying biological processes relating to MS, our knowledge continues to progress: for example, very recent studies cast some doubt on the extent to which successful remyelination can help prevent progressive axonal loss. (Briefly, and with the caveat that this study explored a cuprizone demyelinating model and cuprizone can affect not just myelin but axons, it now is suggested that demyelinated axons which are then remyelinated still can and do degenerate.⁴⁴)

Exploitation of the circulation as a means of widespread, ‘diffuse’ delivery also underpins the alternative emerging cell therapeutic approach that seeks to use bone marrow cells. Circulating mesenchymal stem cells (MSCs), endogenous (released from the marrow in health, and more so in disease) and exogenous (delivered intravenously), ‘home’ specifically to areas of tissue damage or inflammation^{45–47}—including those within the brain and spinal cord.^{48–49}

This therapeutic approach differs in a second major way from the earlier stem cell paradigm in no longer having as its principal aim the replacement of oligodendrocytes to enhance remyelination. Rather, bone marrow cell therapy for MS is based on our rapidly emerging understanding of the many potentially beneficial properties of several bone marrow stem cell populations, properties that could, and in experimental systems do have reparative, neuroprotective and disease modifying elements.

It now seems clear that the *normal* physiological (or perhaps, rather, pathophysiological) function of several bone marrow cell subpopulations is spontaneous tissue repair.^{47–50–51} MSCs have been most studied, and exhibit an almost breathtaking range of properties and behaviours. They have pronounced immunomodulating and immunosuppressive properties.^{52–55} Second, isolated MSCs and non-cultured, bone marrow mononuclear cells promote myelin repair following experimental (non-immune mediated) demyelination.^{56–57} MSCs may indirectly stimulate remyelination, and other reparative effects, by recruiting and activating endogenous neural stem cells.^{58–60} They can reduce gliotic scar formation.^{61–65} MSCs have powerful neuroprotective properties,^{66–67} again independent of their anti-inflammatory activity, although protection against oxidative stress applies to immune and non-immune tissue damage.^{68–69} Finally (so far), MSCs are able to fuse with some specific cell types, particularly during tissue damage (perhaps particularly cerebellar Purkinje cells), apparently representing a further mechanism by which MSCs may offer protection (or ‘rescue’ damaged cells).^{68–70} There is indirect evidence that this happens not just experimentally but in MS itself (Kemp *et al*, *Brain* in press).

Two further points should be stressed: first, that other—indeed, probably all—adult tissues also harbour MSCs,⁷¹ and such tissues may also serve as a source of therapeutic cells.⁷² Second, other

non-MS subpopulations of bone marrow cells could also promote tissue repair, also by using a wide variety of effector mechanisms, including haematopoietic stem cells,^{73–78} Stro-1 positive cells,^{79–83} CD133+ve cells,^{84–86} multipotent adult progenitor cells (MAPCs) and others.^{87–89} In recent fascinating rodent studies, bone marrow-derived monocytes were shown to have remarkable abilities quite literally to ‘rejuvenate’ myelin repair in experimental remyelination.⁹⁰

Concerning possible translation, while it is the case that bone marrow cell therapy in patients with progressive MS would use autologous cells, it would be wrong to assume that adult stem cell therapy would *necessarily* be wholly free from hazard.⁹¹ The repeated cell cycling and expansion required to prepare purified, selected MSCs (or other subpopulations) can induce unwelcome genetic instability^{92–94}—quite apart from compromising repair capacities.^{95–99} And while malignant, donor-derived tumours have not been reported in patients receiving MSCs, including the now several hundred treated in trials for various cardiac diseases,¹⁰⁰ a recent report does indicate that MSCs directly injected intraventricularly can form non-proliferating cellular mass lesions.¹⁰¹

However, the use of non-manipulated, mixed ‘primary’ bone marrow cell harvests—without purification, cell culture or expansion, and delivered intravenously rather than by injection into the brain, avoids these theoretical or experimental hazards, and has been shown to be effective in a number of non-neurological disorders.^{102–103} Trials using such cells have also been commenced in stroke.¹⁰⁴ We have now commenced studies in progressive MS, with promising results in a very small cohort of patients with progressive disease¹⁰⁵; a phase two trial (ACTiMuS)—which will include a discrete subgroup with primary progressive multiple sclerosis—is to commence imminently.

Challenges to PPMS therapeutic trials

Notwithstanding PPMS offering an attractive ‘pure progression’ cohort to study therapeutics for preventing disability progression, there remains a relative dearth in therapeutic trials in comparison with its relapsing counterparts. This is probably multifactorial. Patients with PPMS are generally older, and so are more likely to have concomitant diseases, inevitably complicating trial design, recruitment and interpretation—arthritis, cardiovascular and respiratory conditions can all impair mobility and so affect the EDSS. Such conditions could also limit the use of more ‘aggressive’ therapies in this cohort. Additionally, PPMS patients generally have higher levels of disability and often strained social networks that can limit even the most dedicated of patients and their carers in what are often arduous and demanding clinical trials. In the authors’ experience of such PPMS trials disappointment almost inevitably occurs as the trial participant and their carers watch their disease progress. Modest slowing of disability progression is unlikely to be apparent to the trial participant (or investigator), and waiting for outcomes from such trials often takes many years. Dropout rates therefore for trials of PPMS patients are likely to be considerably higher than their relapsing counterparts. Such potentially high dropout rates must be seriously considered in advance if failure of long and often very expensive studies is to be avoided.

Calculations of population size for therapeutic trials have been deduced from the London, Ontario longitudinal database,¹⁰⁶ based on the likelihood of a PPMS population progressing along each DSS point. The spinally biased DSS is arguably more suited to progressive cohorts rather than its relapsing counterparts, but large numbers of patients and long periods of study are still required to prove a treatment effect. A later

PPMS natural history study from the British Columbia cohort¹⁰⁷ found slower progression, implying that even larger numbers of patients would be needed.

The difference in these studies is, in our view, significant, and likely due to discrepancies in defining patients as having PPMS. Certainly, a proportion of individuals initially thought to have PPMS do *not* subsequently (and often over a period of decades) ‘progress’ along the EDSS. In the British Columbia cohort, 9% had not reached EDSS 3 by 10 years. Whether these are truly PPMS patients is debatable. However, the largest completed PPMS trial to date, the PROMiSe trial¹⁷ comparing glatiramer with placebo over a 3-year period highlighted the difficulties of using PPMS cohorts, with fewer patients sustaining an increase in disability than expected. Patient selection for PPMS trials is crucial to success or failure.

Additionally, the EDSS is not an ordinal scale, either in time or level of disability. PPMS patients at DSS 6–9 have substantially longer ‘staying times’ at each level³; and so recruiting pre-DSS 6.0 patients to trials will reduce overall numbers required. But most PPMS patients present with a DSS of 4.0 or greater (mean initial DSS 5 for London cohort and EDSS 4.9), and PPMS trials often require documented EDSS progression in the preceding year—so the optimum population is greatly restricted, and such patients are already becoming hard to identify. Using early stage ‘PPMS patients’ also increases the risk of recruiting misdiagnosed patients including ‘non-progressors’ and inevitably leads to huge disappointment to those patients deemed ‘past-it’ in the exclusion criteria.

With the renewed emphasis on treating progression, and a wide range of possible new therapeutics, more sensitive methods of monitoring progressive MS are desperately needed. The enormous difficulty facing trial design for studies of interventions to prevent (or reverse) progressive disability in MS is that of end points. Clinical scales are currently imperfect but surrogate measures arguably even more so—and clinical parameters plainly are more relevant to patients than surrogates. But progression is slow, and so using purely clinical measures would necessitate studying large numbers of patients over (probably) a minimum of 5 years. Plainly the costs then become enormously expensive—often prohibitively so.

Better surrogate measures would of course substantially reduce numbers and duration, and so have major impact on trial costs. Potential options include novel MRI techniques, optical coherence tomography, and neurophysiological measures of conduction in multiple CNS pathways (the latter, objective and functional, in our opinion the most attractive). Any such surrogates must, however, be rigorously validated in longitudinal studies before the EDSS can be rationally abandoned.

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