

# Unmet Needs for People with Multiple Sclerosis

a report by  
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It has been 15 years since the first disease-modifying therapy (DMT) for multiple sclerosis (MS) was licensed, and 14 years since it became available in Europe. The intervening time has seen the introduction of other DMTs and clarification of the indications for their use.<sup>1</sup> Physicians who treat MS patients can choose between four available interferons (Avonex, Betaferon, Extavia and Rebif), one polymer (Copaxone) and one monoclonal antibody (Tysabri) before considering the use of cytotoxic agents.

The availability of DMTs helped focus attention on the disease and the high cost of the biotechnical products. Together with self-injection requirements, this focus has caused healthcare providers to reassess service provision and pharmaceutical companies to develop nursing services specifically for people with MS. As a result, the help available to MS sufferers greatly improved: MS clinics were developed and clinicians with expertise were identified, MS specialist nurses were established and their numbers have multiplied, the assessment of individual patients became more standardised and monitored and the concept of a service dedicated to people with MS developed. Therefore, the availability of DMTs is indirectly responsible for a marked improvement in the services available to most people with MS. It is evident that in those countries where most new therapies are available, the service provision to people with MS is most comprehensive.

Sadly, the provision of services and availability of DMT is not uniform. In Europe there is variation in the availability of the newer treatments, which remain expensive, and in the provision of neurological and ancillary services to people with MS. There are national and international organisations working to improve conditions, and the individual national multiple sclerosis societies together with the Multiple Sclerosis International Federation (MSIF) are collating information about service provision, access to neurology and availability of DMTs to devise a template enabling those countries with poorer service provision to achieve the minimum level.<sup>2</sup> In Europe, there is the European Multiple Sclerosis Platform (EMSP), a lobby group based in Brussels that has developed a set of minimum requirements for people with MS within the EU.<sup>3</sup>

## What's New in Multiple Sclerosis?

In the near future, more DMTs will become available to help control the early inflammatory phase of MS.<sup>4</sup> The first is Extavia, a rebranded version of interferon beta-1b, which is a mainstay of therapy with an established benefit-to-risk profile. The next generation of drugs includes oral agents and monoclonal antibodies that, though given by injection, are used at infrequent intervals. Both should be more convenient for patients than currently available DMTs. The drugs currently undergoing trials appear more effective than those being used at present, but such improvements in efficacy by modifying or suppressing the immune system early in the course

of the disease inevitably carry a potential danger. There is risk of toxicity, the possibility of opportunistic infections and the long-term fear of neoplasia. The effectiveness of the agents will be demonstrated in trials and short-term safety ensured, but it will be many years before overall risks can be fully evaluated and their frequency determined. It is essential, in using the newer and stronger agents, that the physician ensures the patient is not only fully informed of their potential benefit, but also advised in detail about possible risks. People with MS are able to determine the degree of risk that they are willing to accept, provided that they are given the necessary information.

In terms of future therapy for people with MS, most of the five standardised DMTs – the four interferons  $\beta$  and glatiramer acetate – are likely to be copied by generic products within the next few years. In the case of the biotechnical products such agents are called 'bio-similars', and it will be for the licensing agencies, such as the European Medicines Agency (EMA), to determine their efficacy and safety. Information in relation to combinations of therapy with cytotoxic agents and DMTs will become available, although the problems of summing the toxicity of two potentially dangerous therapies are self-evident. It is possible that future therapy will include a period of induction with a major immunomodulating agent followed by maintenance therapy with one of the current DMTs.

## Significant Unmet Needs Remain

Physicians and patients recognise that available DMTs work best during the phase of acute inflammation and in relapsing–remitting disease. However, some patients taking the available DMTs still experience exacerbations of the disease, representing a persistent problem. As no current therapy completely prevents exacerbations, deciding when a treatment is 'failing' is extremely difficult. Most MS patients and their physicians perceive that a drug is failing if attacks continue and worsen or when disability progresses. No simple system of clinical evaluation, cerebral imaging with magnetic resonance imaging (MRI) or serological test can positively assure a physician that treatment is failing and that a patient's therapy should be stopped or changed. To complicate matters further, some forms of therapy may develop neutralising antibodies, which may reduce treatment effectiveness. However, there continues to be uncertainty about the extent of this effect and there is great variation from

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physician to physician and from country to country in deciding whether to stop DMTs when sufficient antibodies are persistently present. One continuing unmet need is absolute evidence of the relevance of neutralising antibodies to the efficacy of therapies, particularly the interferons, and advice as to whether their presence should lead to cessation of therapy even if the patient is well.<sup>5</sup>

Another major unmet need in MS is the absence of a simple, reproducible and inexpensive biomarker to determine the nature of the disease and monitor its progress. The recent identification of an antibody to aquaporin-4 in people with neuromyelitis optica (NMO) has re-awakened interest in a possible humeral causation for the disease.<sup>6</sup> It provides a potential marker for the disease and suggests possible therapies, such as plasmapheresis and treatment directed against the  $\beta$  cells. The discovery of other biomarkers – genetic, immunological or via imaging – would improve the accuracy and speed of diagnosis, enable monitoring of severity, assist in making therapeutic decisions and help define when therapy was failing.

It is increasingly recognised that MS affects memory, cognition and intellect. It may be that subtle changes in psychological measures represent the first identifiable problems for many people with MS.<sup>7</sup> Few of the original clinical trials measured psychological parameters as part of their assessment of the individual patient. This has now changed considerably, and people with MS and their treating physicians are increasingly aware of psychological problems that can arise. As a result, patients and physicians now have more rigorous standards for evaluating the benefits of DMT in reducing, delaying or preventing such psychological change. In more recent trials, both the interferons and the monoclonal antibodies have been shown to improve psychometric measures in people with MS who are treated in this way compared with the placebo groups. All current trials of new therapies include psychological testing and an assessment of quality of life, so when these trials are concluded physicians will be able to explain more clearly the patient-related benefits in cognition, memory and wellbeing.

In general, psychological problems are under-recognised when reported in people with MS. There is a dearth of provision of help from psychologists and counselling available for people with MS. A simple assessment of cognition should increasingly play a part in the monitoring of people with MS, early changes should be identified and onward referral to appropriate services should be established. While it may not yet be completely possible to prevent the development of cognitive and memory problems in MS, these problems can surely be reduced by the use of appropriate DMTs and their effects can be ameliorated by adequate psychological help and the timely use of pharmacological therapy.

The unmet need of addressing psychological problems is further exemplified by the lack of extensive service options for recognition, early diagnosis and intervention by medical staff to help MS patients showing the first symptoms of depression, anxiety and other affective problems. This is an important part of the comprehensive service needed for people with

MS and should include an assessment, by completing an inventory or by interview, to determine underlying affective problems. Once evaluated, the patient can be directed towards appropriate help.

Current therapy methods are largely directed to the inflammatory and systemic origins of the disease. This type of therapy does not address the need to restore the underlying neuro-deterioration that patients experience. Furthermore, current therapies do not provide support for the 10–15% of people who have primary progressive MS. There is hope that some of the new agents in trials will show a neuro-protective effect and some are believed capable of stopping further infiltration of immuno-active cells into the brain parenchyma, but none has been demonstrated to affect the underlying progress of the disease in the absence of overt inflammation.

It is likely that agents that encourage remyelination or that protect and preserve axonal function and neuronal energy stores will have a greater effect on that most disabling process of the disease. As with so many degenerative conditions, stem cells are thought likely to have benefit in the long term, but it is extremely unlikely that any of these agents directed towards helping the progressing form of the disease will be available before 2015.

It is important that the interest, enthusiasm and financial support directed towards the development of new DMTs does not detract from the less glamorous research into drugs that may alleviate symptoms in people with MS. The management of symptoms of spasticity or stiffness within muscles, the relief of pain and dysaesthesiae, the improvement of balance and control of dizziness and double vision are all valuable. The management of bladder problems in MS has improved during the past two decades, although most oral agents used to reduce bladder irritability have significant side effects. The use of intra-vesical botulinum toxin together with intermittent self-catheterisation may well replace such systemic therapies in future. Bowel control remains a problem, although there are new techniques involving the implantation of stimulating devices.

Perhaps the most common symptom of all in MS is that of fatigue. There has been no effective therapy for this symptom, although individuals have been given amantadine for physical fatigue and modafinil for mental fatigue. Recent reports of trials of the potassium channel blocker 4-aminopyridine suggest that such agents can benefit almost half of patients, giving significant improvement of the disabling symptom of fatigue.<sup>8</sup>

Throughout Europe, studies have confirmed that people with MS have a significant risk of becoming unemployed within five to 10 years of diagnosis. Therefore, financial problems are common and inevitably linked to service provision and the provision of social help to the individual, family and carers. Service provision varies considerably around Europe, and although systems differ, those that provide finances to the individual with a disability to enable them to be responsible for the provision and funding of carers seem to be most successful. ■

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