Multiple Sclerosis Prevention, Treatment and Care

Summary

Multiple sclerosis is a progressive auto-immune neurological disease which affects 100-120 thousand individuals in the UK, about three quarters of whom are women. It is today the most common non-accidental cause of severe disability amongst adults aged between 20 and 50 years. It causes varying symptoms, from balancing difficulties and sight problems to neurogenic pain and incontinence. Over a third of people with MS ultimately become unable to walk, albeit modern treatment developments should improve outcomes.

In the last 25 years a range of new disease modifying treatments (DMTs) for MS has become available. Yet access to medicines that reduce the frequency of central nervous system damaging relapses and other therapies, including rehabilitative support, has been variable. Problems to be overcome relate in part to a scarcity of NHS neurologists with a specialist interest in MS, of whom there are little more than 100 in the UK.

Fears about side-effects also influence treatment provision and uptake, despite evidence that many individuals are prepared to take risks greater than those associated with modern therapies in return for benefits like fewer relapses. The fact that, because clinical trials have not included wheelchair users, NHS patients living with MS can be stopped from receiving DMTs (which curb destructive immune responses) if they lose the ability to walk is another concern. Sub-optimal treatment access may on occasions reflect issues linked to gender bias.

A new MS treatment algorithm produced by NHS England should help to improve the use of DMTs and reduce care disparities. It will need to be implemented in ways flexible enough to permit constantly improving treatment quality aimed – in an era of evolving therapeutic opportunity – at optimising outcomes on a person by person basis, and ensuring that people with more advanced disease are not unfairly denied care to contain costs. Other key findings and recommendations include:

- Service quality improvement often depends on the timely publication of robust comparative data. Parliamentarians and others seeking to enhance MS care should seek full publication of statistics on all forms of treatment and care quality.
- Increasing the numbers of neurologists with a special interest in MS is an important goal. But in the face of Brexit and other challenges there is unlikely to be any short term way of achieving this. In the near future expanding the numbers and roles of neurological nurse specialists (NNSs) and pharmacists with specialist expertise in MS is likely to be the most effective way of improving service delivery. More investment in GP/primary care training and support could also improve MS related health outcomes.
- At present only neurologists diagnose MS and prescribe DMTs. But the introduction of AI supported diagnostic and disease management techniques could enable other health professionals to help people with MS access optimally effective care in a timely way.
- There is emergent evidence that new treatment approaches can slow progressive forms of MS. Current research is also seeking medicines which stimulate remyelination and protect brain and other nerve cells from damage. At the same time the ongoing development of autologous stem cell transplantation is increasing the possibility of MS cures.
- By the 2030s MS may in at least in a proportion of cases be preventable via, for instance, Epstein-Barr virus immunisation. Yet achieving such progress will, as with all other medical and pharmaceutical advances, depend on adequate public and private R&D funding being available.
- Living well with MS requires not only good biomedical care but support in areas ranging from providing exercise opportunities through to employment support. Assuring high quality multiple sclerosis care is a significant challenge for health and welfare systems in countries such as the UK and should be recognised as an important women’s health issue.

Achieving better outcomes for people living with MS could require increased public service spending. The affordability of this might be questioned when the national economy is growing slowly and may in future decline. But scientific advances are generating increased reason to hope for better outcomes. From a longer term economic and social welfare perspective it is important to ask if the UK can afford not to prioritise meeting the needs of everyone affected by illnesses such as multiple sclerosis in a timely and effective manner.
Introduction

The UCL School of Pharmacy report Greater Expectations: the Future Hopes of People with Multiple Sclerosis was published in December 2017. It reviewed the nature, causes and treatment of MS and presented the findings of an international survey (the TaP-MS survey) of the therapy related beliefs, priorities and expectations of people living with the condition. Greater Expectations highlighted the importance of symptoms such as fatigue and the variability of the disability and distress the disease imposes. Because its impacts can fluctuate on a near daily basis it is often more difficult to adapt to living with MS than it is in the case of stable conditions. The research reported at the end of 2017 also found that many women and men who have multiple sclerosis are prepared to accept a risk of serious side-effects in return for the hope that disease modifying treatments (DMTs) will prevent relapses and slow or stop the underlying progression of the disorder (Box 1).

The introduction of about a dozen DMTs for MS since the early 1990s has created pressures for early intervention. It is increasingly believed that the earlier protective treatment is started the more likely it is that permanent nervous system damage will be avoided or delayed. But concerns about therapeutic hazards mean there is also a need for accurate diagnoses before treatment initiation. (See, for example, Solomon and Corboy, 2017.) There is also, to date, a lack of definitive data as to the degree to which using DMTs for relapsing forms of the condition will delay or prevent the transition from relapsing-remitting MS (RRMS) to more disabling progressive stages of the disease. This complicates risk-benefit calculations and means that the overall cost effectiveness of such therapies cannot as yet be precisely stated. However, this does not provide an ethically acceptable reason for failing to supply treatments likely to be beneficial.

Tensions between the desire to avoid future disabilities and frequent disease exacerbations as against fears of suffering sometimes life threatening side effects (coupled with financial concerns on the parts of both care funders and treatment providers) have contributed to inconsistencies in NHS care provision. Yet there is already firm evidence that people with RRMS who take effective disease modifying medicines are less likely suffer relapses than would otherwise be the case. The available evidence indicates that rates are on average reduced by between 10 and 50 per cent, depending on the drug(s) taken and patients’ individual responses. Some people living with multiple sclerosis (PLwMS) have had their disease stabilised for extended periods. There is in addition some evidence of reduced death rates (Scalfari et al, 2013).

These are important benefits, in part because shifting levels of impairment are especially problematic in contexts such as disability assessment. Conventional approaches to the latter often assume a constant physical burden. With regard to the cognitive aspects of MS less progressive therapeutic approaches may also under-estimate the extent to which it is cause of preventable dementia (Giovannoni, 2017).

In the US the American Academy of Neurology advises that most people diagnosed with MS will benefit from early use of an appropriate DMT (AAN, 2018). Yet in Britain it appears that (notwithstanding recent progress – see, for instance, MS Society 2016a, 2016b) prescribers in some localities have been much more conservative in their approach to treating MS than neurologists elsewhere. One as yet unexplored possibility is that gender related factors can, along with other variables, on occasions influence attitudes to treatment and the acceptance of therapeutic risks. Such problems are already known to exist in the cardiovascular disease context (Greenwood et al, 2018).

Since the release of Greater Expectations a number of important developments have taken place. For example, NICE has published a Multiple Technology Assessment relating to the use of beta-interferons and glatiramer acetate (NICE, 2018). This has helped to moderate the costs of products containing these active ingredients, which have been available for longer than other MS DMTs – see Table 1. In addition, in March 2018 NHS England, with the involvement of the Association of British Neurologists (ABN), issued a consultation on an algorithm intended to guide the use of disease modifying MS medicines. The final version of this treatment algorithm was published in September 2018 (NHS England, 2018).

There has in tandem with the development of these resources been controversy about issues like whether or not it is appropriate to stop providing NHS funded access to DMTs for people with MS, once the disease has progressed enough to stop them walking. Critics of this NHS England policy (which derives from the fact that the available drug trials did not include wheelchair users, partly because they are more likely than people who can still walk to have entered a progressive stage of the illness) argue that withdrawing treatment should be regarded as unacceptable when there is clinical reason to believe that continuing DMT use would be beneficial.

International progress has taken place with regard to the use of recently introduced treatments such as cladribine and ocrelizumab. The latter was the first medicine to be licensed for the treatment of primary progressive MS (PPMS), as well as the relapsing/remitting (RRMS) stage of the disease. Other innovative products may prove able to slow secondary progressive MS (SPMS). In addition, the potential for (autologous hematopoietic) stem cell transplants to cure or control aggressive forms of MS has received growing attention (Atkins et al, 2016). This process in essence involves killing patients’ mature immune system cells and replacing them with newly generated ones.

Ongoing research is also throwing further light on the part that Epstein-Barr virus (EBV) infection plays in causing MS, alongside other factors that influence adaptive immune


2 There is, for example, now approaching 10 years of data showing that members of a group of people with MS treated with the medicine alemtuzumab have not on average progressed. Those showing evidence of clinical progression and increased CNS damage have been counterbalanced by others whose condition appears to have improved (Coles, 2018).
responses (Veroni et al, 2018; Harley et al, 2018). For example, it has recently been observed in Sweden that genetically vulnerable individuals who smoke and have been exposed to relatively high dosages of organic solvents have a 30 fold higher risk of developing MS than average members of the population (Hedstrom et al, 2018; Bell and DeLuca, 2018). Against this background this document offers a brief update on recent developments in MS prevention, treatment and care with special reference to the situation in Britain. The pharmaceutical and public health policy questions it addresses include:

- To what extent might it in future be possible to prevent the occurrence of MS through lifestyle changes and/or technologies such as EBV immunisation?
- How can the early, accurate, diagnosis of MS be further facilitated?
- Will the development of instruments such as the NHS England treatment algorithm mean that NHS patients can access optimal care for MS in ways that they and their families can trust are in line with international best practice, and that will be affordable for the health service in a time of national economic challenge?
- Given continuing public and private investment in multiple sclerosis research and in areas such as immunology, what advances in medicine, pharmacy and psychosocial care are likely to be able to help individuals and families living with MS in the coming 20-30 years?

**Preventing MS**

Until recently there were no evidence-based strategies available for the primary prevention (see Box 2) of multiple sclerosis. There is still no firm evidence that achieving this end will be possible. However, there is an emergent understanding that the condition typically results from interactions between varying forms of genetic vulnerability (see below) and environmental and behavioural variables (Olsson et al, 2017). Even if an individual’s gender – worldwide women are two to three times more likely than men to develop MS than men (Harbo et al, 2013) – and basic genetic (as distinct from epigenetic) endowment cannot be changed, lifestyle-related interventions aimed at protecting young people in their teens and early adulthood might reduce the likelihood that those ‘at risk’ will develop MS. Relevant factors include:

1. Having low vitamin D levels.
2. Being obese during adolescence.
3. Tobacco smoking.
4. Exposure to organic solvents.
5. Suffering Epstein-Barr virus infection, especially after the first ten to twelve years of life.

**Box 1. Multiple Sclerosis – an Inflammatory, Demyelinating, Auto-immune Disease affecting the Central Nervous System**

MS is best seen as a single disorder which, when first diagnosed, normally (in around 85 per cent of cases) takes the form of a relapsing remitting disease (RRMS). At this stage ‘attacks’ of symptomatic illness are followed by a return to apparent good health. But after a period of typically ten to twenty years many (but not all) people with MS develop secondary progressive multiple sclerosis (SPMS). At this point in the natural history of the condition symptoms and disabilities are, although they can still vary, permanently apparent. In most instances their severity will gradually progress. Other commonly used MS terms include:

- **Clinically or radiologically isolated syndromes (CIS and RIS).** These descriptors refer to the condition of individuals who show clinical or MRI observed signs of MS, but cannot definitely be said to have the disease. Historically, about a half of those identified as having RIS or CIS have subsequently developed diagnosable MS.

- **Primary progressive multiple sclerosis (PPMS).** Some individuals – in the order of 10-15 per cent of all new cases – appear to by-pass the relapsing stage, in that they initially present with progressive illness. They are on average some 5-10 years older than people first diagnosed with RRMS, and can expect a rather greater (circa 10 year, as opposed to 5 year) life span reduction as a result of having MS.

- **Progressive relapsing multiple sclerosis (PRMS).** This diagnosis is initially received by about 5 per cent of all MS patients, albeit its use varies between national and local settings. In this manifestation the disorder is progressive from start, but the disabilities it causes develop at markedly varying speeds.

MS results from combinations of protective and vulnerability inducing ‘germ line’ genetic variations and environmental factors like Epstein-Barr virus (EBV) and perhaps other infections and high or low exposures to ‘man-made’ organophosphates and/or sunlight – see text. Affected central nervous system cells can lose and in some circumstances regain their protective myelin sheaths, which are generated by cells called oligodendrocytes. It is now known that in MS particular types of immune system T lymphocyte attack and can kill the latter, with the involvement of given forms of B lymphocyte. MS does not affect the peripheral nervous system, in which some nerve fibres lack myelin sheaths and others have them provided by Schwann cells rather than oligodendrocytes.
For example, women with low levels of vitamin D are twice as likely to develop multiple sclerosis as those with high levels (Munger et al, 2017). Direct causality should not be automatically assumed, albeit recent Mendelian randomisation studies indicate that both low vitamin D levels and obesity play a role in the condition’s aetiology (Harroud and Richards, 2018). One mechanism underlying this (which is linked to how far north or south people live, and their consequent exposure to vitamin D generating sunlight) may be that vitamin D impacts on the expression of genes influencing relevant immune responses. Vitamin D supplementation does not effectively treat MS. Yet there is now a relatively strong argument for guarding against deficiencies amongst healthy children and young adults in the hope of protecting them against MS, as well as (for other reasons) promoting vitamin D supplementation amongst older people living in countries like the UK.

Table 1. FDA and/or EMA Authorised Disease Modifying Treatments for MS

<table>
<thead>
<tr>
<th>Approved name</th>
<th>Mode of action and additional information</th>
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<tbody>
<tr>
<td>Interferon β-1b</td>
<td>Interferon β-1b, given by subcutaneous injection, played a pioneering role in MS disease modifying therapy. The first interferon based medical product approved was approved in the US in 1993. Interferons are cytokines (messenger molecules) that influence immune responses and the activities of T lymphocytes. Interferon β-1b has anti-inflammatory properties. All interferons can cause flu-like symptoms, including headaches and fatigue.</td>
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<tr>
<td>Interferon β-1a</td>
<td>Interferon β-1a presentations are available for both intramuscular and subcutaneous administration. Interferon β-1a differs in its molecular structure from interferon β-1b but is similar regarding its therapeutic impact and mode of action. The first β-1a based DMT for MS was licensed in the US in 1996. It too causes flu-like and other side effects, which may be more easily manageable than those of some newer MS therapies. While interferon based medicines can average reduce RRMS relapse rates by about 10 per cent, highly active treatments reduce them by around 50 per cent below the rate experienced by people on interferon therapy.</td>
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<tr>
<td>Glatiramer acetate</td>
<td>The first glatiramer acetate MS DMT was also authorised in the USA in 1996. Chemically it is made up of four amino acids that exist in myelin. Its therapeutic effects are possibly a function of its capacity to divert immune system cells away from attacking myelin protein in the brain and spinal cord. Like interferon β-1b, glatiramer acetate is injected subcutaneously. It may cause injection site reactions. Side effects can in addition include problems such as breathlessness, but are again likely to be relatively easy to manage.</td>
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<tr>
<td>Peginterferon β-1a</td>
<td>Pegylation is used increase the half-life of molecules in the body. Pegylated products can hence be given less frequently and/or in lower doses than their non-pegylated equivalents. Pegylated interferon β-1a is normally administered subcutaneously on a fortnightly basis.</td>
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<tr>
<td>Natalizumab</td>
<td>This treatment was first approved in 2006. It is administered by monthly infusion and is an anti-integrin monoclonal antibody which acts by moderating inflammatory processes in the CNS. Side effects range from headaches and fatigue to a limited risk of a potentially fatal, but now more avoidable, condition called progressive multifocal leukoencephalopathy (PML)</td>
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<tr>
<td>Fingolimod</td>
<td>Fingolimod is a sphingosine 1-phosphate receptor modulator. Sphingosine accounts for a quarter of the lipid in the myelin sheaths of CNS neurons. Fingolimod curbs T cell attacks on the latter. It was approved by the FDA in 2011, and is taken orally in capsule form. More common side effects include flu-like symptoms, liver problems, sinusitis and pain in parts of the body.</td>
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<tr>
<td>Teriflunomide</td>
<td>This drug inhibits pyrimidine synthesis and acts as an immunosuppressant by reducing the proliferation of activated T and B lymphocytes. Used as a once daily pill it was first approved in the US in 2012. Teriflunomide’s common side effects range from headaches and hair thinning to causing liver abnormalities.</td>
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<tr>
<td>Dimethyl fumarate</td>
<td>Dimethyl fumarate was first approved for use in treating RRMS in the US 2013. It is available as an oral therapy and has a complex mode of action. It influences the production of a variety of cytokines. This drug reduces autoreactive T cell activity and also has an anti-inflammatory action. Common side effects include flushing/titching and gastrointestinal problems.</td>
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<tr>
<td>Alemtuzumab</td>
<td>Alemtuzumab is an anti-CD52 monoclonal antibody that has been licensed in Europe for the treatment of relapsing MS since 2013, albeit it was first used in an individual with MS in 1991. CD52 is found on the surfaces of both B and T lymphocytes. The therapeutic effects of anti-CD52 therapy are related to the depletion of autoreactive lymphocyte populations. Alemtuzumab is normally administered via infusions given in two sessions, separated by a 12 month period. Side effects include causing infections and blood pressure changes through to infusion associated reactions such as rashes, fever and nausea. More rarely alemtuzumab can cause serious conditions such as immune thrombocytopenia (ITP).</td>
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<tr>
<td>Ocrelizumab</td>
<td>Ocrelizumab became the first MS DMT to be licensed in the US for both RRMS and PPMS in 2017. It is a humanised anti-CD 20 monoclonal antibody. CD20 is found on the surface of B lymphocytes. Ocrelizumab reduces the number of these cells. It is administered via intravenous infusions given on a six monthly basis. Unwanted side effects may range from injection site reactions to – as with all immunosuppressive therapies – serious infections and impaired cancer defences.</td>
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<tr>
<td>Cladribine</td>
<td>Cladribine is an oral therapy which was licensed by the EMA for use in RRMS treatment in the summer of 2017. Its use results in the build up of toxic cladribine phosphates in B and T lymphocytes. This reduces the numbers of such cells. Cladribine is given as a pill in two brief courses a year apart. Common side effects range from fever and fatigue to neutropenia.</td>
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Note: This Table does not offer a complete description of the side effects caused by and warnings relating to the use of any of the medicines mentioned. Daclizumab, a CD 25 receptor blocker, was first marketed for the treatment of MS in 2016 and voluntarily withdrawn in March 2018.
Obesity in early life/adolescence, smoking (albeit that nicotine ingestion per se appears to have either no effect or to be protective – Olsson et al, 2017) and organic solvents (such as benzene, acetone and toluene) can alter adaptive immune responses and cause inflammation in the lungs and elsewhere in the body. Public health programmes designed to help individuals to protect themselves and others in their lives against such disease causes might also help to reduce the incidence of MS.

**Box 2 Primary, Secondary and Tertiary Prevention**

Primary prevention involves protecting people from ever being exposed to the causes of a disease, or intervening before any form of frank illness develops. Stopping smoking or helping individuals to avoid obesity can be a forms of primary prevention, as may immunising against disease risks. Secondary prevention involves treating early disease manifestations in order to avoid more serious later stage complications. Tertiary prevention involves protecting the quality of life of people living with illnesses and disabilities by interventions which prevent social exclusion, promote health and wellbeing generally, and permit individuals to play social roles which they and their peers value. In MS such support may, for example, include options like supplying mobility aids, providing suitable exercise facilities and supporting employment.

With respect to genetics, the reported concordance rate for diagnosed MS in identical (monozygotic) twins is in the order of 25-30 per cent. Over 200 genetic associations with MS have now been found. The strongest known single gene/allele variant (technically referred to as HLA-DRB1*15:01) increases the relative risk of developing the condition by around three fold in Europeans living in Europe. Once again, most of the genes associated with MS affect immune system functioning. Such observations offer further support the view that multiple sclerosis results from complex interactions between environmental and genetic factors, leading to epigenetic (in essence, gene expression related – see Feinberg, 2018) and other acquired bodily changes (phenotype variations) that promote auto-immune responses leading to demyelination and central nervous system damage.

In the coming 10-20 years the aetiology of MS will be understood in more detail. But from a health policy perspective it is worth emphasising that there is already powerful epidemiological evidence that Epstein-Barr virus (EBV) infection, particularly after an individual has reached their teens or twenties, is often (if not always) a key part of the causal chain leading to MS (Wald, 2016; Wolfson Institute of Preventive Medicine, 2017).

3 If one individual develops MS her or his identical twin will have a roughly one in four chance of also developing it. Regardless of issues such as the extent to which underlying MS-like lesions can be found in those twins not formally diagnosed with MS, these data imply an important role for environmental triggers.

4 HLA molecules, for instance, present antigens to immune system T cells.

There is also a strong body of immunological theory and research evidence relating to the mechanisms involved. (See, for example, Pender, 2003; Pender and Burrows, 2014; Laurence and Benito-Leon, 2017.) Some authorities believe that EBV infected and/or transformed immune system B lymphocytes initiate T lymphocyte attacks on the myelin that protects neurones in the central nervous system. Research published in 2018 also indicates that the EBV protein EBNA2 can drive genetic expression changes associated not only with MS but other auto-immune conditions. These include systemic lupus erythematosus (SLE), rheumatoid arthritis, inflammatory bowel disease and type 1 diabetes (Baecher-Allan et al, 2018). Such findings have potentially profound implications for health in the 21st century, and – given that females are at special risk of being diagnosed with most forms of auto-immune illness – for women's health in particular.

It would be beyond the scope of this brief UCL School of Pharmacy update report to further explore how EBV and the other factors noted above cause MS. Nevertheless, from a policy perspective it is worth noting that there is reason to hope that the development of an effective immunisation against Epstein-Barr – which is a human herpes virus best known for causing glandular fever – could have important primary protective effects. This is so not only in relation to MS and other auto-immune conditions, but also in respect to a number of cancers.

Publicly (National Institutes of Health) funded work on a vaccine that might confer 'sterilising' immunity (that is, of stopping permanently infected or transformed B cells from being formed in EBV immunised subjects) is currently being conducted in the US. But there will be many barriers to be overcome in undertaking safety and effectiveness trials and introducing EBV immunisation into child and (if necessary) adult vaccination schedules.

Were private industry unable to support the R&D effort required the development of a technology capable of benefiting many millions could be delayed for decades, if not indefinitely. If Britain is to maintain a global biomedical R&D role post-Brexit this is the sort of opportunity that members of both Houses of Parliament could usefully seek to monitor, with the objective of ensuring that it receives informed attention and adequate funding.

**Promoting early diagnosis**

Before the introduction of beta-interferon based therapies in the mid-1990s and the pharmaceutical developments that have since followed there was no prospect of altering the course of multiple sclerosis, albeit that palliative therapies relieve distress. The fact that MS was often seen as ‘medically untreatable’ may sometimes have led to a belief amongst clinicians and policy makers that there was no...
need to encourage early diagnosis because it would only cause ‘patients’ to have to live longer with the knowledge of having an incurable, often progressively disabling disease. Yet even before the introduction of disease modifying treatments such attitudes were questionable.

Long periods of time spent living with unexplained problems such as a loss of physical coordination, fatigue, sight abnormalities, neurogenic pain and/or incontinence are likely to cause avoidable distress to anybody. In any circumstance, including when only symptom moderating treatments are available, clear diagnoses can provide a route to understanding symptoms, and allowing adequately supported individuals to plan their futures as constructively as possible.

 Rising expectations associated with the introduction of increasingly effective DMTs have helped to highlight care quality failings and promote the case for early diagnosis and treatment aimed at relieving current distress and preventing future harm. To achieve optimal outcomes clinicians must be able to exclude alternative diagnoses quickly and – given that about a third of MS cases will naturally run a relatively benign course – make broadly accurate prognostic judgements (Brownlee et al, 2017).

The available evidence indicates that people who develop MS at first go through an asymptomatic period likely to last several years. As yet there is no viable way of screening for such very early stage MS, even amongst people whose history shows them to be at raised risk. Likewise to date there is no single definitive test for multiple sclerosis once symptoms have become discernible. There is also no fully reliable method of predicting its course, albeit as a general rule the more rapid the observed progression the more likely it is that MS will ultimately result – especially when left untreated – in severe disability.

In the past individuals developing MS may have suffered a decade or more of distress before their condition was identified. Even after diagnosis, standards of NHS and social care could be poor. Until the 1980s there was a danger of young people with MS being inappropriately placed in facilities such institutions for the care of older people with conditions like dementia.

However, as new treatment options have become available, overall attitudes appear to have become more positive. The identification of improved diagnostic criteria (see Thompson et al, 2018) and the introduction of enhanced genetic and serological testing has helped to speed diagnosis, as could in future the introduction of artificial intelligence (AI) supported computer programmes for use in both primary and secondary care. At the same time the work of organisations such as NICE (the origins of which in the 1990s related to political fears that the costs of supplying interferon based treatments for PLwMS would ‘bankrupt the NHS’) has contributed to defining the standards of care that people – and families – living with the disease should feel entitled to expect (NICE, 2014; Perry, 2014; NICE, 2016).

Such progress is to be welcomed. Yet there are still concerns about the overall quality of NHS care available – particularly for less advantaged individuals living in relatively poor localities – and the extent to which early MS diagnoses and timely treatment can be universally assured. These in large part centre on the fact that there are only about 1,000 NHS consultant neurologists (including those with part time contracts) serving the whole of the UK. Of these, only about 100 have a special interest in MS (ABN, 2011; ABN, 2017; Reilly, 2018). Countries such as Germany have up to three times more neurologists per capita than the UK.

Given that only neurologists are presently regarded as capable of confirming a diagnosis of MS and making appropriate decisions in contexts such as prescribing DMTs, shortages of specialised medical staff undermine care quality. In this country it is not only the case that GPs sometimes say that they have difficulties contacting neurologists, but that non-specialist neurologists who have diagnosed cases of MS may not be able to consult in a timely manner with specialists about optimising therapy.

It is also the case that as compared with other developed nations the UK has limited numbers of resources like MRI scanners. These play an important role in the diagnosis of MS and managing its treatment. Recent Eurostat (2017) data indicate that Britain has from a fifth to a half of the number MRI scanners available in nations like Germany, Italy, Spain and France. Despite intensive NHS equipment usage, the number of scans taken is also below that recorded in a range of other European countries. Key points to be made in the context of facilitating the early diagnosis of MS and opening the way to protective treatment include:

• Over the next decade shortfalls in the number of consultant neurologists working in the NHS are unlikely to be significantly reduced. Relevant factors include the unwillingness of sufficient numbers of UK trained doctors to devote their careers to this field and the likely impacts of Brexit on the capacity of the NHS to attract and/or retain highly skilled doctors. In such circumstances there may well need to be further emphasis on increasing specialist nursing capacity. This is an area in which Britain is already relatively well advanced (Kobelt et al, 2016). Neurological Nurse Specialists (NNSs) can make important contributions to both community and hospital care (Multiple Sclerosis Trust, 2014). With appropriate political and professional support, NNSs specialist in MS could assume greater diagnostic responsibilities. It might also be possible to build on the skills of specialist neurology pharmacists to provide better clinical care for people with MS. At present no well specified national plan for achieving this exists, albeit interviews with neurologists conducted during the preparation of this update suggest that this could be an important professional development opportunity for pharmacy.

• Advances in computer based/artificial intelligence driven diagnostic and treatment selection and management technologies should in future improve MS care quality, given adequate investment in
Increasing the levels of MS related training and support for GPs could also reduce diagnostic and treatment delays, especially when good communication exists between primary care practitioners and secondary and/or tertiary care based specialist teams. The average GP will only see one new MS case every five years, although at any given time she or he will probably be treating five individuals living with it as an established condition (Mackenzie et al, 2013). Some GPs order tests needed to diagnose MS or manage events such as disease exacerbations before referring (Leach, 2018), but still report having difficulties in contacting neurologists and having patients seen by them as rapidly as they would like. Such delays lead to wasted professional effort and avoidable patient distress. Primary care home or local GP network 7 MS detection and care strategies could contribute to better outcomes, when well implemented.

• Greater public awareness of the nature, symptoms, causes and consequences of MS would inform service demands and in time raise care standards.

Greater population-wide knowledge about MS could facilitate better recognition of the disease and enhance decision making in contexts like the acceptance or rejection of optimally effective treatment. However, desirable as an enhanced public understanding of MS may be, the likelihood of significantly accelerated directly service user led progress towards enhanced NHS outcomes taking place within the next decade is limited. Advocacy and representation by organisations such as patient groups can never fully substitute for active and well informed individual demand. But in such situations it can and should play a robust role in promoting better care.

Voluntary bodies have in recent years needed to balance arguments favouring extensions in the use of DMTs and other radical options against calling for caution with regard to using potentially hazardous therapies. In the UK there has also been a perceived need to foster informed consensus in the neurological community. Their position has differed from that of groups working in areas such as, say, HIV or breast cancer, where the risk of premature death due to untreated disease is higher and specialist opinion has been more homogenous. Yet as the evidence base relating to the benefits of early and active treatment for MS develops, more assertive approaches to promoting nationwide access to maximally effective care should emerge.

Optimising access to DMTs and other forms of MS care

The early diagnosis of MS is of most value when it permits interventions which reduce fear, anxiety and depression, moderate immediate symptoms and prevent or delay the onset of disabilities. The importance of the new NHS England algorithm for guiding the use of DMTs lies in the fact that it promises to reduce treatment disparities between localities and promote – in part by guaranteeing the funding of recommended treatments – better standards of care for all women and men diagnosed with MS. At best it will eliminate ‘post-code rationing’ and arbitrary variations in the prescribing of disease modifying therapies in England. This could indirectly help raise care quality elsewhere.

Nevertheless, it is also true that the algorithm’s practical value will in large part depend on the manner in which it is implemented and the speed with which it can be adapted, as new evidence and further treatment innovations emerge. If used as a flexible aid to improving therapeutic outcomes by clinicians who are willing to change their opinions when enhanced information becomes available in order to make the best possible individual treatment decisions it will be of unquestionable value. But if for cost saving reasons attempts were made to rigidly impose ‘expert’ recommendations based on the evidence available at a particular point in time the algorithm could end up enshrining its authors’ conclusions in a structure resistant to constructive evolution.

An allied danger to be guarded against is that the needs of older and more disabled MS patients will not be appropriately met, even as the treatment available to younger and less disabled NHS users improves. Notwithstanding the costs of new therapies (total spending on DMTs and other medicines for people with MS in England will in 2018 be in the order of £300 million – see Box 3), under-investing in treatment provision could in time impose significant financial and other welfare burdens on not only individuals and families, but also health and social care providers and funders.

In any therapeutic area that has developed as rapidly as MS treatment has since the early 1990s there will inevitably be lags in the identification and application of best practices. In the case of multiple sclerosis such difficulties have on occasions been amplified by factors like the difficulties surrounding the collection of efficacy data in the context of innovative treatments for the later stages of the disease. As Box 3 discusses, this is in contrast with the situation in cancer care, where it has often proved most viable to collect information relating to the use of anticancer new medicines in late stage disease.

Key points to stress from the perspective of this MS update report are that:

• MPs, Peers and other UK policy makers and influencers seeking to improve MS care should, while welcoming the introduction of the NHS England treatment algorithm, monitor its implementation and its ongoing development as an adaptive – individual needs sensitive – instrument. Multiple sclerosis treatment quality is an important indicator of the overall standard of health and social care available. Improving NHS performance in this field should be a national priority. Achieving this will in part require the
Box 3. The Costs of MS Medicines and the Challenge of Developing Late Stage Treatments

Pharmaceutical spending is often controversial, not least because patented or similarly protected products are typically expensive relative to the basic cost of their production. This is in well-regulated circumstances because each new generation of treatments ‘pays’ for the ongoing research and development investments needed to deliver future innovations, rather than profit taking that is not consistent with public interests. However, to budget holders and others concerned to maximise present benefits for minimum outlays this may seem unfair and undesirable.

In the NHS the best available data indicates that, allowing for discounts and other relevant factors, pharmaceutical spending has – while varying somewhat – accounted for around 11 per cent of total annual health service costs since the 1960s. The basic reason for this stability, which stands in contrast to claims that ‘high cost drugs are bankrupting the NHS’, is that when new pharmaceuticals lose intellectual property protection and are exposed to competition they become progressively cheaper. At the same time doctors, pharmacists and other health professionals become more aware of how to use them to best effect.

In England total spending on NHS medicines for people with MS (including DMTs and other items) will be about £300 million in 2018, as against total pharmaceutical outlays of approaching £12 billion. That is, they account for circa 2.5 per cent of all health service drug costs, incurred for a total patient community that directly numbers little more than 0.15 per cent of the English population. Total English NHS spending on MS is about £1 billion, just under one percent of all costs.

open publication of data on topics such as which groups of PLwMS are most likely to receive what types of NHS treatment, presented in ways designed to facilitate clear understandings of how place of residence, class and ethnicity affect access.

- Promoting the use of MS DMTs in ways which minimise the occurrence of unwanted side-effects and maximise their positive impacts on health outcomes is an important goal. But this should not obscure the significance of providing good access to other forms of care. For instance, there ought also to be population wide access to stem cell transplantation for individuals with rapidly developing disease, together with the resources required for the timely and effective treatment of acute relapses amongst people with RRMS. Likewise, providing good quality community nursing, social and rehabilitative services is critically important, and will in some circumstances be cost saving at a system-wide level. There is evidence that in the UK the importance of matters like promoting exercise amongst PLwMS has not to date been adequately appreciated (Hart, 2017; Mott et al, 2017). Britain also has a ‘patchy’ record in supporting employment for people living with physical and mental disabilities, which reflects other forms of inequality in society.

- The ‘ThinkHand’ Campaign has criticised the practice of stopping MS patients’ access to DMTs once they have become unable to walk. Those concerned about this restriction believe that it is a discriminatory policy that causes some patients to suffer avoidable relapses and preventable neurological damage, as well as exposing them to experiences of rejection and loss of hope (Schmierer and Giovannoni, 2018). Given difficulties like those involved in differentiating clearly between RRMS and SPMS as the condition develops, and that it is now emerging that some treatments can slow even progressive forms of MS, the case against current DMT withdrawal rules is becoming increasingly powerful.

- The ageing of the MS population should be addressed as a priority issue, alongside challenges like meeting care needs in a gender sensitive manner. There is some evidence that after a long period
in which – particularly amongst women – the incidence of multiple sclerosis has been rising countries like the UK, its occurrence rate is now stabilising and might be falling (Mackenzie et al, 2013). However, the prevalence of MS is still increasing. This trend, and that of MS population ageing, is partly linked to improving MS survival (Sanai et al, 2016) and is likely to strengthen in the coming decade. Achieving optimal care standards will require that increased attention is paid to problems such as those associated with managing increased comorbidity rates, alongside issues like whether or not gender linked factors affect access to therapies.

Funders point to the financial pressures currently affecting the NHS and social service providers, and stress the need to ration services like home care and the supply of treatments which are not curative but can increase service demands. Such concerns have some legitimacy from a short-term affordability and narrow cost effectiveness perspective. However, it is worth noting that:

- **The original objective of the NHS was to provide the best care the country could afford for everyone in need, not merely a cost effective service which limits the rights of individuals requiring treatments judged expensive relative to their average benefit levels.** People will lose trust in the NHS and the wider health and social care system if it is not believed that it provides first class care in a comprehensive manner.

- **Organisations such as NHS England should purchase and use specialist and other medicines economically, remembering that the UK has interests in respecting intellectual property rights and encouraging investment in biomedical and other science based innovation.** Although manufactured items like pharmaceuticals can be expensive at the time of their introduction their prices relative to the cost of health sector labour fall markedly as they are exposed to competition and when they become available as generic products. Their use also becomes more productive as their clinical properties are better understood. Such phenomena underlie the fact that despite the many pharmaceutical innovations introduced since the 1950s the total cost of medicines, taking into account discounts and related factors, has stayed at little more than 10 per cent of total NHS spending for the past fifty years.

- **In the medium to long term (that is, by or before 2050) it is probable that advances in the biomedical/biopharmaceutical sciences will mean that conditions such as MS will be preventable or functionally curable.** The economic and social gains that such prospects imply are so great that they may be regarded as incalculable. If Britain is to profit as fully as its occurrence rate is now stabilising and might be falling (Mackenzie et al, 2013), it is probable that some drugs already in use for other indications will be shown to be of value in the prevention or management of MS. Relevant illustrations include:

  - the anticipated marketing, subject to licensing, of sipimiod. This drug is an orally taken selective modulator of several sphingosine-1-phosphate (S1P) receptor subtypes. Its mode of action is therefore similar to that of fingolimod (see Table 1), which is already used in paediatric MS and adult RRMS. There is trial evidence that sipimiod may in addition slow the progression of SPMS (MS Trust, 2018). It might be that its mode of action within the CNS differs from that observed elsewhere in the body; and

  - the possibility that high dose simvastatin (and probably other statins) use will improve cognitive functioning and protect the brain tissues of women and men living with MS. There is presently a large UCL Institute of Neurology led trial of simvastatin’s utility in MS therapy. This will add to the findings of an earlier smaller scale investigation (Chataway, 2018).

With regard to hopes that new methods of promoting re-myelination will be developed, biotin is a B vitamin normally found in enzymes involved in actions such as fat and carbohydrate metabolism. There is some evidence that in high doses (that is, in amounts that are orders of magnitude greater than those found in normal diets) it promotes myelin regeneration, albeit recent attempts to develop biotin as an MS therapy have faced setbacks. It is possible that other ways of achieving the goal of stimulating CNS re-myelination will be developed. For instance, research dating back to the 1970s suggests that a substance called lipoic acid might be of value in this context, and work is also being undertaken on the development of what may be safe and effective ways of activating what is known as retinoid x receptor gamma signaling (Huang et al, 2011). It could in addition be that medicines which promote the production of, or replicate the actions of, a protein called Activin-A on myelin producing oligodendrocytes will prove viable (Dillenburg et al, 2018).

Looking to the coming decade, advances in the safety and application of stem cell transplantation techniques could also lead to improved outcomes for PLwMS, as should...
better understandings of the genetics and epigenetics of the disease. As noted earlier, it may be that by the start of the 2030s substantial progress towards the introduction of a protective EBV vaccine will have taken place, given the political will required for supporting such a development and sufficient private and/or public financial backing.

Achieving better MS outcomes will additionally require good quality nursing and social care and effective psycho-social support. Important opportunities in these areas include protecting the interests of adults with MS in maintaining employment. Even if new pharmaceutical and other biomedical therapies do not prove curative or able to arrest the disease in all cases, their informed use ought to play a role in further raising expectations of a fulfilling life amongst individuals and families affected by MS. This should in turn help drive increased political awareness, and further improvements in the health care and social support available for PLwMS.

**Conclusion**

Until recently only good fortune could protect people living with multiple sclerosis from increasingly severe disability and ultimately death from the disease. During the twentieth century it imposed growing burdens on relatively young women, although MS also affects children, working age men and older people of both genders.

However, the pharmaceutical and other bio-medical science based advances of the last two to three decades have opened the way to effective treatment. Claims that MS can be cured must still be considered with caution. But ameliorating its course and delaying or stopping its progression is already a realistic goal. Given pro-active approaches on the part of policy makers, researchers and clinicians, multiple sclerosis could by the 2050s have largely become a problem of the past in countries that can afford good health care for their citizens.

Historically, the UK’s performance has been variable. There is evidence that NHS service quality for people with MS has in some respects lagged behind the standards achieved in the most advanced European nations, in part because of limited numbers of specialist MS and other neurologists. People living in less privileged circumstances are most likely to have received inferior care. Yet there are now important opportunities for making optimally effective treatments and good quality services available to everyone. The introduction of NHS England’s new treatment algorithm should, provided it is implemented well and developed appropriately as new evidence of therapeutic benefit emerges, prove a valuable step towards the universal provision of high standard MS care.

At a time when the challenges surrounding the UK’s exit from the European Union are drawing political and media attention away from health and welfare service issues, there is good reason to seek to raise awareness of the opportunities available for improving MS treatment outcomes. In addition to the value to be derived from reducing suffering and distress amongst people with the disease and their relatives, decision makers should understand the economic returns to be made from decreasing disability levels and ensuring that the country’s health care environment is of world-class quality. Otherwise ‘Brexit Britain’ will be unlikely to be able to retain a strong, research based, biological science based industrial sector, and enjoy the social and financial benefits it generates.

There are many ways that Parliamentarians and others who wish to contribute positively to public policy making can foster ongoing improvements in services for and the quality of life of people living with MS. They include:

- supporting progress in MS prevention, while remembering that in the short to medium term better disease modifying medicines delivery and offering stem cell transplantation will be the main keys to achieving enhanced outcomes;
- promoting early diagnosis and prompt treatment through increasing public and professional knowledge of MS, disseminating the skills needed to identify it accurately, and funding the screening and diagnostic resources (like MRI scanners and genetic and serological testing capacities) that will in coming years increasingly be needed to manage the condition well;
- checking how the new NHS England treatment algorithm impacts access to pharmaceutical therapies for individuals at all stages of the illness, including the ability of people with later stage/progressive MS to obtain therapies as and when there is evidence of benefit, and monitoring stem cell transplantation rates;
- requiring the open publication of performance and outcomes data relating to all forms of MS care, presented in ways that enable geographical, class linked and other (for example, gender) quality variations to be clearly visible;
- seeking to increase the numbers of appropriately skilled neurologists, while recognising the value of and aiming to enhance the numbers and roles of specialist neurology nurses and neurology pharmacists;
- providing better support for GPs and their primary care colleagues; and
- encouraging investment in rehabilitative care and social support, including services aimed at helping individuals to stay in work and enjoy other normal opportunities in life.

Achieving better outcomes for people with MS may well require increased public service spending in coming years. The affordability of this will be questioned when the national economy is growing slowly and could enter a period of decline. But advances in the medical and pharmaceutical sciences are generating increased reason for hope that ought in time to translate into greater public and patient health expectations. From an overall economic and social solidarity perspective it is arguably more important not to be excessively concerned with the costs of better NHS care, but to ask if the UK can afford not to prioritise meeting the needs of individuals and families affected by illnesses such as multiple sclerosis in a timely and effective manner.


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