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Greater Expectations: the Future Hopes of People with Multiple Sclerosis

This report presents the key findings of a new international survey of the treatment related beliefs, priorities and expectations of people living with multiple sclerosis (the TaP-MS survey) and, against the background of the available literature, discusses their implications for health and social care policy makers. It concludes that increased access to more effective treatments, enhanced rehabilitative care and better social and economic support will curb disease progression, prevent disabilities and improve the quality of life of people living with all forms of MS, together with that of their partners, children and other family members

Summary

- Multiple sclerosis (MS) is today the most prevalent form of serious non-traumatic disability in young adults in regions like North America and Europe. It directly affects approaching 2.5 million people world-wide. MS typically starts as a disease which cycles between symptomatic illness and remission. In time it becomes progressive without remissions.
- About a third of people diagnosed with MS do not become severely impaired. But without effective disability delaying treatment most others will become wheelchair dependent within 15-20 years. People living with MS (PLwMS) experience fluctuating symptoms, ranging from pain and fatigue through to visual difficulties, bladder control problems and lost cognitive abilities.
- Treatments for MS can relieve immediate distress or change its natural course. Disease progression is the root driver of MS related symptoms and harm. Disease modifying treatments (DMTs) that slow the evolution of relapsing remitting MS (RRMS) were initially licensed in the early 1990s. An increased range of medicines for limiting disease progression is now available. All carry risks of side effects that must be balanced against their likely benefits.
- This report assesses evidence relating to MS prevention and care and analyses the findings the **TaP-MS** survey of the treatment related expectations and priorities of PLwMS. In the summer of 2017 researchers gathered responses from 1040 individuals in Australia, Canada, France, Germany, Italy, Spain, Sweden, the UK and the US.
- Constantly varying – and consequently highly intrusive – symptoms make MS more difficult to live with than ‘static’ forms of disability. The **TaP-MS** findings underline the significance of fatigue caused by MS and the importance PLwMS attach to reducing relapse rates, avoiding wheelchair dependence and protecting their cognitive abilities. The highest priority treatment expectation is slowing or stopping disease progression, which is the driver of all MS symptoms.
- Other key expectations highlighted by the **TaP-MS** survey are wanting more vitality and energy and being able to manage bladder and bowel control problems more effectively. Symptoms like incontinence, pain, anxiety or visual difficulties all require effective management. Further care advances will free more people with MS to achieve their most important goals in life.
- Individuals living with MS want freedom from the disease and its symptoms. Until effective cures become available optimising MS outcomes will often require individually tailored, holistic, combinations of pharmaceutical, psychological, social and other forms of care and support.
- No one wants side effects from any medical treatment. But they cannot always be avoided. The **TaP-MS** survey findings indicate that side effect and treatment harm avoidance is for many PLwMS a ‘second order’ priority compared to curbing disease progression. The available evidence indicates that most PLwMS will knowingly accept a degree of therapeutic risk in return for an improved chance of stopping disease progression.

- The **TaP-MS** results also indicate that ‘practicality’ linked considerations like whether or not a therapy has to be injected are a lower order priority for most PLwMS than either slowing disease progression or side effect avoidance. Nevertheless, to the extent that convenience in use affects medicine taking, adherence related issues must be well managed.
- Seventy percent of **TaP-MS** participants agreed with the statement ‘*I expect that MS will be effectively curable in 20 years*’. Over 80 per cent of Americans agreed. But amongst UK respondents just 49 per cent agreed. This could reflect varying national approaches to health care cost control and adopting innovative therapies. Low expectations of treatment advances may negatively impact on levels of hope and optimism and impair coping abilities.
- There is evidence of major variations in the standards of care available to MS patients living in neighbouring countries. These can affect both early diagnosis rates and access to DMTs. The **TaP-MS** survey found that reported DMT use amongst respondents with RRMS was just over 70 per cent in the UK and the US, as compared to 83 per cent for the rest of the sample combined. (The survey did not differentiate between older and newer disease modifying medicine use.)
- By contrast, 90-95 per cent of Americans who said they have a progressive form of MS reported taking a DMT. This compares to 25-33 per cent of Swedish respondents. Such figures suggest international differences in medical practice and the level of understanding people in different countries have of the MS treatments they are taking. Greater ‘pharmaceutical literacy’ is needed to optimise the benefits relative to the costs of medicines use.

Conclusions and Recommendations

1. Improving the prevention and treatment of MS is an important health objective. Reducing the burdens MS imposes on individuals, families and communities will require ongoing investment in public and private research and universal access to high quality health and social care. Governments should commit to pursuing these goals in ways that permit monitoring.
2. Care funders should provide adequate facilities for the early identification of MS and monitoring treatment outcomes. This includes assuring good access to MRI scanning and establishing and maintaining high quality disease registries.
3. More evidence of the long term benefits and costs of MS DMT use will emerge. But there is already sufficient data to support the conclusion that people with MS ought to be given access the treatments that they and their neurologists judge will offer them the maximum possible net benefit.
4. PLwMS and organisations representing them have a vital part to play in raising MS care standards, preventing access inequalities and contributing to pharmaceutical literacy. Care quality data should be gathered and communicated in ways that permit more robust intra- and inter-national comparisons and inform health policy debate and individual choice.
5. Cost concerns need not delay the timely provision of effective care. Economists and others involved in evaluating therapeutic advances ought to ensure that the benefits of relieving symptoms like fatigue and depression and the societal costs associated with MS are comprehensively assessed.
6. Medical, nursing, pharmaceutical, psychological and rehabilitative care should be provided in ways that maximise their synergistic value and offer patients an auditable record of coherent treatment and support.
7. National standards of social and economic provision for offsetting the impacts of disabilities on individuals, families and communities should be in place throughout Europe and similar regions.
8. Programmes aimed at raising public awareness of MS and the value of early diagnosis and treatment are needed to improve outcomes.
9. Prevention programmes should highlight the roles of smoking and adolescent obesity in MS, and of the links between low vitamin D levels and the disease. Policies to protect children, adolescents and young adults from vitamin D deficiencies should be robustly evaluated.
10. Governments and pharmaceutical companies ought to consider evidence linking Epstein Barr Virus infection to MS and other illnesses, and if necessary invest jointly in vaccine development or alternative public protection programmes.

Introduction

The identification of multiple sclerosis (MS) as a discrete disease is normally attributed to the pioneering nineteenth century French neurologist, Jean-Martin Charcot. Some descriptions of what is today called MS date back to well before his time. But it was Charcot who in the 1860s characterised the symptoms of multiple sclerosis and linked his clinical observations to pathological changes seen in the brains and spinal cords of patients after their deaths (Kumar et al, 2011).

The term Charcot's triad (which refers to a combination of 'intentional tremor'¹, abnormal eye movements and staccato speech) is still sometimes used today in relation to MS, albeit the condition is now known to cause many additional forms of difficulty, disability and distress. Because it can impact on virtually any part of the nervous system with varying degrees of severity, MS is often a potent cause of uncertainty. This is so not only for those individuals whose lives are directly affected by it, but for doctors and others seeking to diagnose the condition and predict its course.

In the 150 years or so since the English term multiple sclerosis was derived from Charcot's original *sclerose en plaques* (nervous system lesions and patches of damage) much success has been achieved in discovering the causes of and developing at least partially effective treatments for many commonly occurring infectious and non-communicable disorders. The latter include vascular diseases such as atheroma and its acute consequences; cancers like, for example, leukaemias and lymphomas; and mental illnesses such as depression.

Even in the context of neurological diseases like the dementias (Alois Alzheimer first reported on the condition named after him in 1906) there was limited therapeutic progress in the latter half of the twentieth century. But in the case of multiple sclerosis progress was until recently slow. Despite its emergence as the major cause of non-traumatic major physical disability amongst young adults – and particularly young women – aged up to 50 years in regions like Europe and North America its causality has remained unknown and it was not until the 1990s that the first (interferon based) disease modifying treatments (DMTs) capable of slowing the progression of the most common form of MS became available.

Before then care standards were often poor. Because those disabled by MS were – despite palliative care options – often regarded as medically untreatable they were sometimes admitted to, and neglected in, long term care settings typically used to 'house' much older individuals.

Even in the most affluent twentieth century societies much of the economic burden imposed by MS has fallen

on people living with the condition (PLwMS) and their families, rather than being more fairly shared with health and social service providers and their wider communities. However, since the start of this century the introduction of an expanding range of DMTs for multiple sclerosis has helped to generate rising expectations that PLwMS should be able to enjoy a more satisfactory quality of life than in the past. New hopes are emerging that in future functional cures and/or effective preventive interventions will be developed for all forms of MS. Such trends could in turn generate further changes in public and patient attitudes and service standards.

The diagnostic techniques and MS therapies presently available are of varying utility. Medicines for preventing MS-related disabilities can on occasions cause serious side effects. Their use is also increasing health care costs, particularly in relation to early stage disease treatments delivered in the outpatient setting (Kobelt et al, 2017). But against this they offer the promise of a reduced rate of disease progression (Frohman et al, 2006; Giovannoni et al, 2015) and lower – or at least delayed – later stage treatment and support costs.

The fact that optimising pharmaceutical care for people with MS requires achieving an agreed balance of possible harm against likely benefit is also driving closer patient involvement in therapeutic decision making. This should help promote further improvements in the ways that both patients and health professionals address and cope with the challenges MS presents.

Against this background, this UCL School of Pharmacy report offers an outline of what is known about the nature and consequences of multiple sclerosis and an analysis of the issues facing women and men living with it. It presents the findings of a new international survey of the treatment beliefs, priorities and expectations of people living with the disease (the TaP-MS survey) and discusses their implications for health and social care decision makers. Topics explored range from the extent to which hopes of future functional 'cures' – almost 70 per cent of the TaP-MS respondents agreed with the statement '*I expect that MS will be effectively curable within 20 years*' – are creating new patterns of service demand, through to which symptoms those living with the condition most want to be alleviated and the risks they are prepared to accept in return for slower disease progression.

For up to a third of the people who receive a diagnosis of MS having the disease is likely to prove to be a relatively benign – if at times worrying and discomfiting – experience. Yet for others it is a highly intrusive condition that, even if its impacts on life expectancy are relatively modest, causes physical and mental suffering in uniquely distressing ways and often ends in profound disability.

1 Intentional (or cerebellar) tremor intensifies as individuals deliberately reach out for objects they see.

MS in total affects approaching 2.5 million people across the world² (MSIF, 2013), together with a significantly greater number of carers and other family members whose lives are impacted by it. Seen from this standpoint, investing in developing and assuring appropriate access to better treatments for multiple sclerosis is arguably one of humanity's more important goals at this point in history. Scientific understanding of the immune system and other factors influencing the development of the condition is now at a stage in which further fundamental treatment advances are increasingly likely to emerge. Achieving such progress will require continuing investments of money and human resources. But the longer term benefits it will bring will be of very much greater – in some respects incalculable – value.

Multiple Sclerosis – a Progressive, Inflammatory and Demyelinating Disease

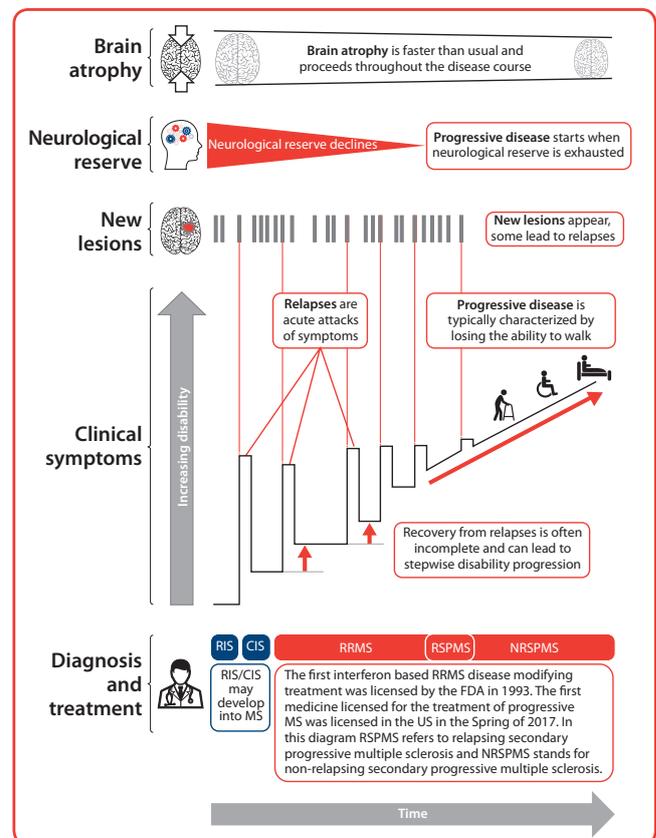
MS is today regarded as a progressive, autoimmune/immune response modulated, inflammatory condition. It involves a variety of biological mechanisms, including immune system T cells attacking the myelin sheaths protecting central nervous system neurones. This, together with other inflammatory processes involving 'scavenger' cells such as macrophages/microglia (Luo et al, 2017) harms the thread-like axons which pass impulses from one nerve cell to another. Affected neurones eventually die. As the disease progresses oligodendrocytes responsible for generating myelin in the central nervous system are also killed, and the brains and spinal columns of PLwMS incur increasing damage. At first there may be sufficient reserve brain/nervous system capacity to compensate for such harm. However, as neuronal losses build up permanent disabilities become manifest.

For the purposes of this analysis four main categories of MS exist, together with clinically or radiologically³ isolated syndromes. The latter terms refer to the condition of individuals who show clinical signs or MRI (magnetic resonance imaging) revealed lesions like those associated with MS, but who cannot be definitely said to have the condition. Estimates vary and the accuracy of diagnostic processes is improving. But historically around a half the people said to have clinically isolated syndrome (CIS) have gone on to develop MS.

At confirmed onset around 85 per cent of PLwMS have the relapsing remitting form of the disease (RRMS), in which episodes of symptomatic illness are followed by periods of full or partial recovery. But within 10-15 years from their initial diagnosis about two thirds of people with RRMS will, if not effectively treated, develop secondary progressive multiple sclerosis (SPMS). During this second stage the disease takes a continuing course of accumulating neuronal loss which may or may not be marked by periods of exacerbation – see Figure 1. At any given time up to 60 per cent of the total population living with MS has the relapsing remitting form. Some 25-30 per cent will have SPMS.

By contrast, about 15 per cent of people with MS are at diagnosis categorised as having the primary progressive (PPMS – circa 10 per cent of the total number of the initial diagnosis total) or progressive relapsing (PRMS – about 5 per cent) forms of the disease. In this type of MS, which on average is first identified in individuals about 10 years older than those receiving an initial diagnosis of RRMS, there are no periods of recovery. Rather, there is a continuing (albeit often gradual) increase in the severity of the condition. Because untreated people living with PPMS have life expectancies in the order of 5-6 years

Figure 1. Relapsing Remitting and Secondary Progressive MS



Source: After Giovannoni et al, 2015

Note: Primary Progressive and Progressive Relapsing MS following a continuing course of functional loss without remission from the time of their initial diagnosis. It is not known whether or not this reflects differences in underlying causality.

2 Of whom in the order of 500,000 live in Europe and about 400,000 live in the US and Canada

3 MRI scanning has since the 1980s emerged as a key technology for identifying areas of demyelisation in the brain, and – via the use of gadolinium as a contrast agent – differentiating between long standing lesions and areas of currently active disease. MRI 'tests' do not expose individuals to potentially damaging forms of radiation, and can thus be conducted as frequently as clinical needs and health service resources permit.

less than those of individuals with RRMS/SPMS (who in turn currently have projected life expectancies that are 3-4 years less than the population average) they at any one time account for little more than a tenth of the total number of identified patients.

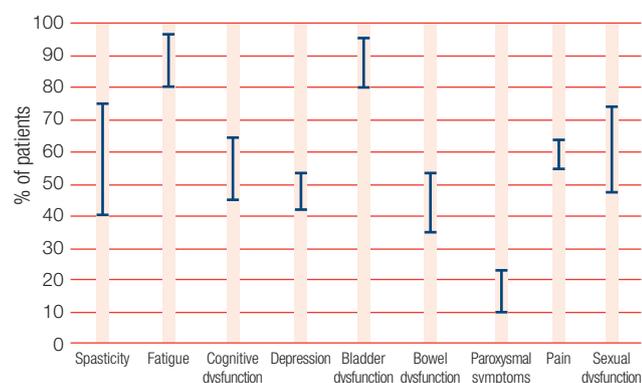
MS is most frequently diagnosed in individuals aged between 20 and 40 years. But around 10 per cent of 'cases' are first identified in children and adolescents aged 16 or under (Schreiner, 2015). There is in addition evidence that during the twentieth century the ratio of women to men with diagnosed MS increased (Harbo et al, 2013; Kock-Henriksen and Soelberg Sorensen, 2012). In typical northern European and American communities women living with MS now outnumber men with the condition by between 2 and 3 to one. Its recorded prevalence is in higher risk settings between 2 and 3 per 1000 amongst females, compared to close to 1 per 1000 for males.

Common symptoms

Because MS exacerbations have varying impacts on different parts of the nervous system the symptoms experienced can differ on more or less a day-to-day basis. Short term fluctuations, coupled with long term uncertainties about how and at what speed the condition will progress, make living with MS very different from having 'stable' disabilities such as a missing limb or, say, a learning difficulty. Periods of recovery are followed by relapses and new, on occasions painful and confidence draining, losses of ability. It is therefore not surprising that people with MS are at a raised risk of psychiatric and other co-morbidities like depression and severe anxiety. Even if they are not – as is the case with cognitive deficits – caused by MS at the physiological level, such mental health problems are intimately linked to its personal and social impacts.

Figure 2a summarises some relatively long standing information relating to likelihood of people with MS

Figure 2a. Percentages of People with MS likely to experience commonly occurring symptoms



Source: Crayton et al, 2004

Notes: The graph illustrates the higher and lower symptom prevalence rates recorded in the studies reviewed.

experiencing its more common symptoms (Crayton et al, 2004). They range from spasticity – muscle contractions or extensions caused by damage to parts of the brain and spinal column concerned with 'motor control', which can cause feelings of stiffness and movement abnormalities – through to paroxysmal symptoms like sudden stabbing sensations. Other common symptoms include pain; loss of bladder and bowel control; and sexual problems such as erectile dysfunction.

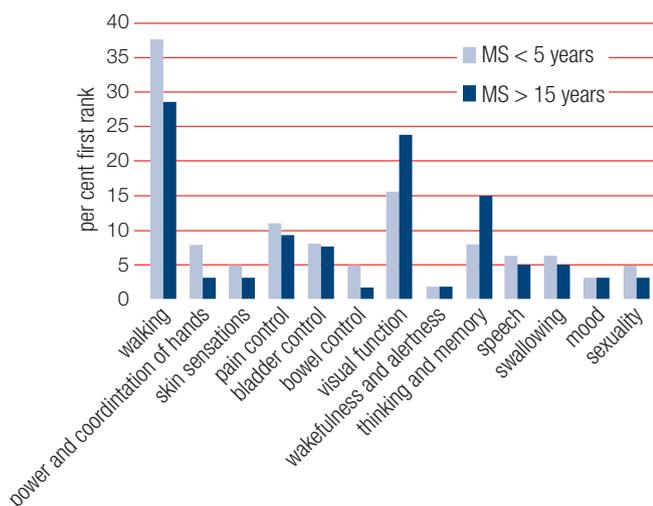
Abnormal feelings of fatigue are often experienced by not only people with neurological disorders but also patients living with cancer or long term conditions like rheumatoid arthritis and renal failure (Whitehead et al, 2016). The mechanisms involved are not fully understood. But they are probably linked to immune responses coupled with brain and spinal column changes stemming from prolonged exposures to stress and distress (Braley and Chervin, 2010). Such neurological phenomena can also affect sleeping patterns and pain thresholds. In addition some drug treatments may cause feelings of fatigue, which can also follow surgical interventions and traumatic injury.

In cancer care there are important examples of fatigue being recognised as a major problem for patients. But its full significance has on occasions been neglected in the MS context. Like pain, fatigue is a subjective experience that (as opposed to factors such as impaired muscle control) clinicians cannot measure via direct observation. This might help explain why some medical approaches fail to recognise the importance of fatigue to people with MS. In reality it can – as the TaP-MS survey results discussed later in this report confirm – be a major barrier to being able to enjoy normal family, social and working lives.

Unlike difficulties like, say, needing help with dressing or having to use a wheelchair, fatigue cannot be adapted to in ways that permit a satisfactory way of life. This is another reason why its importance may be under-estimated by traditional medical (and economic) assessments that use static and, from a social science perspective, disappointingly limited sets of measures such as the Expanded Disability Status Scale or the EQ 5D – see Box 1 – to quantify complex phenomena like an individual's 'quality of life' (QoL).

Other frequently encountered MS symptoms include loss of vision (typically in one rather than both eyes), speech abnormalities and swallowing problems. The available evidence indicates that for many PLwMS becoming wheelchair dependent is the disease progression step they say they most fear (Isaakson, 2006; Heesen et al, 2008). The data presented in Figure 2b compares the key concerns reported by a sample of just over 80 people who had a diagnosis of MS for five years or less with those of a similar sample of individuals who had lived with MS for fifteen years or more.

Figure 2b. Levels of concern about symptom areas and disabilities expressed by people a) with less than 5 years of living with MS and b) with more than 15 years MS experience



Source: Heeson et al, 2008

Both groups rated maintaining lower limb function as their highest priority. But amongst those with a longer experience of MS the perceived importance of visual and cognitive (thinking and memory) problems was higher than in the more recently diagnosed group. The level of priority given to maintaining walking abilities was by contrast lower amongst those who had lived with MS for fifteen or more years.

In the context of wheelchair dependence another group of researchers showed that people who had recently been diagnosed with MS tended to over-estimate their 2 and 5 year chance of becoming wheelchair dependent, but to under-estimate their life-time risks (Janssens et al, 2003). One third of those responding to this survey said that they thought their 10 year probability of becoming wheelchair dependent was 50 per cent. The actual figure in untreated populations is in the order of 20-25 per cent (see, for instance, Myhr et al, 2001; Weinshenker et al, 1989).

At the same time newly diagnosed individuals contributing to Janssens et al's research similarly estimated their lifetime risk of becoming wheelchair dependent to be 50 per cent. The observed proportion before the advent of disease modifying treatments was 70 per cent. A key finding of this study was that people who over-estimate the rate of their illness's progression to the greatest extent are – perhaps not surprisingly – those most likely to experience anxiety and depression, and to have more extensive problems than others with MS in adapting to living with the condition.

These results highlight the importance of supportive communication at around the time of diagnosis – see below. They are also indicative of the vulnerability of PLwMS with regard to the uncertain prognosis of their condition, and the limitations of both research and

therapeutic approaches which place undue reliance on patients being able to make judgements about problems they have not directly experienced.

The environmental, genetic and lifestyle linked causes of MS

It is outside the scope of this report to discuss in detail the causes of MS, which are not yet fully understood. But the incidence and prevalence of MS have long been known to be correlated with latitude. This was first noted by researchers surveying US Army recruits shortly after WW I (Davenport, 1922). The further north and south on the globe people live in childhood and early adulthood the more likely they are to contract MS. In equatorial communities MS is much more rarely diagnosed⁴.

Such discrepancies still exist today. MS incidence in Canada is, for instance, higher than that for the US, and within the US it is on average twice as high in northern States than in those located below the 37th parallel (Pietrangolo and Higuera, 2015). Similar gradients exist in Australasia and Europe, albeit exceptions exist. There is, for example, a high rate of MS incidence in Sardinia. This is linked to a specific genetic variant found in that island's population (O'Gorman et al, 2012).

The significance of MS's geographic distribution became better understood the end of the 1950s when Acheson et al (1960) observed that its occurrence was inversely related to solar radiation levels. Low levels of sunlight exposure result in below average vitamin D synthesis, added to which vitamin D is now known to affect the expression of some genes responsible for modulating immune system functioning (Aranow, 2011).

It was also soon after WW II that evidence indicating that multiple sclerosis is an autoimmune disease became available (Hafler, 2004). Other factors associated with MS's occurrence range from whether or not individuals carry certain immune response modifying genes⁵, through to the fact that in pregnancy (during which

4 Even allowing for diagnostic capacity variations and the fact that in the US black Army recruits have relatively high observed MS risks this is likely to be a real observation. It may be related to earlier exposures to infectious agents such as EBV – see main text – and/or variables such as differing microbial and parasitic loads. The latter may, for instance, help account for other latitude linked epidemiological phenomena like the fact that TB vaccination is less efficacious in equatorial countries than in those located closer to the poles (Rennie, 2017).

5 An association between multiple sclerosis and the Major Histocompatibility Complex/human leukocyte antigen system genes located on chromosome 6 was first noted in the 1970s (Naito et al, 1972). For example, Europeans with what is called the HLA-DR15 haplotype have been reported to be at significantly raised risk of the disease, and may also contract it at a younger average age than others with MS. There are now well over 100 genes thought to contribute to the occurrence of MS, although only about 15 per cent of PLwMS have relatives with MS (MST, 2016). Even an identical twin who has a sibling with MS only has a 20 per cent chance of also developing the condition. Such observations highlight the likely role of chance as opposed to consistently shared environmental exposures in the aetiology of MS.

Box 1. The EDSS and the EQ5D as measures of MS

There are a variety of measures used to assess the impacts of MS. The one most commonly employed in clinical trials is called the Expanded Disability Status Scale or EDSS (National Multiple Sclerosis Society, 2017). With an associated instrument called the FSS (Functional Systems Scores) it was first developed in the 1950s and refined in the 1980s. The EDSS is an ordinal rating scale – one which indicates a direction – with the points along it ranging from 1 (minimal loss of function, no disability) through to 5 (can walk without aid or rest for about 200 meters, but disability severe enough to impair full daily activities like being able to work a full day without special provisions) to 7 (unable to walk unaided for more than 5 meters) and 9 (a so-called ‘helpless bed patient’). Point 10 on the scale is – questionably – death from MS.

Appropriately used, the EDSS has considerable value. Kobelt et al (2017) showed that across Europe it correlates strongly with the likelihood of people with MS being in employment. These researchers also found that EQ5D (see below) and EDSS ratings for PLwMS match well with each other and with per capita care costs, albeit that at around point 6.5 (defined as needing constant bilateral assistance – including the use of canes, crutches or braces – to walk 20 meters or more) the gradients of the EDSS versus QoL and care cost curves become markedly steeper.

Such observations mean that a one point difference in one part of the EDSS does not necessarily represent the same interval as a one point difference in another. This can make interpreting findings based on its use problematic, as can variations in test-retest findings and limited inter-rater consistency. The fact that the EDSS is mainly focused on ambulatory criteria means that relying on it could on occasions have led neurologists and others to under-rate the importance of MS linked symptoms such as fatigue or anxiety.

Scores generated via the FSS and the EDSS also have little or no power to explain phenomena such as the

‘disability paradox’. The latter exists when severely disabled individuals report a high quality of life because of their psychological resilience and factors such as their retaining social status via a valued role in life. Similar concerns relate to the fact that while physical limitations can often be accommodated over time, this is not as often the case with problems such as, say, intermittent acute pain.

The Euroqual 5D (so termed because it has 5 dimensions – mobility, self-care abilities, usual activities, pain/discomfort and anxiety/depression) is aimed at providing a generic measure of the quality of life of people with any disease in order to permit service priorities to be set and economic assessments of alternative treatments to be made. Since its development at the start of the 1990s its use has come to dominate health economic evaluations in the UK and to a lesser extent other countries.

Yet the EQ5D (the use of which typically involves healthy people imagining what it is like to live with conditions like MS as described to them by experts like neurologists) may also be relatively insensitive to the significance of variables such as prognostic uncertainty. As an essentially static and ‘a-social’ (that is, individual experience focused) measure it is also blind to matters such as historical and scientific context and the varying capacities of biomedical technologies to evolve dynamically and foster social changes relevant to the wellbeing of minority groups and entire communities (Taylor, 2016).

For the purposes of this report the key message to be taken from such observations is that PLwMS and those seeking to support them should treat data generated by tools like the EDSS and the EQ5D with caution, and be critical of their limitations. The need for this is arguably highest in circumstances in which inadequate measurements may cause the value of useful innovations to be under-estimated and access to better care counter-productively restricted.

immune responses are down-regulated to protect babies *in utero* from rejection) women with MS tend to be free of relapses. By contrast, when estrogen and progesterone levels fall after childbirth they become at raised risk of exacerbations.

There is additional data showing links to ‘life style’ variables such as smoking⁶ and being overweight in adolescence, both of which can influence immune

responses via inflammatory mechanisms (Milner and Beck, 2012). Early life obesity and use of tobacco increase the risk of developing MS, and might in addition influence its course (Olsson et al, 2017).

First exposures to Epstein-Barr virus in adolescence and early adulthood may also be a cause of multiple sclerosis – see Pender and Burrows (2014) and Box 2. At the present stage of history the complex interactions between the genetic, environmental and life style linked causes of MS and other autoimmune conditions are becoming understood. So too is the working of the immune system as it both prevents and causes disease. This is creating new opportunities for therapeutic innovation and improved outcomes for people living with MS. Adequate levels of investment could also bring effective preventive technologies.

⁶ One suggested reason for the increase in MS prevalence amongst women recorded over the last century in countries such as the US and those of Western Europe is, in addition to altered diagnostic practices, increased cigarette smoking. Yet this factor alone cannot explain why male MS occurrence rates have remained much more stable. Wider social trends linked to lifestyles and role changes might well have played an important part in influencing gender related shifts in the incidence of MS, but as yet no clear mechanism has been identified (Sellner et al, 2011).

Box 2. Epstein-Barr Virus (EBV) Infection and MS – Future Prevention and Treatment Opportunities

The causes of MS are not yet fully understood. But in the case of RRMS they involve the functioning of the immune system in a way that leads T lymphocytes to damage the myelin sheaths protecting central nervous neurones. They also involve genetic (and probably epigenetic), environmental and life style factors that work synergistically to drive the disease process. Established examples of this relate to the relationships vitamin D synthesis and consumption (25-hydroxyvitamin D plays a role in regulating the expression of many genes linked to MS – see Gourraud et al, 2012) and the presence of certain major histocompatibility complex (MHC) gene variants in an individual's genome.

One of these (called DRB1*15:01) is alone believed to raise the risk of developing MS by about three fold above the average in Europeans. At the same time recent research on vitamin D amongst women indicates a two-fold difference in the incidence of the disease between those with high recorded levels of serum vitamin D – who are at reduced risk – and those with low levels (Munger et al, 2017).

Suggestions that infections such as measles constitute another cause or co-cause of MS have been disproved. But there is evidence that the Epstein-Barr virus (EBV) does play such a role. EBV was discovered in the early 1960s by Professor Michael Epstein and Dr Yvonne Barr, who were investigating Burkitt's Lymphoma amongst young children in sub-Saharan Africa. EBV is now known to cause – in some instances in association with other infectious agents – a wide range of leukaemias, lymphomas and other malignancies. The virus may be globally responsible for up to 200,000 malignancy related deaths a year.

EBV (which is also known as human herpes virus IV) also causes glandular fever (infectious mononucleosis or IM), the occurrence of which is linked to that of MS. In overall terms teenagers and young adults who contract glandular fever (earlier childhood exposure to EBV appears less risky, in much the same way that polio virus infection does not usually cause paralysis

in infants) have double the risk of developing MS as compared with those without a history of IM. The relative risk for developing MS is an order of magnitude greater amongst individuals with key HLA type variations combined with high EBV antibody titres. (See, for instance, Sawcer et al, 2009; Sundqvist et al, 2012; Moutsianas et al, 2015; Münz, 2016.)

In addition to her recent work on vitamin D, another study by Munger et al (2011) found that amongst individuals in the US armed forces with the highest levels of EBV related antibodies the risk of developing MS was over 30 times that of those displaying no evidence of infection by the virus. In epidemiological research statistical relationships of this strength are normally evidence of causality (Wald, 2017).

It may take several more decades for all the interactions leading to the occurrence of MS to be identified in detail. Questions yet to be answered include 'do other microbes like, for instance, human herpes virus VI act with EBV to help cause MS in some people?;' 'in the context of MS and other auto-immune conditions, what is the significance of B lymphocyte transformation associated with EBV infection?;' and 'do progressive forms of MS involve mechanisms other than those responsible for RRMS?'. But efforts to apply knowledge of the causes of MS should be delayed until all aspects of its aetiology are understood.

There is a public interest based case for investing in the development of an EBV vaccine suitable for use in children, difficult and costly though this might well prove to be – see main text, page 26. Alongside further efforts to reduce the prevalence of vitamin D insufficiencies (which affect many more people than rare genetic variations) ways forward may include pro-actively using combinations of EBV antibody and genetic testing to identify individuals at high risk of developing MS. This could facilitate early treatment and complement programmes aimed at finding medicines for prophylactic use during or after episodes of glandular fever.

Symptom relieving and disease modifying treatments

Treatments for MS are of two basic types. First, therapies that can make it easier to live with the condition as it progresses. Second, disease modifying therapies, designed to slow and ideally halt the natural course of the disorder.

Illustrations of the former range from antidepressants and cognitive behavioural therapy for countering the psychiatric consequences of MS through to anticholinergic and other medicines that may relieve bladder control and swallowing difficulties. Providing physiotherapy and/or rehabilitative care like that available

some European Spas, using cannabis to relieve problems such as spasticity and pain, and taking amantadine to reduce fatigue are additional examples of treatments that fall into this category. The latter might act on fatigue via an antiviral mechanism, although it is also used as a Parkinson's Disease therapy because of its ability to increase the availability of dopamine in the brain. This is linked to both mood and movement control.

Up until the end of the 1980s there were no disease modifying treatments for MS. But in the last 30 years around a dozen such medicines have been introduced to the world market. They in the main work by influencing the actions of cytokines (messenger substances) responsible for modulating immune responses or

reducing the numbers of T and/or B lymphocytes responsible for the neurological damage people living with MS incur. At the same time there has also been increasing interest in the concept of preventing or delaying the onset of the disease and perhaps slowing its course via lifestyle related interventions aimed at preserving brain capacity. Although the population level effectiveness of such strategies is unproven in the MS context stopping smoking, moderating alcohol use, taking regular exercise and controlling weight are all capable of generating general health benefits.

Taking vitamin D supplements can also provide health benefits for some individuals and groups, most notably amongst people in later life and children at risk of rickets. There is data linking vitamin D levels and MS incidence rates (Munger et al, 2017) and in individuals being treated for RRMS there is an association between low levels of 25-hydroxyvitamin D and relapse frequency (Rotstein et al, 2015). This does not constitute evidence of direct causality and there is as yet no definitive evidence that using supplements will prevent or beneficially alter the course of multiple sclerosis. But from a precautionary viewpoint the case for seeking to avoid vitamin D deficiencies in all children, adolescents and young adults looks strong.

With regard to DMT use clinicians and PLwMS need, as noted in the introduction of this report, to balance the risks of unwanted side effects against the degree to which they are likely to slow the rate of MS progression and/or, in the context of RRMS, reduce the number of relapses (ICER, 2017). Therapies that suppress or otherwise alter immune responses can leave those taking them vulnerable not only to infections (one of the best of known of which is in the MS context progressive multifocal leukoencephalopathy – PML) but also non-communicable conditions such as cancers. This is because protection from developing the latter in large part depends on immune responses that stop tumours developing at an early stage.

In the case of PML, which is caused by a microbe called the JC (John Cunningham) virus that is widely found amongst – but is normally successfully held in check by – healthy individuals, screening for JCV antibodies can now help reduce the risk of this side-effect occurring in MS patients. Other forms of biomarker testing should in future be able to guard against other unwanted iatrogenic (treatment induced) events.

At worst, doubts and questions about the value of new or existing therapeutic options increase feelings of uncertainty and fear, and undermine welfare. Some individuals appear to be more concerned with avoiding drug side effects than they are with slowing the natural course of MS. Others may prefer not to have to face explicit treatment choices. But the available evidence indicates that most PLwMS are – when given robust

information about their options – prepared to accept what are in every-day terms relatively high levels of risk in return for a reduced probability of disease progression.

For instance, in a study by Heesen et al (2010) amongst a sample of patients and neurologists, participants were given comprehensive information about PML risks. Their willingness to continue using a treatment on occasions capable of causing PML was subsequently assessed. It was found that patients were willing to accept higher therapeutic hazard levels than clinicians, and also that they tended to regard MS as a more malignant condition than did the physicians treating them.

Another study by Johnson et al (2009) involved over 600 people with MS in a series of risk-versus-benefit ‘trade off’ choices. It was observed that in return for a cut in the number of relapses from 4 to 1 over a five year period and an extension in the delay between each stage of disability progression (as assessed by a measure called the Patient-Determined Disease Steps Scale or PDDSS) from three to five years, respondents were on average prepared to accept a circa 0.4 per cent (or 1 in 250) annual chance of death from side effects.

Such a risk level is well in excess of those actually associated with licensed MS medicines. Results like these suggest that health professionals should be confident that they are ethically justified in informing PLwMS about and providing them with disability delaying treatments, and in encouraging those who are uncertain to consider accepting therapies that offer long term rewards in return for limited chances of harm.

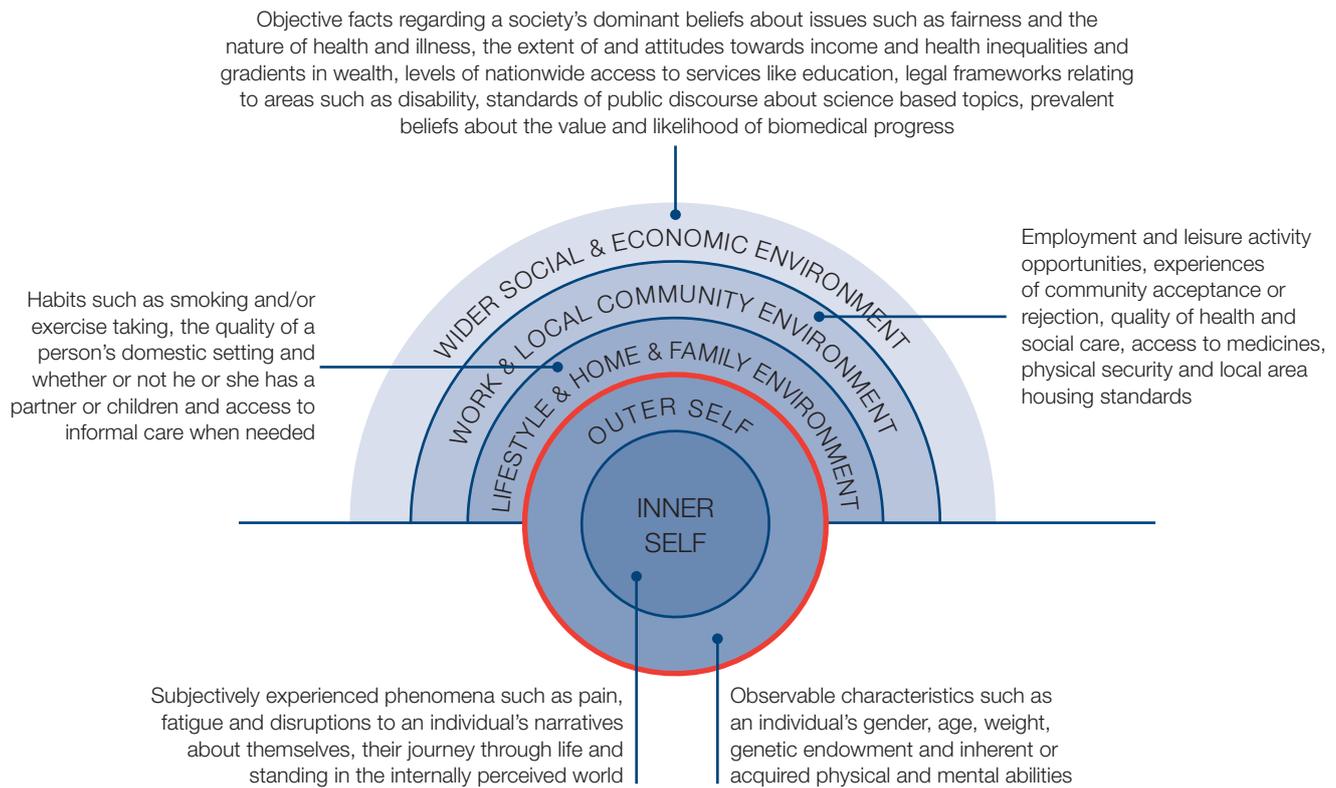
The full value of starting optimally effective disease modifying treatment as soon as possible after the initial diagnosis of MS, and making the latter as early as possible, is yet to be determined⁷. But there is already from a patient and wider public interest perspective a powerful case for pursuing such options – see, for example, Kanavos et al (2016).

Until recently people with progressive forms of multiple sclerosis had no licensed therapy available to them anywhere in the world. Nevertheless, a proportion have in recent years been given what some doctors believe might be prove disease modifying medicines on an ‘off-label’ (ie unlicensed) basis by their physicians.

One drug which a number of responses to the TaP-MS survey described later in this report indicate is

⁷ A new £10 million investigation into the extent to which early aggressive MS treatment is beneficial was announced by the Multiple Sclerosis Society of Great Britain in September 2017. This should build on existing evidence of reduced relapse rates and slower disease progression. In addition to wanting more information about which treatments can most effectively curb disease progression and stop or delay disabilities from developing PLwMS wish to prioritise research in fields such as MS prevention; alleviating fatigue; supporting self care; the value (if any) of vitamin D as a DMT; and preventing or alleviating symptoms like mobility problems, impaired cognition and MS associated pain.

Figure 3. A Public Health and Medical Sociology Oriented Model for Understanding MS



occasionally prescribed for this purpose is rituximab, a monoclonal antibody licensed in the late 1990s for the treatment of conditions such as lymphomas. This product is now becoming available in the form of relatively low cost bio-similar presentations. However, the only major trial of it in the context of PPMS yielded disappointing results (Hawker et al, 2009)⁸.

Building Confidence – Meeting the Challenges of MS

Models of disability can aid assessments of the impacts of long term conditions and other forms of ill health and help determine the value of and degree of priority that should be given to providing alternative forms of care and support for health and social service users. For example, the WHO (WHO, 1980; Wood, 1980) has in the past differentiated between *impairments* (the biomedical changes caused by a disease such as, say, optic nerve damage in the case of MS), *disabilities* (the immediate

functional consequences of such effects, like loss of vision) and *handicaps* (the eventual loss/deprivation of valued social roles like being employed).

This three level classification remains useful in that, for example, it underlines the fact that although understanding neurological and other disorders at the biomedical and functional levels is vital if they are to be managed effectively and for developing more effective future treatments and preventive interventions, optimising outcomes additionally requires social and political action. This is needed to maximise the chances people with disabilities have for enjoying life via community wide supportive interventions which complement personal efforts (Simmons, 2010).

Other potentially valuable approaches to understanding MS and ways that people living with it can be effectively supported range from applying Maslow's 'hierarchy of need' theory⁹ (Maslow, 1943) in the disability context to using the adapted public health model outlined in Figure 3. The former in part involves ensuring that individuals' requirements for 'higher level' fulfilment are not ignored or actively denied during the provision of basic personal care.

⁸ Rituximab is not licensed for the treatment of MS. This UCL School of Pharmacy report does not recommend its use for this purpose. However, its mode of action – in common with those of some licensed DMTs – suggests that in MS B cells (groups of which are permanently transformed by exposures to EBV infection) play a role in directing T cell and perhaps other attacks on myelin. See, for example, Salzer et al, 2016; Montalban et al, 2017; Hauser et al, 2017.

⁹ Maslow did not base his work on direct empirical observations. He differentiated between basic needs for safety and those linked to physiological functioning, such as having shelter and enough to eat; psychological needs such as those for 'belonging' and social esteem; and self-fulfilment needs related to the expression of creative abilities. It is sometimes thought that he believed that basic needs should be prioritised over others. But he on occasions warned against this, indicating that all individuals seeking a satisfactory life require self-realisation opportunities as well as more immediate necessities.

The public health approach described by Figure 3 is based on the work of researchers such as Dahlgren and Whitehead (1991; 1996) and Bury (1982; 2017). It combines an emphasis on the environmental determinants of illness occurrence and disease experience with sociological and psychological insights into the disruptive impacts of disabling conditions on individuals' biographies, and the internal narratives which define their identities and influence their positioning in the world.

Patients' thinking about themselves is frequently invisible to doctors and others providing day-to-day health services. Yet preserving each person's biographical integrity and sense of being in an acceptable reality can be regarded as a core objective of all good quality care.

Special dimensions of demyelinating disease

Models of disease and disability impact such as that embedded in the EQ 5D (see Box 1) are employed in economic evaluations of what interventions offer sufficient 'value for money' to be judged cost effective. However, as the British statistician George Box has been widely quoted as saying, '*all models are wrong, (even if) some are useful*'. The dangers of uncritically applying simplified representations of disability and lost opportunity in life to disorders as multifaceted as MS centre on the fact that important aspects of the burdens they impose may be overlooked. A number of specific issues related to living with multiple sclerosis are therefore described below in order to provide further context within which to place the new TaP-MS survey findings presented in the next section of this report.

The unique challenges that fluctuating demyelinating illnesses create relate, as previously noted, to uncertainty and the variability of the disabilities it causes coupled with its to a considerable extent unpredictable progression. There are also special issues relating to factors such as how it can be diagnosed as accurately and early as possible; how people can most effectively seek to cope with it and live happily as an individual who happens to have MS, rather than being defined by their illness; and the needs of those who care for individuals with multiple sclerosis. The economics of MS service provision are also worth consideration in the light of the pressures that new MS treatments are putting on health care budgets at a time in which the proportion of national wealth being spent on health and social care is in many countries under close scrutiny.

The importance of early diagnosis and effective communication

Historically, many neurologists and other doctors appear to have believed that because only symptom relieving therapies were available it was not desirable to seek to

diagnose MS as early as possible, or to explain the full implications of having the disease to patients before its disabling consequences began to impact upon their lives. Such beliefs were often accompanied by considerable practical difficulties in identifying the condition in its initial stages before MRI scanning was available, and when the diagnostic criteria in use were less finely tuned than is so today.

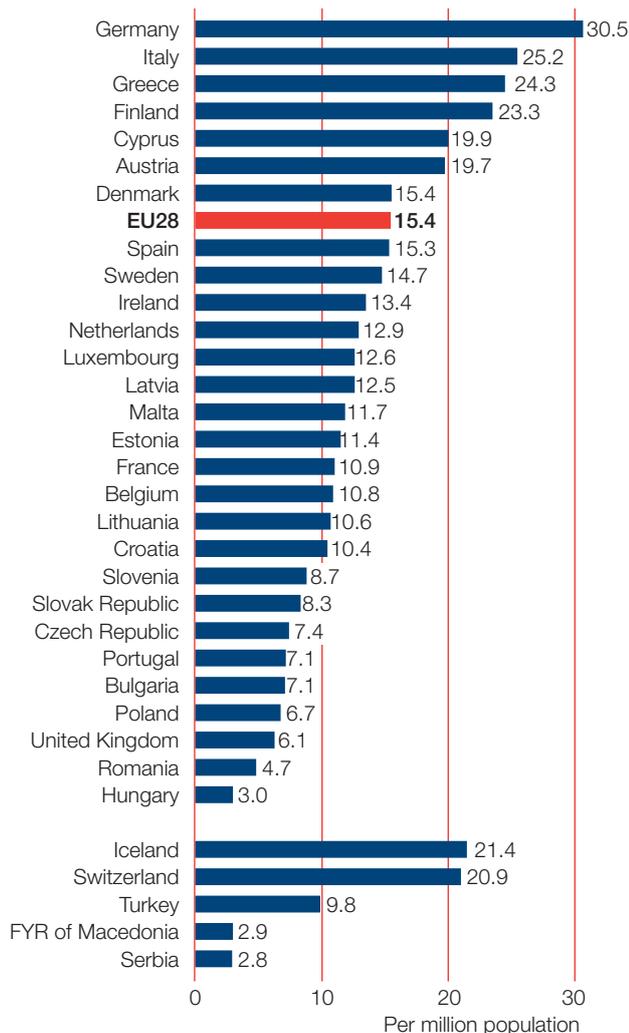
For some patients limited information provision may offer benefits if they are enabled to live for an additional period without worry and fear. But for others it can lead to avoidable distress associated with feelings that they are being ignored or are becoming mentally ill, and being beset by imaginary concerns. There is evidence that a heavy emotional burden is often experienced by individuals waiting for a diagnosis of MS (O'Connor et al, 2004) and that a majority would, even before the availability of the current range of DMTs, prefer earlier rather than later disclosure of information about their condition (Janssens et al, 2004).

The available literature offers reports of people with MS saying that receiving a positive diagnosis was accompanied by feelings of relief because they at least knew the reason for their symptoms and could start to address the problems likely to lie ahead of them in a constructive manner (Murphy Miller: 1997; Russell et al, 2006). Even for people at one time suspected of having MS but who did not subsequently develop it, those given uncertain labels like 'clinically isolated syndrome' followed on occasions by years in which no further information was forthcoming may have been forced into making life changing decisions about matters such as whether or not to have children that could not be reversed after their situation was eventually clarified.

In the developed world today such difficulties are less likely to occur than in the past because of improved diagnostic criteria (Polman et al, 2011) and better access to MRI scanning, even though there are marked inter- and intra-national variations in the availability of latter – see Figure 4. Recent OECD data indicate that there are around five times more MRI units per head of population in Germany than in, say, the UK or Romania. Variations in the numbers of MRI scans undertaken appear to be even greater (OECD, 2016: Wilsden et al, 2014) and there may in some settings be additional problems associated with the available equipment being out dated (CIB, 2017).

Earlier and more accurate disease identification coupled with high quality progression monitoring opens the way to more effective treatment, aimed at stopping observable disease activity and preventing disabilities. Receiving a diagnosis of MS can be a shocking event leading to intense feelings of fear, loss and abandonment (Johnson, 2003). Yet there is evidence that shortening the time spent waiting for a diagnosis curbs anxiety and

Figure 4. Numbers of MRI Units per million population in Europe



Source: OECD, 2016

generates long term benefit. Providing effective support and comprehensive information at the time of first diagnosis also improves patients' subsequent chances of coping well with their condition (Thorne et al, 2004).

The causal relationships between levels of health knowledge and health behaviours are not as straightforward as is sometimes assumed. Nevertheless, there are observed links between the quality of the information PLwMS receive, how much they understand about their condition and how successfully they cope with their diagnosis and MS symptoms (Lode et al, 2007). Good communication and information provision practices for health professionals involve using clear but not simplistic language; being open about the nature of MS and its uncertain course, while at the same time showing confident biomedical expertise; and spending sufficient time to ensure that patients' questions and concerns are listened to and addressed as fully as possible – see, for instance, Kopke et al (2014).

Coping strategies, personality types and MS outcomes

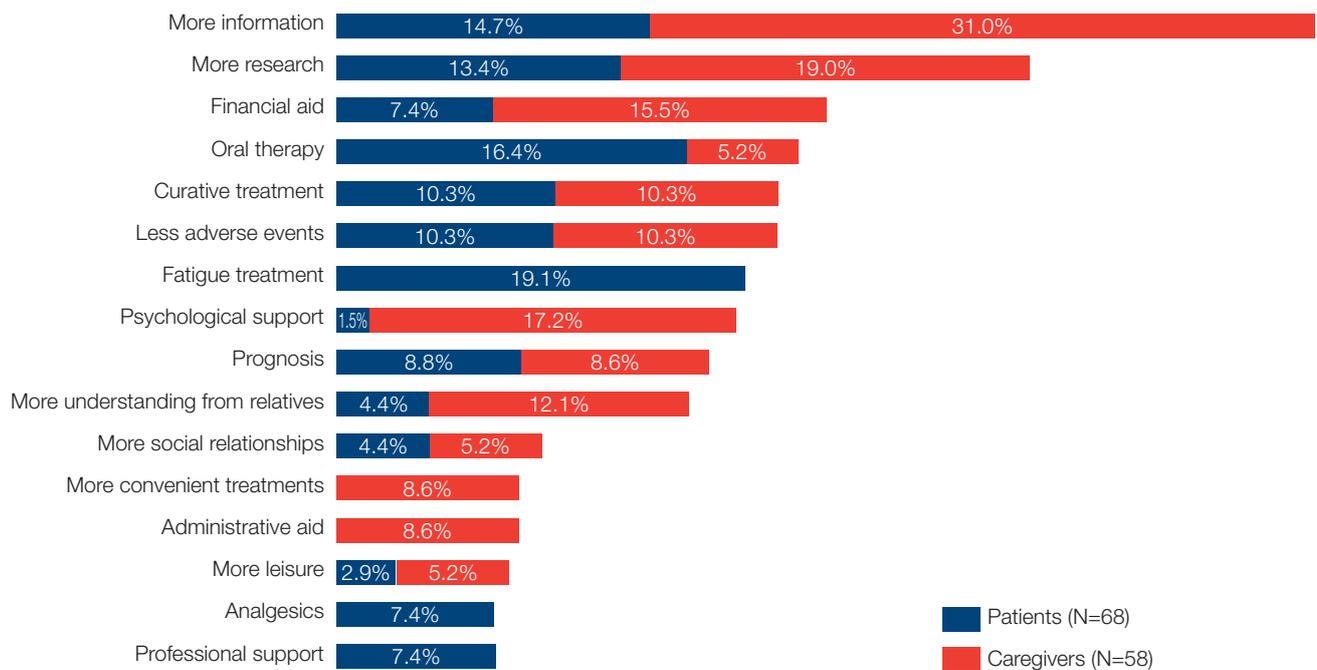
Disabilities caused by MS are often challenging to live with. So too, for most people, is the prospect of further losses of valued attributes such as the capacity for independent mobility, or cognitive competencies like those relating to memory. The distress that such possibilities generate can lead individuals with MS to 'live for the day' and avoid thinking about the future. A significant proportion report ambiguities about whether they would like a more precise prognosis because they fear more bad news.

For some people trying not to think about MS is beneficial (Aronson, 1997). But, as with delaying or limiting diagnostic disclosures, there is empirical evidence that if such strategies lead to the habitual avoidance of unwanted feelings and hence 'emotion focused' coping styles (as opposed to problem oriented coping, which concentrates on changing the individual and her or his environment in order to overcome difficulties) they undermine self-efficacy. This is associated with raised risks of psychological distress and psychiatric illness (Beatty et al, 1998; Pakenham et al, 1999). High levels of mental stress/distress may in turn impact on the numbers of new nervous systems lesions (Mohr et al, 2012).

Psychologists differentiate between coping styles and strategies that are learned and can be changed relatively easily and personality types, which are more stable in nature. In the latter context so called 'blunters' – see, for instance, Baker (1996) – try to avoid receiving potentially distressing information. 'Monitors' on the other hand tend to seek repeated updates about their condition's progression and to be continuously searching for new information about their situation. It is likely that blunters living with MS will more often opt for emotion focused coping strategies than monitors, albeit rigid assumptions about any given individual's preferred ways of learning and handling difficult information should be avoided.

In reality, the dividing lines between acquired and more deep rooted behaviours and ways of thinking are blurred. Furthermore from a sociological perspective it is important not to exaggerate the extent to which people can in any given social and economic context choose their approaches towards disease acceptance and disability accommodation. But for the purposes of this report the most important conclusion to draw is that wherever possible clinicians and others seeking to support people living with multiple sclerosis and other long term conditions should seek to adjust flexibly to the needs and preferred learning and communication styles of each individual with MS without losing sight of the desirability of fostering optimally effective behaviours when opportunities arise.

Figure 5. Contrasting Patterns of Unmet Need Reported by PLwMS and Care Givers



Source: Donze et al, 2016

Contrasting patient, clinician and carer views and needs

As already observed, doctors and other health professionals cannot directly see the inner thoughts and subjective feelings of patients in the same way that they can observe and quantify physical symptoms like, for instance, an inability to walk. It is not, therefore, surprising that the available evidence indicates that neurologists and other doctors tend to rate the importance of the physical aspects of MS more highly than do their patients. In relative terms the latter tend to be more concerned with problems such as fatigue, emotional and social role limitations, depression and loss of vitality (Rothwell et al, 1997).

Recent research by Tintore et al (2017) has also identified potentially important differences in perception between patients and neurologists concerning treatment expectations, selection and satisfaction. This study also found variations in attitudes towards issues such as treatment costs (which may perhaps be more likely to deleteriously impact on a proportion of people living with MS in the US than in most other affluent countries) and the significance of side effects, together with perceived patient ‘failures’ to accept their illness. Such factors are significant in the context of non-adherence to medication regimens. PLwMS and neurologists in addition identified uncertainties as to whether therapies are working as hoped as a ‘top challenge’ in relation to taking DMTs.

With regard to the extent to which the 982 Europeans and Americans with MS who took part in this survey

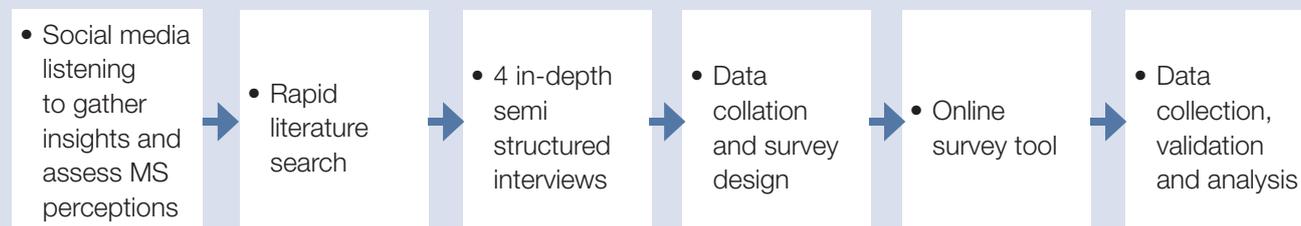
said that they or their physicians controlled treatment selection, there was a normally distributed response relating to each main type of MS. Overall, just under 40 per cent of PLwMS reported that their doctor was the sole or primary therapeutic decision maker. A like proportion said that they, the DMT user, had been the main decision maker. The remainder of a little under a third of the total sample reported an equal partnership between themselves and their physicians.

Respondents with RRMS were markedly more satisfied with their treatment than those with SPMS and PPMS, pointing to the existence of unmet need. Like others, the authors of this study stressed the value of good communication and active patient involvement in MS care decisions, not least because of its capacity to enhance treatment acceptance and hence its outcomes.

There are also significant differences between the perceptions and needs of people with MS and their informal carers. Individuals providing care and support for partners or other relatives with multiple sclerosis are likely to be motivated by feelings of love and duty. But they may at the same time experience sadness and loss coupled with a reduced quality of life compared to their peers without such responsibilities. For those of working age having a caring role may be associated with career disadvantages (Bassie et al, 2016; Donze et al, 2016). Such problems raise risks of developing depressive illnesses and other forms of psychiatric distress. Figure 5 highlights research findings on the unmet needs reported by caregivers and compares them with those identified by PLwMS.

Box 3. The MS-TaP Survey Methodology

Work on the MS-TaP survey began in the UCL-linked medicines use optimisation company Spoonful of Sugar in early 2017. Social media sites were scrutinised in order to gain insights into the interests, views and beliefs of people living with MS. A rapid literature review was also undertaken by SoS, in addition to the searches separately conducted for the preparation of this UCL School of Pharmacy report. The SoS work involved 31 texts being read in full along with the abstracts of some 200 other academic papers and reports. As illustrated below, this then led on to four qualitative interviews being undertaken with people living with MS in the UK.



Following an evaluation of the information gathered in the first three stages outlined above, an initial version of the online survey instrument was designed and piloted. The final version was subsequently produced. It asked a total of 15 questions and employed proven priority assessment techniques as well as provisions for enabling respondents who were not taking disease modifying treatments to explain why this was the case.

Survey participants were recruited online through national patient organisations, charities, prominent patient bloggers and online forums. In the UK prospective respondents were also contacted via the network links of those people with MS who in the early stages of the project had provided insights used to support the development of the survey instrument. Over the summer of 2017 a total of 1040 completed responses were returned to SoS. The final version of the full SoS report on the TaP-MS survey findings is available at <http://sos-adherence.co.uk/research/tap-ms>

These data re-emphasise from the viewpoint of those with MS the importance of relieving fatigue. From the care giver perspective they point to their requirements for psychological support, which reflect their importance in maintaining the morale of people living with disabilities of all types. If the needs of carers are neglected this will impact on formal service demand pressures and costs.

Economic concerns

MS is a costly disease for both individuals and communities. A recent study by Kobelt et al (2017) found average annual outlays on MS across the EU to be €23,000 (at 2015 PPP adjusted values) per patient in relation to mild (EDSS 1-3) disease, €37,000 for moderate disease (EDSS 4-6.5) and €57,500 for the severest (EDSS 7-9) expressions of the condition. Within these totals health care costs (including pharmaceutical spending) accounted for 68 per cent, 47 per cent and 26 per cent respectively, representing some €15,000 a year in each case.

These data are consistent with estimates that MS accounts for about 1 per cent of health service outlays in the EU nations and similar countries like Canada and Australia. Outside the US this is equivalent to around 0.1 per cent of GDP. Within this total, some 2-2.5 per cent of all pharmaceutical costs¹⁰ (or approximately 0.03 per cent of

the average nation's GDP) may be being incurred in relation to symptom relieving and disease modifying MS drug usage. However, Kobelt and her colleagues warn that in reality price discounting means that drug costs tend to be overstated compared with other health sector outlays.

One per cent of total health spending is a very substantial sum on a condition that typically affects little more than 0.2 per cent of the average European or similar population. Yet it is below the direct and indirect financial burdens incurred by people with MS and their families in the shape of informal care inputs and wage losses linked to production shortfalls. Other key observations made by the authors of this large survey (which gathered information from almost 17,000 Europeans with MS) include:

- **before the 1990s MS related health care costs were strongly skewed towards providing hospital and institutional care for those most disabled by the disease.** The availability of DMTs has effectively eliminated this gradient. Their advent should in time lower overall spending requirements as the prices of treatments fall after the expiry of intellectual property rights and when disability levels amongst older MS patients decline. But presently the overall amounts spent on DMTs for multiple sclerosis are sometimes regarded as a problem for health service budget holders. In the UK, for instance (where Kobelt et al reported – for 2015 – only about half the overall level of DMT taking observed in countries like France, Germany, Italy and Spain and two thirds of the access recorded in Sweden and Denmark) the

¹⁰ Authors' estimate based on various sources. The world market for DMTs for MS is presently valued at about \$US 20 billion, out of a global pharmaceutical sales total of circa \$US 1.1 trillion. PLwMS also consume a range of other pharmaceutical products.

Table 1. The TaP-MS Sample

Country	Total no. of respondents male & female combined	% female	Average age at time of response (M&F)	Average time since diagnosis (years)	% of total (including 'don't know') with RRMS	% with SPMS	% with PPMS, including PRMS	% don't know
Australia	28	93%	47.0	7.1	71.4%	10.7%	14.3%	3.6%
Canada	28	50%	42.0	9.6	50.0%	25.0%	25.0%	0.0%
France	102	58%	37.8	7.5	65.7%	7.8%	11.8%	14.7%
Germany	85	86%	36.2	7.7	68.2%	5.9%	14.1%	11.8%
Italy	18	72%	46.1	12.3	50.0%	11.1%	16.7%	22.2%
Spain	61	52%	47.7	15.1	60.7%	21.3%	14.8%	3.3%
Sweden	337	79%	50.9	11.8	43.9%	26.1%	13.6%	16.3%
United Kingdom	139	59%	42.0	9.3	76.3%	8.6%	15.1%	0.0%
United States of America	242	56%	39.2	7.6	49.6%	19.4%	30.6%	0.4%
	1040							
Total split by gender								
Male (all countries)	308		43.4	8.9	48.7%	18.2%	27.3%	5.8%
Female (all countries)	727		44.1	10.1	58.6%	17.7%	14.3%	9.4%
Preferred not to say	5		42.5	6.5	60.0%			40.0%

Source: Spoonful of Sugar, 2017

establishment of NICE in 1999 was linked to (false) fears that interferon based treatments for MS would 'bankrupt the NHS' (Taylor, 2002; 2016).

- **health and other service provisions for people with MS vary significantly between nations in Europe and elsewhere.** In Sweden, for example, there is an exceptional level of investment in social support. Access to neurologists is high in settings like Germany and France, while MS patients are more likely to see specialist MS nurses in the UK and nations such as Denmark and The Netherlands.

These authors concluded that for the future there should be more emphasis on studying the epidemiology of MS and the quality of care available to people living with it by the level of disease severity, rather than by condition 'type'. They also stressed the importance of understanding more about how fatigue, cognition problems, depression and anxiety affect employment and other aspects of daily life, and how health care funding differences impact on service standards in otherwise similar nations.

The MS Treatment Expectations and Priorities (TaP-MS) Survey – Key Findings

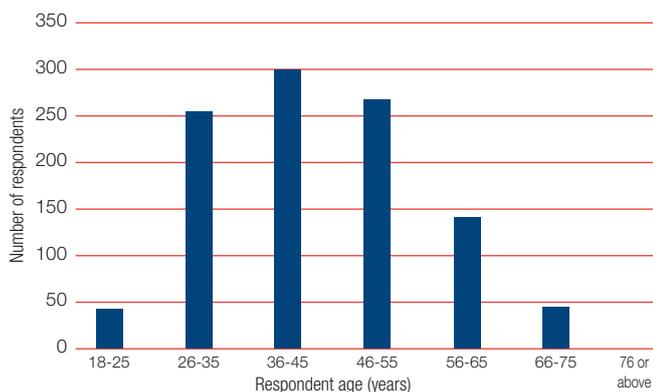
The TaP-MS survey was conducted in the summer of 2017 by the UCL spin-out company *Spoonful of Sugar* (SoS), the name of which reflects the title of a seminal report on medicines taking published at the start of this

century (Audit Commission, 2001). SoS specialises in undertaking studies of health behaviour change and in facilitating improved medicine use. Details of the research methods the TaP-MS survey team employed are presented in Box 3.

Table 1 and Figures 6a and 6b provide data relating to the sample of 1040 PLwMS gathered during the study period. Swedish, American, British, French and German patients together accounted for almost 80 per cent of the respondent total. The average participant was in her or his early 40s and females outnumbered males by 2.4:1. The typical individual reported that they had been diagnosed with MS for about 10 years. Overall, 55 per cent said they had RRMS, and 18 per cent SPMS. Another 18 per cent of respondents indicated that they had either PPMS or PRMS – the absolute numbers recorded were 145 and 43 respectively. The remaining 8 per cent gave 'don't know' replies.

Over half the latter (55 out of 88) respondents were Swedish. A sub-analysis of this group did not show it to be different from the overall body of Swedish PLwMS. It should not be assumed 'don't know' answers reflect ignorance or a lack of understanding of MS. It may be, for instance, that those saying they were uncertain of their diagnosis were in transition between RRMS and SPMS (which is a testing period for patients and carers alike) or had another informed reason not to provide a precise answer. For example, the distinction between PPMS and PRMS can be difficult to make.

Figure 6a. Distribution of TaP-MS Respondents by Age



Source: Spoonful of Sugar, 2017

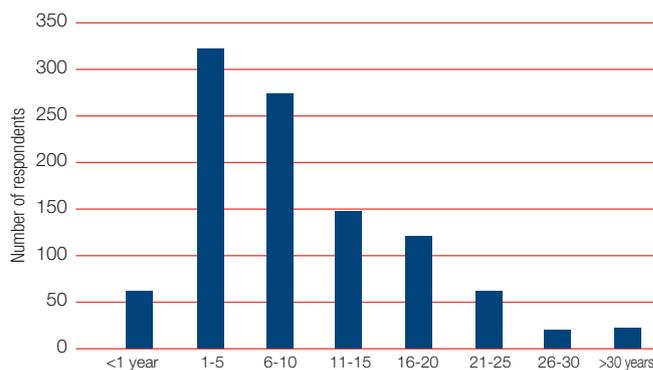
Table 2 provides a country by country breakdown of the self-reported use of DMTs by diagnosis. Some 81 per cent of all those who said they had RRMS indicated being in receipt of a disease modifying therapy. National level figures ranged from 71 to 73 per cent being on DMTs in the UK and the US respectively through to well over 80 per cent in countries such as Australia, Canada, France and Spain.

These national level statistics should not be over-interpreted. In the case of Australia, for instance, just 28 PLwMS took part in the TaP-MS survey. Nevertheless, the fact that the US figure is comparable to that for the UK and that the aggregated proportion of people with RRMS who reported being on DMTs in these two countries is over 10 per cent less than the average for all other countries combined raises questions about access to care.

It suggests, for example, that some people in the US RRMS community may be being under-treated, perhaps because of socio-economic inequalities linked to risk taking in the health and health care contexts. From a US patient interest and public policy perspective it might be worth further investigating the possibility that individuals who have – despite the medicines access support provisions available – perceived problems with paying for MS therapies or for other reasons have restricted access to services needed to facilitate their use are being exposed to an avoidable long term risk of developing MS related disabilities.

Despite the existence of the NHS in the UK there is also evidence that British policies have on occasions required clinicians to make subjective judgements about the ‘suitability’ of patients for MS treatment (Owens et al, 2013). Such observations cannot explain the low overall level of DMT use in Britain reported by various sources. But they serve as a warning as to how social class related MS treatment inequalities can be fostered in systems that do not explicitly guarantee individuals’ rights to treatment.

Figure 6b. Distribution of Tap-MS Respondents by Time Since Reported Initial Diagnosis



Source: Spoonful of Sugar, 2017

In fact, the levels of UK patient DMT use reported by the TaP-MS survey respondents were not as low as sources such as the *European Burden and Costs of MS* study (Kobelt et al, 2017) or data like that quoted in Giovannoni et al's *Brain Health: time matters in MS* (2015) indicate is the case. It may be that, following the active involvement in health policy debate by UK MS organisations and the release of revised clinical guidance by NICE in 2014, access to MS disease modifying treatments has recently improved in Britain. However, TaP-MS respondents were not asked to differentiate between older and newer MS DMT use. From a global patient interest perspective it would in future be desirable to have open access to reliable, up-to-date, figures on all forms of advanced MS treatment usage on a country by country basis.

Turning to people living with SPMS and PPMS, Table 2 shows average reported levels of DMT use of 59 per cent and 57 per cent respectively. These data include a limited number of replies from individuals indicating they are taking rituximab on an off-label basis. In the context of SPMS treatment only a third of Swedish respondents said they were using a DMT, compared with 96 per cent of US patients. In the case of PPMS and PRMS the overall figures referred to above were skewed by the fact that although 89 per cent of American respondents said they were taking a DMT little more than a third of Europeans with these diagnoses said that they were using one.

In Sweden and Spain less than a quarter of those reporting a diagnosis of PPMS or PRMS said they were taking a DMT. Once again, over-interpretation should be avoided. During the period in which the TaP-MS investigation took place (that is, the summer of 2017) only the American and Australian pharmaceutical markets contained a DMT licensed for any form of progressive disease treatment. Yet this had only been so for a very limited time period and cannot therefore account for such discrepant findings.

Table 2. Disease Modifying Treatment/Drug Use

Diagnosis	RRMS			SPMS			PPMS+PRMS			Don't Know		
	On DMT	All	%DMT	On DMT	All	%DMT	On DMT	All	%DMT	On DMT	All	%DMT
Australia	19	20	95.0%	2	3	66.7%	2	4	50.0%	1	1	100.0%
Canada	12	14	85.7%	6	7	85.7%	4	7	57.1%			
France	57	67	85.1%	7	8	87.5%	7	12	58.3%	12	15	80.0%
Germany	46	58	79.3%	3	5	60.0%	6	12	50.0%	6	10	60.0%
Italy	7	9	77.8%		2		1	3	33.3%	1	4	25.0%
Spain	36	37	97.3%	9	13	69.2%	2	9	22.2%	2	2	100.0%
Sweden	126	148	85.1%	29	88	33.0%	11	46	23.9%	36	55	65.5%
United Kingdom	76	106	71.7%	9	12	75.0%	9	21	42.9%			
Total (US not incl.)	379	459	82.6%	65	138	47.1%	42	114	36.8%	58	87	66.7%
United States of America	88	120	73.3%	45	47	95.7%	66	74	89.2%		1	
Grand Total	467	579	80.7%	110	185	59.5%	108	188	57.4%	58	88	65.9%

Source: Spoonful of Sugar, 2017

One possibility is that they reflect significant differences in prescribing practices between doctors in the US and other settings. But even European and Canadian respondents who said they had a progressive form of MS reported a surprisingly high level of disease modifying medicine use. Alternative reasons for the reported figures range from sampling biases through to much higher than expected off-label prescribing rates or respondent misunderstandings about either the treatments being taken or the meaning of 'disease modification'. Further investigations of the patterns of care provided for people with PPMS/PRMS in each national setting will be required to further explain such observations and their welfare implications.

Existing therapy concerns and expectations

Figures 7a, b and c offer over-views of the reasons given by people with MS for not using DMTs. In the case of RRMS the main factors involved related to the perceived risk of suffering side effects and long term harm (labelled Concerns) and a lack of belief in the need for therapy (labelled Needs)¹¹. By contrast, in both the SPMS and PPMS/PRMS categories the most significant barriers to access reported by respondents were unavailability (that

is, the belief that no suitable medicine for treating their condition exists) followed by Concerns and Needs linked explanations.

The patterns of drug use and patient beliefs about problems like side effects observed during the TaP-MS investigation were by and large consistent across national boundaries. However, the issues touched on above may reflect differences in areas like, for instance, how Swedish neurologists and/or service funders employ treatments in the Secondary Progressive setting as compared with relevant decision makers in other parts of Europe. If this is so it might help explain diagnostic ambiguities at the RR/SP borderline. Were, for instance, some patients transitioning from RRMS to SPMS to fear restrictions in their ongoing therapeutic opportunities they might be more inclined to express uncertainty about their diagnoses than PLwMS living elsewhere.

This particular hypothesis is by no means proven. Nevertheless, the TaP-MS findings point to a need to understand better the knowledge and beliefs that people with PLwMS have about taking DMTs. They also signal that it would be useful to explore cross-national variations in medical practices in greater depth. To the extent that therapeutic conservatism or liberalism impacts on service users' welfare, practice variations in areas like fostering early MS diagnosis and treatment are not matters of concern to the medical profession alone. As the range of effective therapies grows, patients and their representatives across the world will share interests in ensuring optimal access and use.

11 Horne's Necessity and Concerns Framework can be used to predict adherence in medicines taking. Individuals who believe strongly that taking MS DMTs or other medicines is necessary for their future wellbeing and who have relatively low levels of concern about side effects or other possible causes of treatment related harm are more likely to accept and continue using recommended medicines than those with a strong concerns/weak necessity balance of medication associated beliefs.

Figure 7a Reasons for Not Using DMTs (RRMS)

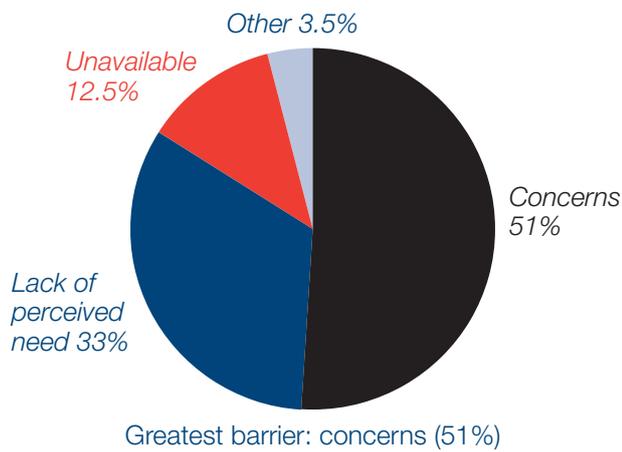


Figure 7b Reasons for Not Using DMTs (SPMS)

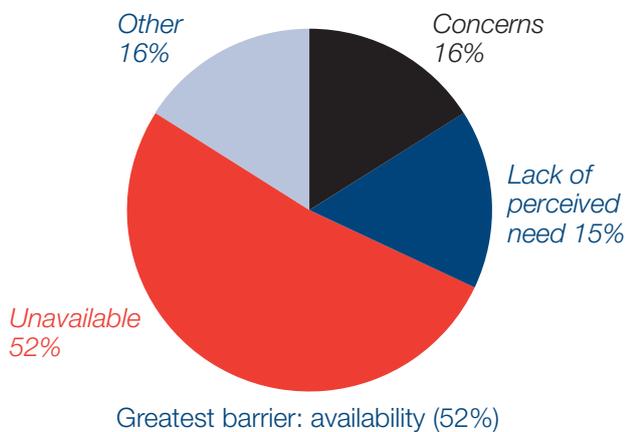
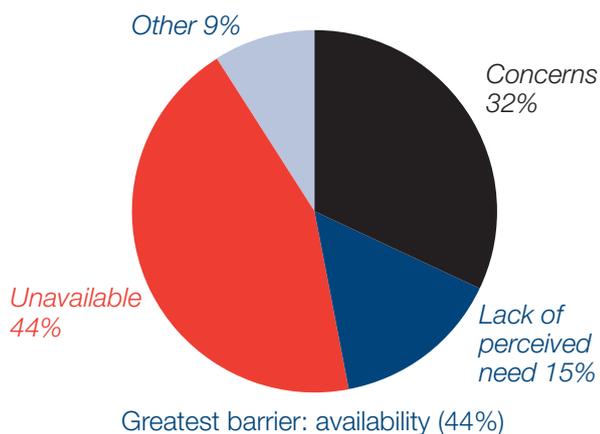


Figure 7c Reasons for Not Using DMTs (PPMS and PRMS)



Source: Spoonful of Sugar, 2017

Turning to other expectations relating to currently available DMTs, Figures 8, 9 and 10 summarise the replies given to a set of questions aimed at establishing respondents' priorities regarding the benefits they want from their medicines. The TaP-MS findings confirm and augment those of earlier research. They in particular

highlight the importance that people with MS attach to combatting fatigue, maintaining their walking/mobility capabilities and alleviating problems like bladder and bowel control difficulties and sight impairments.

They also confirm that DMT users attach high priority to reducing relapse rates and slowing or ideally halting disease progression. In that the latter can be seen as the ultimate driver of all the unwanted aspects of MS, these results indicate that stopping disease progression is the highest priority expectation of patients taking DMTs. However, this is not to deny the importance for patients of other aspects of disease and symptom improvement like alleviating fatigue and, if and when possible, reducing levels of disease fluctuation.

The TaP-MS responses in addition show that while people with MS, like others, do not want to suffer unwanted side effects as a result of taking medicines of any type, most are prepared to accept a degree of risk in return for symptom moderation and disease stabilisation. The results shown in Figure 8 confirm that – although important – treatment harm minimisation is for most people a second order priority as compared with disease modification.

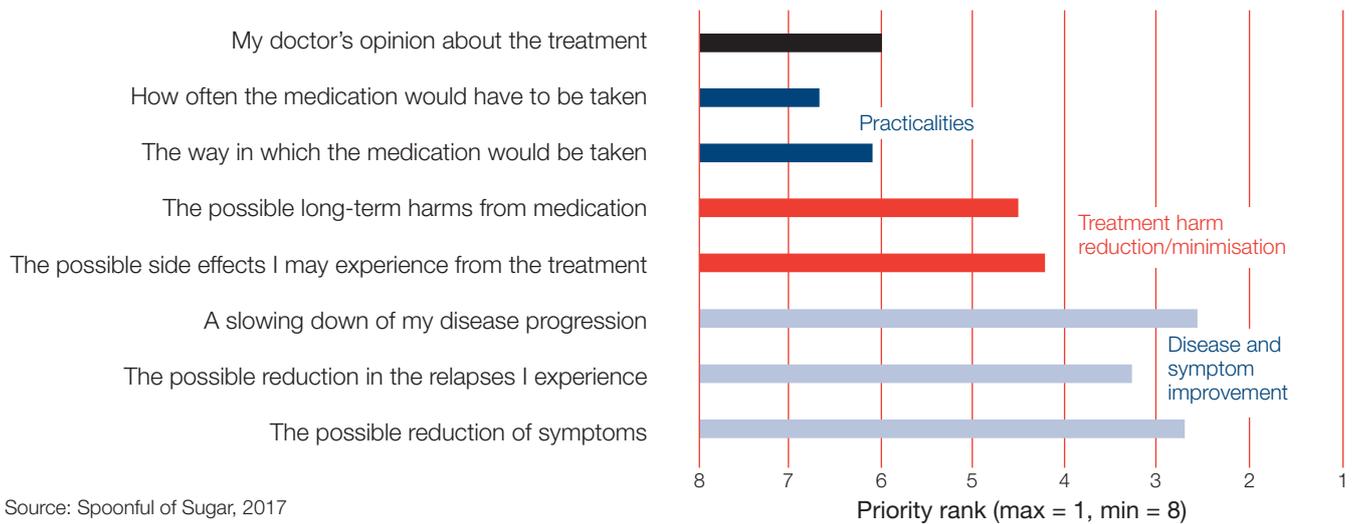
These findings, which are again consistent with those contained in the literature summarised earlier in this report, offer a warning about the undesirability of undue therapeutic risk aversion. In bureaucratic and other 'status and order preservation' focused social systems there is often a strong desire to prevent actions which could result in external criticism. But clinicians and service managers should be aware of service users' preferences. Care should be taken to fully respect the requirements of people seeking to maximise the chances of stopping MS progression as against minimising the possible risks of treatment.

'Practicality' linked considerations like those associated with alternative medicine administration routes¹² can be seen as third order priorities for PLwMS. This is not to say that ease-of-use linked factors do not influence medicine taking, and so *de facto* therapeutic effectiveness. But from a health policy viewpoint there is no patient expectation based reason to prefer any one route or pattern of DMT administration over another, provided adherence issues are well managed.

In short, '*what works best matters most to most people with MS*'. From a pharmaceutical research and development perspective this conclusion underlines the need for enhanced outcomes rather than improved medicinal properties. However, if therapeutically equivalent choices are available then factors like convenience and freedom from even minor side effects can and should shape both patients' and clinicians' preferences.

¹² Such as, for example, whether or not medicinal products can be taken orally – and if so how many times a day – or must be delivered over time via infusion.

Figure 8. Key Considerations/Expectations Related to Deciding Whether or Not to Start Taking a New DMT



Source: Spoonful of Sugar, 2017

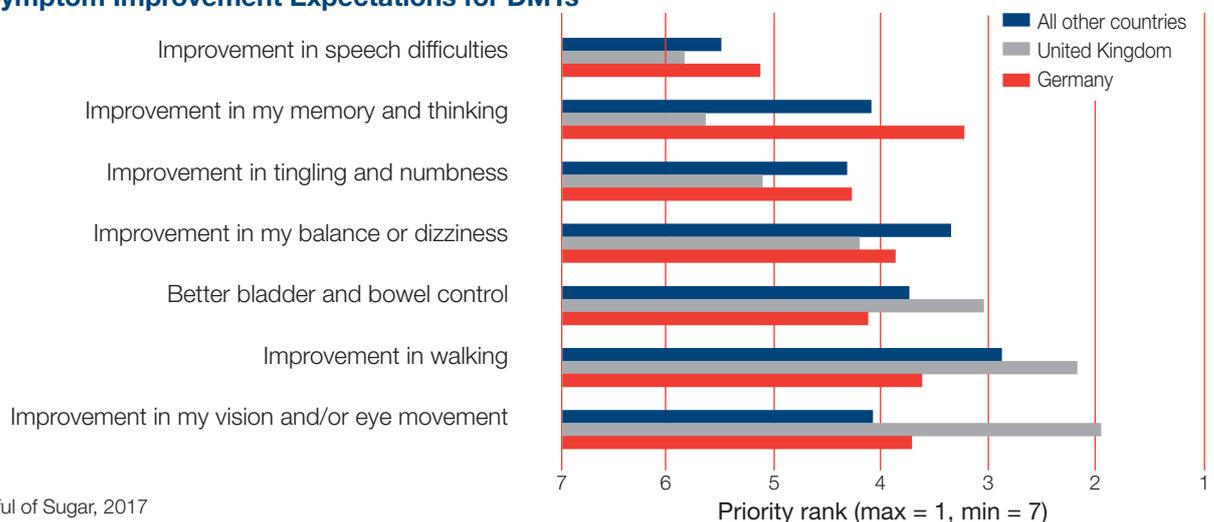
With regard to the low level of priority given to doctors' opinions recorded in Figure 8, the interpretation offered here is not that most people with MS do not value their neurologists' or other doctors' advice. It is rather that they want evidence based guidance rather than arbitrary direction or medical judgements that are not based on a respect for patients' highest priority expectations. This implies that other professional groups such as pharmacists could in future play an extended role in providing medicines and other treatment related information and facilitating therapeutic choices.

Finally, the data generated by the TaP-MS survey suggest that (with the possible exception of Australians) English speaking country respondents are, when compared to their mainland European peers, more likely to say they value symptom reduction as opposed to progression slowing. These expectations are not fully independent of each other. Yet even so, this apparent difference may

be relevant to optimising care in contrasting cultural settings. It is possible, for example, that they could in some cases relate to less adequate symptom control causing patients avoidable distress.

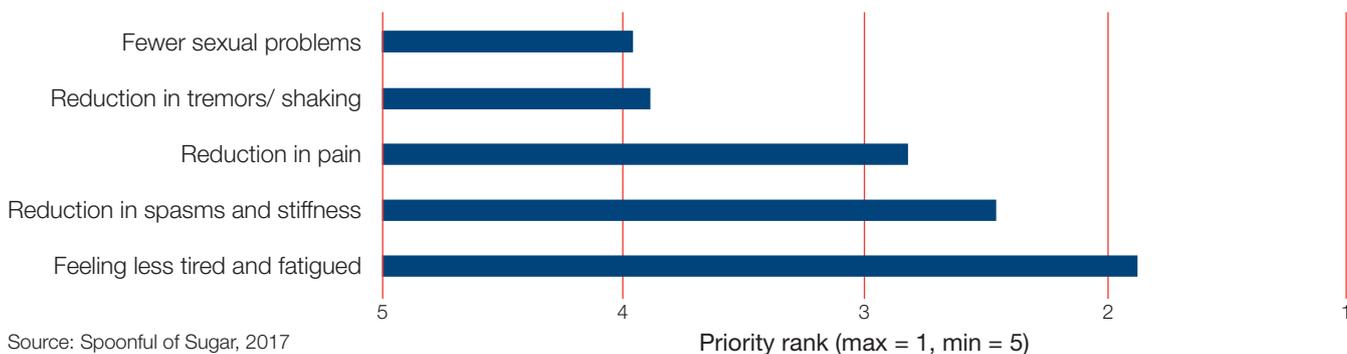
The responses given to the question set covered in Figures 8, 9 and 10 were in overall terms consistent across the countries covered. Yet the pattern of British and to a lesser extent the German priorities expressed differed from that of the main body of respondents. Further research would be needed to fully validate and/or explain this observation. But in the UK context there is evidence indicating that the MS care provided could in certain respects have lagged behind that in some other parts of the EU. It might be that British treatment access and standards have been sufficiently different from those in settings such as, say, France to account for variations in expressed patient preferences and needs.

Figure 9. Symptom Improvement Expectations for DMTs



Source: Spoonful of Sugar, 2017

Figure 10. Symptom Reduction Priorities



Source: Spoonful of Sugar, 2017

New treatment expectations

Just under three quarters of respondents to the TaP-MS survey said that they would expect side effects from any new medication, ranging from a high of over 90 per cent in Germany to a low of about 50 per cent in Spain. There is robust evidence that experiencing treatment side-effects can alter individuals’ medicines taking. Recent studies have also highlighted the extent to which perceived personal sensitivities to treatment side effects are influenced by factors such as media and informal reports alongside other social and behavioural variables (Faasse et al, 2015). Such observations point to the importance of evidence based contributions to public debates about health generally and medicines use in particular.

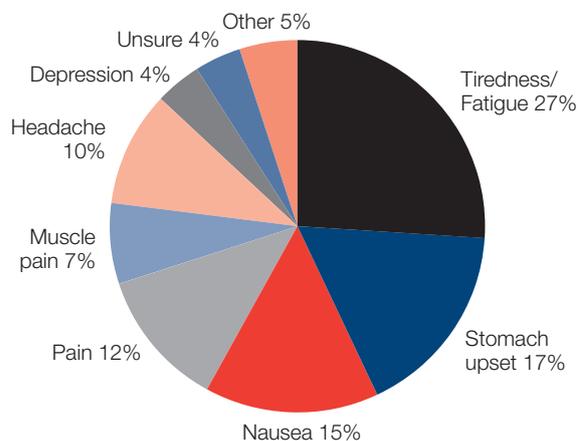
The data generated by the TaP-MS investigation indicate very similar patterns of DMT use amongst people saying they expect new medicines to have side effects and those saying they do not expect side effects. This observation holds for all forms of MS. It indicates that simply asking people living with the disease whether or not they expect negative treatment consequences is not likely to be an effective predictor of medication rejection.

However, against this there is evidence that individuals who have unrealistic expectations of medicines they are taking may over time be more likely to stop using them than others, should problems occur (Zivadinov et al., 2003). There is therefore a case for seeking to improve the information and support available to people who appear not to know (or to have not accepted) that DMTs for MS – along with all other treatments – carry risks of harm. This, together with other information about the benefits of treatment and coping with MS, should be offered in ways consistent with each person’s preferred learning and coping styles.

Figure 11 provides an overview of the types of side effect TaP-MS respondents said they expected to suffer. Stomach aches, nausea, headaches and muscle attacks are associated with many forms of medicinal drug use. However, the most commonly identified side effect expectation was fatigue. A significant number of respondents also cited depression as an unwanted

consequence of treatment. MS DMTs can cause such effects. Yet as fatigue and depression are commonly experienced facets of the disease itself these responses suggest the existence of an ambiguity in the minds of some people with MS as to the desirability of DMT use.

Figure 11. Most Frequently Expected DMT Side Effects

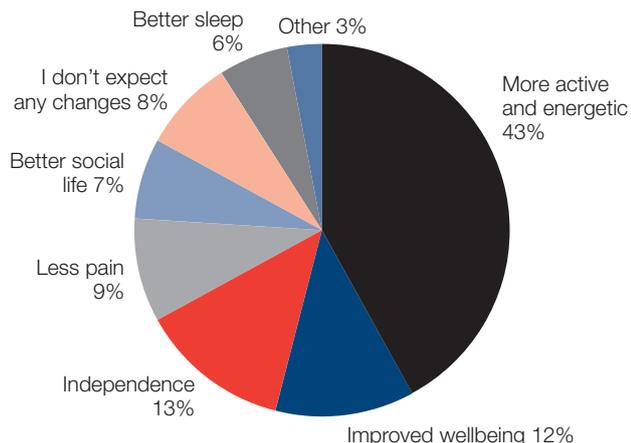


Source: Spoonful of Sugar, 2017

It is possible that knowledge relating to the side effects of established therapies (such as interferon based products that can cause flu-like symptoms and depression) may on occasions being projected forward into people’s thinking about taking new, previously untried, treatments. If this hypothesis can be validated clinicians and service users should be warned of the risk that misplaced concerns could undermine beneficial medicines use and impede efforts to enhance outcomes. The scale of the health and financial costs this could result in may be sufficient to justify significantly increased spending on improving medicines taking related support.

Figures 12 and 13 describe expectations observed in the context of the impacts that new medicines should have on the quality of life of people with MS and their ability to live as they want without intrusive symptoms limiting their freedoms. These data again highlight the importance of fatigue reduction and the degree to which people living with MS seek more energy and mobility, coupled with fewer relapses and slower or halted disease progression.

Figure 12: Quality of Life Improvements Most Expected from New Treatments



Source: Spoonful of Sugar, 2017

Such findings are not unexpected. But considered against the background analysis offered earlier in this report they signal that to meet the expectations of PLWMS as well as possible treatment providers should not confine their attention to meeting basic care needs. They ought in addition be seeking to care for people with MS in a holistic manner that enables individuals to pursue all their goals in life. This favours seeking to combine the benefits of nursing, pharmaceutical, psychological, rehabilitative and other interventions in a co-ordinated manner.

Socially defined expectations

Following on from the above, the responses given in relation to the four test statements shown in Figure 14 underline the fact that most individuals are not only concerned with their immediate wellbeing. Overall, 44 per cent of all those taking part in the TaP-MS survey agreed or strongly agreed with the statement 'I would

prioritise a long life, regardless of any physical disabilities I might develop'.

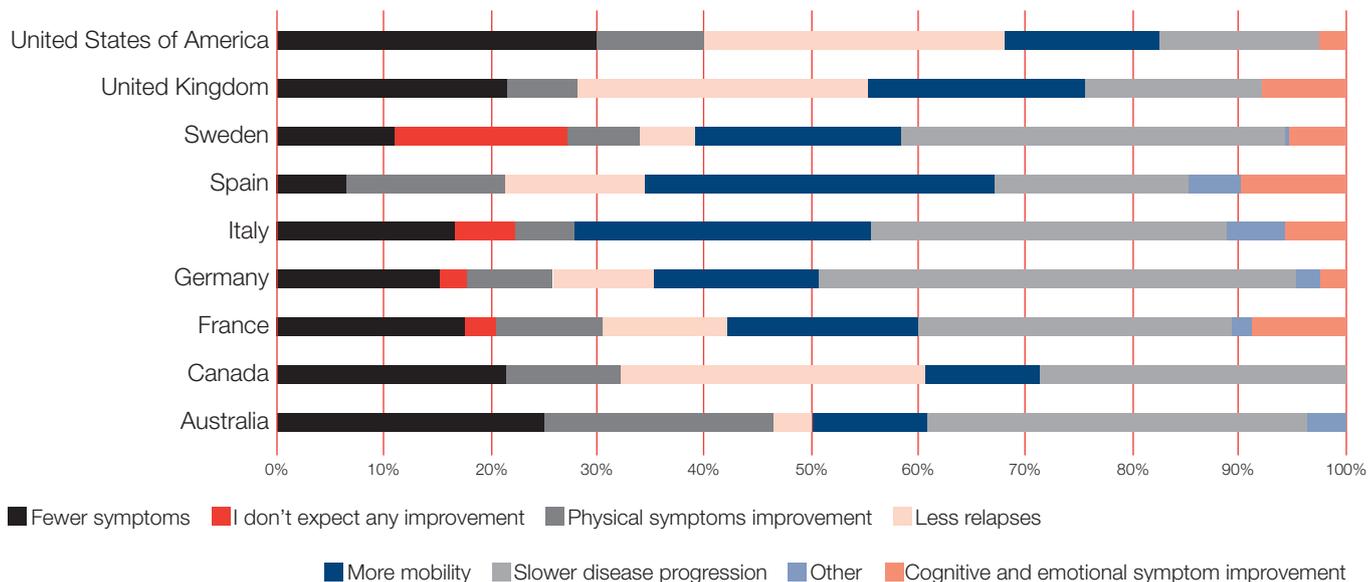
Just over 30 per cent disagreed. The remainder neither agreed nor disagreed. On a country basis American (71 per cent), Canadian (64 per cent), British (61 per cent) and Australian (57 per cent) respondents were most likely to say that they would prioritise a long life above all other considerations. By contrast, less than 30 per cent of those living in France, Germany, Italy, Spain and Sweden expressed agreement with this statement.

'Mainland' Europeans were about twice as likely as were their English speaking counter-parts to actively disagree. This observation is again suggestive of cultural variations that could impact on health and social care provision. Although its applicability outside the MS context needs further investigation it might, for instance, offer insight as to why service funders and other health care related decision makers in settings such as France may be prepared to give more weight to quality of life linked considerations independently of survival durations than their equivalents in countries like the UK.

There was stronger and more uniform agreement with the statement 'I would prioritise a treatment that assures me that my MS will not progress any further over a medicine for symptom relief.' Overall, approaching four fifths (78 per cent) of respondents said that they agreed, about half of them strongly. Little more than one person in twenty (circa 6 per cent) said that they disagreed.

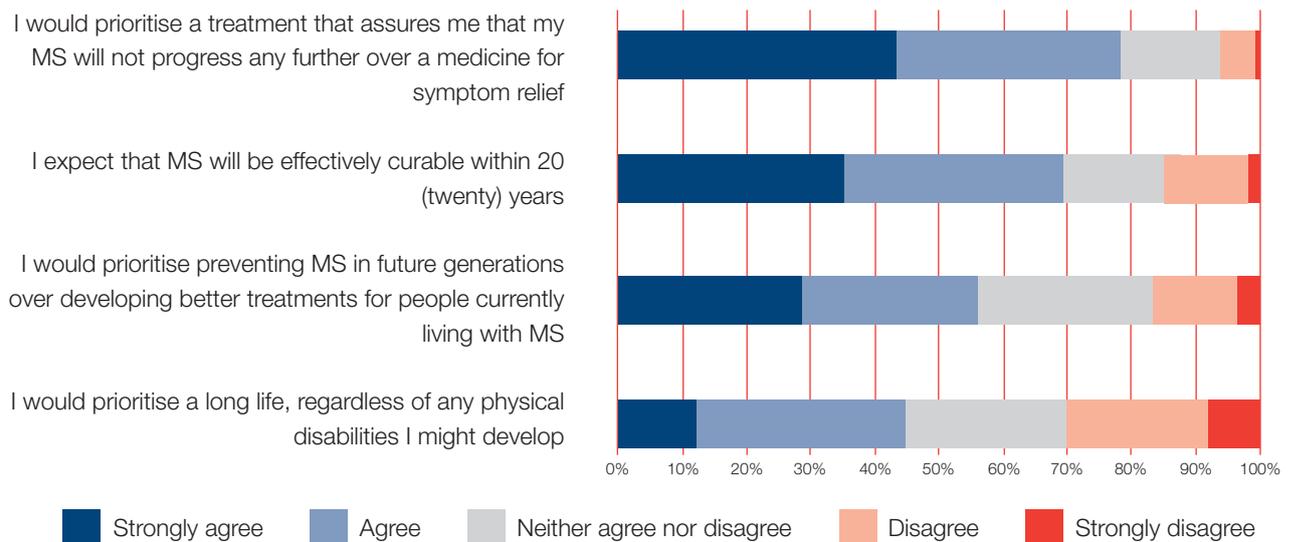
Symptom relief and stopping or slowing disease progression are often closely intertwined. Nevertheless, these responses validate findings about the value of slowing or stopping disease progression reported earlier and imply that, from a patient-centred standpoint, agencies like pharmaceutical companies and public

Figure 13: MS Symptom Improvements Most Expected from New Treatments



Source: Spoonful of Sugar, 2017

Figure 14. Levels of Agreement and Disagreement with Test Statements



Source: Spoonful of Sugar, 2017

research funders should concentrate their investments in projects aimed at developing more effective means of halting the disease processes at the heart of MS. However, if alternative opportunities to treat symptoms such as fatigue arise they should not be ignored, not least because they may have important applications in areas outside the MS sphere.

With regard to the statement ‘I would prioritise preventing MS in future generations over developing better treatments for people currently living with MS’ 56 per cent of all respondents expressed agreement. At the national level support for this view was strongest in France, where 82 per cent of respondents with MS indicated positive support. In the US 76 per cent agreed or strongly agreed. The average level of concurrence in all the other countries included in the overall TaP-MS sample was in the order of 45 per cent.

One interpretation of this finding is that although Americans may report a value driven desire to stay alive even if they have to endure serious disability/distress, they also have a strong collective ethic favouring future disease avoidance. The results outlined here imply the existence of similar national/cultural values relating to population wide disease prevention in the French Republic, alongside a more nuanced approach to personal survival as against well-being.

Finally, seven in every ten respondents (69 per cent) agreed or strongly agreed with the statement ‘I expect that MS will be effectively curable in 20 years’. Amongst the overall population taking part in the TaP-MS survey only 12 per cent of respondents expressed disagreement, including just 7 per cent of the Americans involved.

However, the proportion disagreeing amongst PLwMS from the UK was 29 per cent. Just 49 per cent of British respondents agreed. This is unlikely to be a

chance observation. In the context of individuals living with PPMS and PRMS, approaching 95 per cent of Americans with these conditions said that they think MS will be effectively curable in twenty years. This compares with a figure of 76 per cent for people with PPMS/PRMS from the other countries covered in the survey who said they were taking a DMT. The figure for all those with diagnoses of PPMS or PRMS living outside the US who expect MS to be effectively curable in twenty years was, for DMT users and non-users combined, 65 per cent.

Once again, research would be needed to verify the significance of these findings. Yet for the purposes of this policy report two possibilities are worth highlighting. The first is that the UK’s central taxation based funding approach to health care has led to a relatively strong emphasis on the need for rationing and cost limitation, as opposed to believing in the positive benefits of improving treatment outcomes and fostering pharmaceutical and other forms of innovation.

A consequence of attempts to achieve ‘therapeutic austerity’ could perhaps have been that it has not only undermined public and patient confidence in service standards, but reduced expectations as to the benefits of treatments for conditions like MS. In this context it may be relevant to record that the United Nations’ Committee on the Rights of Persons with Disabilities (2016) was recently highly critical of UK, and in particularly English, authorities for failing to protect the well-being of people with disabling disorders and permitting health and social care standards to be degraded.

A second, linked, hypothesis is that lowered expectations of therapeutic advance actively harm some individuals. There is limited but nevertheless potentially important qualitative evidence that having positive attitudes towards scientific progress and the ongoing evolution of more effective treatments can help people with

conditions such as MS maintain hope and live with their illness as well as possible – see, for instance, Murphy Miller (1997) and Soundy et al (2011).

There is a need for appropriate economy and affordability in all areas of health and social care. Yet maintaining good morale and optimism amongst people living with progressive, disabling and life threatening conditions is also important. It in part depends on promoting informed understandings of the value of therapeutic developments like those now taking place in the MS field. Agencies that may be trying to limit public service spending via delaying the uptake of new therapies should try to avoid doing so in ways that engender pessimism, damage future expectations and undermine day-to-day levels of confidence and hope.

Policy Issues and Political Choices

There are many examples of new medical and pharmaceutical technologies having long-term impacts extending well beyond their value to patients seen only as isolated ‘personal utility maximising’ individuals. The introduction of oral contraceptives (OCPs) in the 1960s is one of the best known. In the decades since then OCPs have contributed to freeing many women to take part in higher education and acquire social roles once enjoyed only by men (Goldin and Katz, 2002).

This has in turn brought benefits for their partners and children. Vaccines for conditions like polio and medicines used to prevent and treat conditions such as peptic ulcer disease and vascular disorders have also had important impacts that may be invisible to observers who are unduly reliant on short term measures of individual benefit like the EQ 5D.

The introduction of more effective treatments and eventually functional or complete cures for MS will also generate a range of individual and societal benefits extending beyond conventionally measured QoL gains, including reducing the numbers of people living what may be regarded as unfairly limited lives¹³. It is also important to record that from a longer term economic perspective the prices of medicines decline as the patents and other forms of intellectual property protection needed to encourage further investment in research and innovation expire. Competition between suppliers coupled with production and clinical practice improvements enhances their cost effectiveness.

¹³ The uncertainties and fears surrounding MS can impede long term planning in ways that harm not only individuals but entire families. Even if the clinical benefits of better therapies relate to the stabilisation of disabilities rather than eliminating them, their value can be considerable. Independently of this, reduced levels of disease linked social inequality could also generate additional welfare gains for all community members, including the healthy individuals and groups.

However, attractive as this long term vision is there are a variety of barriers to its realisation. They range from policies which impede the introduction of better ways of preventing and alleviating disease through to cultural biases that draw attention away from the importance of reducing health inequalities and protecting the interests of minority groups affected by relatively rare conditions such as, for instance, PPMS. The brief analysis offered below is intended to be of particular relevance to policy makers concerned with promoting improvements in MS related health outcomes, and ensuring that people with all disabling illnesses are as advantaged as possible in life.

Improving service performance

Opportunities for enhancing the benefits generated by current MS service provisions include:

- facilitating MS prevention or onset delay whenever possible;
- fostering early diagnosis and the prompt initiation of disease modifying treatment in order to slow or halt disease progression and stop major disabilities emerging;
- psychologically supporting PLwMS at all stages of their disease experience;
- assuring optimally appropriate therapy selection at all times;
- combining medical, nursing, pharmaceutical, psychological and rehabilitative and social care in ways that maximise their synergistic value and provide patients with an auditable record of coherent support; and
- further strengthening social and economic provisions that offset the impacts of disabilities on individuals, families and communities – in this context national or supra-national standards should be put in place in order to permit performance evaluations.

At present there is no method of preventing MS that is comparable to, say, polio vaccination and its proven value in guarding against the ill effects of polio infection after the first one or two years of life. But as described earlier in this report, there is evidence that not starting or stopping smoking as soon as possible, eating well and reducing obesity rates, taking regular exercise and controlling blood pressure levels and allied vascular disease risk factors can – as well as offering gains like cutting type 2 diabetes rates – maintain ‘brain health’ and reduce central nervous system tissue losses throughout life (Giovannoni et al, 2015). The time may now also have come for health professionals, parents and policy makers to act on the increasing body of data linking vitamin D deficiencies to MS.

The extent to which, in current circumstances, increased public awareness of such opportunities could lead to significant cuts in disease incidence remains debateable. Yet the fact that lifestyle choices combined with the appropriate use of medicines can have important preventive effects could well be an important pointer to the future of MS linked harm reduction.

Some observers involved in the provision of 'evidence based care' may argue that the benefits of prompt DMT use are not as yet fully proven. Concerns about the effectiveness and side effects of current therapies can increase the anxiety and uncertainty felt by some people with MS when they are asked if they wish to accept or forego treatment. However, there is already a strong logical and value based case for questioning therapeutic conservatism and seeking to optimise the chances that people with early stage multiple sclerosis have to avoid in future having to live with major disabilities.

Interventions designed to support early diagnosis include introducing school based and wider public (health) programmes aimed at raising MS awareness and community-wide willingness to report what may be initial symptoms. Investing more in the identification, where possible, of genetic risks and providing good universal access to MRI testing should also have the capacity to generate additional benefit. National policy makers might, for instance, in addition to establishing or strengthening MS registries in order monitor treatment quality and outcomes, seek to institute free standing audits that compare access to MRI based diagnostic and disease progression testing on a locality by locality basis. Disseminating the findings of such projects could help create the political will needed to address service shortfalls linked to socio-economic disadvantage.

Regional and global health policy makers may also wish to commission and publicise the results of high quality, statistically robust, analyses of the extent to which, even after GDP variations are accounted for, access to timely MS diagnoses and optimally effective treatments is in some countries markedly better than in others. Such studies are already available in the oncology field, along with outcome data.

Another quality and performance improvement tool would be to monitor the time taken for people labelled as having CIS or RIS (clinically or radiologically isolated syndromes) to receive either a confirmed MS diagnosis or be told definitively that they do not have the condition. The views of those eventually found to be free of MS regarding the support they received during periods of diagnostic uncertainty could be particularly valuable.

In addition to the stresses associated with their initial diagnosis (Bogosian et al, 2009) people with RRMS are likely to have to face a series of 'progression points' at which new disabilities or symptoms appear.

They are eventually likely to have to 'transition' to an SPMS diagnosis. At worst, this can be experienced as a form of personal failure or defeat, similar to the feeling experienced by women initially diagnosed with a potentially curable breast cancer can have if they are subsequently found to have a metastatic illness (Taylor, 2017). The TaP-MS findings reviewed previously highlight the importance of being sensitive to patients changing requirements, as well as to their wishes to be free from symptoms such as fatigue and being deprived of energy throughout all disease stages.

The quality of communication and information provision that exists between health care providers and service users with MS can be a critical determinate of how well such challenges, together with issues relating to understanding and adapting to prognostic information, are handled. One problem with quantitative research can be that pre-determined questions based on conventional medical models of disease are unlikely to reveal unanticipated issues.

Some investigations show relatively high levels of MS patient satisfaction regarding communication with doctors (see, for instance, Messina et al, 2015). But qualitative studies suggest the existence of complex and deep-rooted communication difficulties between health care professionals and people living with MS (Dennison et al, 2016). The discussion offered in Box 4 indicates that opportunities to investigate such problems and foster appropriate service improvements deserve more attention. Techniques employed in the TaP-MS study could in future be used to test communication quality linked hypotheses.

Good quality pharmaceutical care also requires high standards of communication and respect for patient preferences, coupled with expert knowledge of the pharmacological and other properties of existing and new therapies. Delivering pharmaceutical care well involves being sensitive to both direct and indirect warnings of unwanted drug interactions and side-effects as well as signs of renewed disease activity, and a commitment to providing whatever therapies best meet the needs of each individual at each point in their illness.

In the context of combining different forms of treatment, care and support as effectively possible, the available research shows that even in adjacent countries the service mixes offered to people with MS vary widely. For example, Sweden invests more in social care relative to health care than other nations; in Denmark people with MS appear to have an unusually high rate of specialist nurse contacts; in Germany people with MS see their neurologists more frequently than do other European MS patients; and in Hungary and Poland there are high rates of hospital admission (Kobelt et al, 2017).

Box 4. Opportunities for Better Communication

Because of the nature of MS as a fluctuating, progressive condition with varying symptoms and an uncertain course, good supportive communication between health and social care professionals and women and men with the condition has a special part to play in optimising outcomes. If PLwMS can be helped through challenges like those surrounding their initial diagnosis in ways that enable them to accept the disease with as little avoidable distress as possible and plan constructively for the future they are likely to enjoy a better quality of life than those who to 'blank out' awareness of their situation – see, for example, NICE (2014).

However, individuals with established ways of coping that involve 'blunting' (defined as flattening their responses via denial and other avoidance strategies) can find it very difficult to change their approaches. Those who constantly seek to be present focused and '*live for the day*' may see it as the most viable way forward in what they might otherwise experience as a hopeless situation. They might in practice prefer not to consider their likely future, even if when asked they say they want prognostic information.

The development of more reliable instruments for predicting the path of MS is therefore in some respects problematic. Insensitive communications could, even if well intended, do more harm than good. Awareness of this possibility might in turn discourage professional attempts to share knowledge and useful insights.

A qualitative study by Dennison et al (2017) on how people with MS experience prognostic uncertainty and acquire information about the likely course of their illness illustrates this dilemma. It found evidence that

although patients develop expectations about their disease trajectories they often do so with minimal input from health professionals. This can create ambiguous feelings. It might, even as new therapeutic options with improved capacities to prevent disease progression emerge, limit the development of enhanced treatment expectations and impede the optimal use of effective DMTs.

As noted in the main text, good communication and information provision practices involve using clear language while not 'talking down'; being open about the nature of MS and its variable course, while at the same time showing confident biomedical expertise; and spending enough time to ensure that the questions and concerns of individuals with MS are 'visibly listened to' and addressed empathetically. This requires the skills needed to assess the personal learning styles of each service user (for instance, 'blunters' may respond well to generalised information, while others want direct, fully personalised, messages) and craft communications appropriately.

On the service user side an understanding of the problems that talking in a fully engaged way about MS may present for both informal and formal carers should prove valuable. But for the purposes of this report the main point to emphasise is that as diagnostic, prognostic and therapeutic technologies go on improving there will be a continuing need to invest in high quality communication between people who have MS and their professional advisors and supporters. This will include developing and using instruments that reveal individuals' preferred ways of coping and exchanging confidences about their inner thoughts and experiences.

Alongside such variations there are dangers of 'siloes' service provisions and of inadequate levels of cross-national research into which patterns of service are likely to be affordable and most satisfactory from the patient/user viewpoint. It might be of global value, for instance, to people with MS if more medical and allied research were to be focused on evaluating the extent to which the forms of social care provided in Sweden influence health service use and the likelihood of patients with RRMS and other fluctuating disorders requiring emergency health care admissions during relapses. Understanding more about how cultural differences shape health and social care policies and public beliefs about the value of innovations in areas such as genetics and treating non-communicable disease could open the way to both enhanced well-being and efficiency gains.

Funding innovation aimed at resolving unmet needs

Despite the advances of recent years there are still many ways in which the technologies presently available for diagnosing and treating multiple sclerosis require improvement (Mehr and Zimmerman, 2015). In addition to the broad goals of disease prevention and finding more effective ways of halting or slowing MS progression, priorities range from developing better ways of countering fatigue to identifying new biomarkers for use in personalising therapeutic regimens and minimising the danger that treatments will cause iatrogenic harm. Advances are also needed in areas like improving the measurement of the functional and patient experienced outcomes of MS therapy provision, and in supporting adherence to patient agreed medication regimens.

It would be beyond the scope of this review to attempt to offer a technical evaluation of emergent opportunities for treating MS covering areas such as gene therapy and

immunotherapy¹⁴ or – as touched on in Box 2, page 8 – developing a vaccine that might prevent cases from occurring. But it is relevant to highlight two sets of points relating to the funding of health sector related research and development.

The complexity of the causes and impacts of multiple sclerosis is a good illustration of the fact that because much ‘low hanging biomedical fruit’ has already been picked the research challenges facing agencies such as Universities and pharmaceutical companies today are greater than in the past. They are also likely to be much more expensive to resolve than was the case in the twentieth century, partly because regulatory requirements were not as extensive then as they are today and partly because of the sophistication of the research methodologies now required.

Even if it were demonstrated that, for example, immunisation against Epstein-Barr virus infection could play an important future part in protecting children and young adults from MS, developing a vaccine approved for mass paediatric use might take several decades and cost more than a billion Euros or US Dollars. It is less than certain that trials could be conducted as safely as regulators would demand. But even if this barrier were to be overcome the financial risks involved would be very considerable. Alone, even the largest of private companies might be unwilling or unable to accept them.

It is possible that similar difficulties will be encountered if and when attempts are made to develop alternative ways forward, such as producing potentially curative immunotherapies for people with MS. The ‘moon-shot’ scale of the tasks and challenges involved suggests that new forms of Governmental and industrial collaboration may be required if public and patient expectations of a functional cure for conditions like MS are to be met by or before the middle of this century (European Commission, 2016; Bell, 2017).

Following on from this, some commentators fear the prices of new medicines are or will become unsustainably high and that assuring universal access to all in need is not possible. But from the viewpoint of people with MS and others wishing to see continuing therapeutic innovation in areas like neurology and immunology there are strong arguments in favour of building as constructively as possible on the existing IP (intellectual property) based model of ‘market funded’ private sector therapeutic innovation backed by publicly funded fundamental research. In this context it is relevant to record that:

- the overall proportion of health spending devoted to pharmaceutical outlays has been relatively stable in the OECD nations for several decades. Since the

economic crisis of 2008/9 it has in many instances fallen (OECD, 2015). Pharmaceutical spending is currently believed to account for about 15 per cent of the average OECD country’s health care costs (that is, around 1.5 per cent of GDP) although because of discounting this may be an over-estimate;

- key aspects of pharmaceutical sector economics include the fact that, as already alluded to, the prices of products like medicines normally fall significantly after they lose IP protection. It is also of note that in recent years increases in the average launch prices of innovative products have been offset by the fact that their volume sales are often lower than those of previous generations of novel pharmaceuticals; and
- as and when new biological science based methods of preventing or curing NCDs like MS become available the age-specific costs of health care will over time fall, despite the fact that all new products (from electronic goods to novel forms of transport) are relatively expensive at the point of market entry as compared with established technologies. Short term financial barriers to the use of beneficial innovations should not be permitted to unfairly delay less advantaged consumers’ access to them, or obscure the long term social and economic gains they will provide for entire communities.

These and allied observations indicate that supplying better treatments to all in need would be affordable with sufficient political will. One way or another research and development and the associated costs of ‘risk capital’ (that is, money invested in areas in which any one project has only a low chance of yielding returns) will have to be met if societies wish to benefit from ongoing bio-pharmaceutical and bio-medical advances. But the amounts involved are not prohibitively large, and will over time be counter-balanced by the economies generated by better health outcomes.

‘Patient led’ scientific and service development

People living with conditions like RRMS, SPMS and PPMS can offer unique insights into living with their disorders to professional and other audiences. The more that robustly appointed patient representatives are in a position to witness and influence how research and resource allocation decisions are made the more they should be able to prevent institutionalised injustices and protect national and global public interests in the prevention and alleviation of mental and physical disabilities and social handicaps. They can also play key roles in areas like promoting greater pharmaceutical literacy and informing public debate on issues such as understanding medicines side effects in ways that do not discourage their beneficial use.

Critics of patient involvement in areas such as the governance of clinical trials and the management of

¹⁴ Which might, for instance, eventually involve removing immune system cells from patients, enhancing their biological properties and then re-introducing them in the hope of eliminating MS.

health and social care sometimes question the expertise and objectivity of those living with conditions like MS. It may be claimed that inputs from patient groups and individuals with disabling conditions into policy debates can lead to decision making being distorted by ‘special pleading’. It might also be implied that patient groups that receive funding from sources like research based pharmaceutical companies are serving sectional ends. (See, for example, Arie and Mahoney, 2014.)

The opportunity cost of the latter could – assuming fixed health sector resource allocations – be that other groups with legitimate claims to better care suffer neglect. Transparency and managing conflicts of interest appropriately are therefore important. However, this is not to say that people with conditions such as MS should not press as robustly as possible for good care standards and ongoing research that could in future benefit the entire community. In response to concerns about accepting industry linked funding, advocates of better care might point out that accepting public funding can also carry risks should, for instance, it on occasions be associated with pressures to accept questionable limits on access to pharmaceutical or other forms of care.

The burdens imposed by multiple sclerosis on individuals and families are still not widely understood by many of those who come into contact with people living with the disease, even in the most economically advanced parts of the world. Nor – arguably – is the full potential of immunologically based and other forms of biomedical innovation to benefit humanity as a whole as widely appreciated as it ought to be.

The view taken here is that MS patient groups have, along with independent individuals working to make a difference, a vital role to play in correcting this situation and promoting better outcomes. Competent and well-motivated service user representation can also make valuable contributions in areas such as, say, establishing disease registries and the data bases needed for monitoring variations in diagnostic service performance and treatment outcomes.

Conflicts of interest of all types should be addressed whenever there is reason for fearing harm. This applies to everyone in society, from health professionals to economists, journalists and politicians. But awareness of this should not discourage advocacy groups from joining with other stakeholders with whom they share common interests to press for better support for people with MS. The fact that working to build greater service expectations might cause people with different priorities to ask critical questions when demands for further investment are successfully expressed is not a reason for patient groups to stop calling for the best possible health and social care.

Conclusion

Charles Dickens published *Great Expectations* at the start of 1860s, the decade in which in Paris Charcot conducted his pioneering work on multiple sclerosis. A core message of Dicken’s novel is that although it may be highly desirable to approach life with enthusiasm and hope, chance often leads to unfairness and injustice. Even for the most fortunate, early expectations are rarely fully realised.

The continuing burdens imposed on individuals who as adolescents or young adults develop MS are, 150 years after the era of Charcot and Dickens, a robust illustration of the truth of this insight into the human condition. Yet important therapeutic progress has recently been made, and further advances are to be expected as the twenty first century unfolds. Access to more effective treatments coupled with appropriate social and economic support can and should curb disease progression, prevent disabilities and improve the quality of life for people living with all forms of multiple sclerosis.

Such advances will also enhance the wellbeing of the partners, children, parents and other relatives of people living with MS. Thanks to the progress already achieved since the 1990s people living with MS in regions like Europe, North America and Australasia are now in a better position than ever before to enjoy their lives and play active parts in promoting ongoing improvements in their own treatment and care, as well as that of other members of society.

For individuals who already have established MS related disabilities the importance of disease modifying treatments alone should not be overstated. They need access not only to good quality pharmaceutical care capable of slowing or stopping the further progression of their illness but other forms of support aimed at providing them and their carers with an optimal quality of life. Yet as scientific and therapeutic developments continue people with early stage MS will be able to expect with increasing confidence a better future derived more exclusively from a growing capacity to control the fundamental biological mechanisms lying at the heart of the disorder.

Pharmaceutical and other advances against disabling conditions like MS ought also, in addition to their benefits for individuals, help make societies more equal, and everyone in them collectively less vulnerable to random misfortunes. Seen from this perspective improving MS prevention and developing better treatments should in the final analysis be regarded as everybody’s business, not just that of those most at risk of having their lives defined by a disease with which they have through no fault of theirs been obliged live.

References and Further Reading

- Acheson E. D., Bachrach C.A. and Wright F.M. (1960) Some comments on the relationship of the distribution of multiple sclerosis to latitude, solar radiation, and other variables. *Acta Psychiatrica Scandinavica supplement* 35, 132-147
- Airas L. (2015). Hormonal and gender-related immune changes in multiple sclerosis. *Acta Neurologica Scandinavica*, 132(199), 62-70. doi: 10.1111/ane.12433
- Aranow C. (2011) Vitamin D and the Immune System. *Journ Investigative Med* 59(6) 881-886
- Aranson K.J. (1997) Quality of life among persons with multiple sclerosis and their caregivers. *Neurology* 48(1), 74-80
- Arie S. and Mahony C. (2014) Should Patient Groups be More Transparent About their Funding? *British Med Journ* 349 doi: <https://doi.org/10.1136/bmj.g5892>
- Audit Commission (2001) A Spoonful of Sugar. London: The Audit Commission for England and Wales
- Ascherio, A., Munger K. L. et al. (2012). "The initiation and prevention of multiple sclerosis." *Nat Rev Neurol* 8(11): 602-612.
- Baker, L. M. (1996). A study of the nature of information needed by women with multiple sclerosis. *Library & Information Science Research*, 18(1), 67-81.
- Baker, L. M. (1998). Sense making in multiple sclerosis: the Information needs of people during an acute exacerbation. *Qualitative Health Research*, 8(1), 106-120.
- Bassi M., Falautano M., Cilia S et al (2016) Illness Perception and Well-being among Persons with Multiple Sclerosis and their Caregivers. *Journ Clin Psych in Med Settings* 23(1) 33-52
- Beatty W.W., Hames K.A., Bianco C.R. et al (1998) Correlates of coping style in patients with multiple sclerosis. *Multiple Sclerosis journal* 4(5), 440-443
- Bell J. (2017) Life Sciences: Industrial Strategy. London: Office for Life Sciences
- Boeije, H. R. and Janssens, A. C. J. (2004). 'It might happen or it might not': how patients with multiple sclerosis explain their perception of prognostic risk. *Social Science and Medicine*, 59(4), 861-868.
- Bogosian A., Moss-Morris R., Yardley L. and Dennison L. (2009). Experiences of the Partners of People in the Early Stages of Multiple Sclerosis. *Multiple Sclerosis Journal* 15(7), 876-884
- Bove, R., Alwan, S., Friedman, J. M. et al (2014). Management of multiple sclerosis during pregnancy and the reproductive years: a systematic review. *Obstetrics and Gynecology*, 124(6), 1157-1168.
- Bralley T. J. and Chervin R. D. (2010) Fatigue in Multiple Sclerosis: Mechanisms, Evaluation, and Treatment. *Sleep* 33(8) 1061-1067
- Bury M. (1982) Chronic Illness as biographical disruption. *Sociology of Health and Illness* 4(2) 167-182
- Bury M (2017) Personal communication
- CIB (2017). *Magnetic Resonance Imaging (MRI) Equipment, Operations and Planning in the NHS*. Available at https://www.rcr.ac.uk/sites/default/files/cib_mri_equipment_report.pdf Last accessed October 2017
- Compston, A. and Coles, A. (2008). Multiple sclerosis. *Lancet*, 372(9648), 1502-1517. doi: 10.1016/s0140-6736(08)61620-7
- Confavreux, C., Hutchinson, M., Hours, M. M., Cortinovis-Tourniaire, P., & Moreau, T. (1998). Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. *New England Journal of Medicine*, 339(5), 285-291. doi: 10.1056/nejm199807303390501
- Crayton, H., Heyman, R. A. and Rossman, H. S. (2004). A multimodal approach to managing the symptoms of multiple sclerosis. *Neurology*, 63(11 suppl 5), S12-S18.
- Dahlgren, G. and Whitehead, M. (1991) Policies and strategies to promote social equity in health, Stockholm: Institute of Futures Studies.
- Dahlgren G. and Whitehead M. (2006). European Strategies for Tackling Social Inequalities in Health – Levelling Up, Part II. Copenhagen: WHO Regional Office for Europe.
- Davenport C. (1922) Multiple sclerosis: From the standpoint of geographical distribution and race. *Arch Neurology and Psychiatry* 8, 51-58
- Daumer, M., Neuhaus, A., Lederer, C., Scholz, M. et al (2007). Prognosis of the individual course of disease-steps in developing a decision support tool for Multiple Sclerosis. *BMC Medical Informatics and Decision Making*, 7(1), 11.
- Degenhardt, A., Ramagopalan, S. V., Scalfari, A. and Ebers, G. C. (2009). Clinical prognostic factors in multiple sclerosis: a natural history review. *Nature Reviews: Neurology*, 5(12), 672-682. doi: 10.1038/nrneurol.2009.178
- Dennison, L., Smith, E. M., Bradbury, K., and Galea, I. (2016). How Do People with Multiple Sclerosis Experience Prognostic Uncertainty and Prognosis Communication? A Qualitative Study. *PLoS One*, 11(7). doi: 10.1371/journal.pone.0158982
- Devins, G. M., Edworthy, S. M., Klein, G. M. et al (1993). Differences in illness intrusiveness across rheumatoid arthritis, end-stage renal disease, and multiple sclerosis. *The Journal of nervous and mental disease*, 181(6), 377-381.
- D'hooghe, M. B., and Nagels, G. (2010). Long-term effects of childbirth in MS. *Journal of Neurology, Neurosurgery and Psychiatry*, 81(1), 38-41.
- Donze C., Lenne B., Deleglise J. et al (2016). EVASEP: A Noninterventional study Describing the Perceptions of Neurologists, Patients and Caregivers in Caregivers' Role in the Support of Patients Suffering from Multiple Sclerosis Treated with Subcutaneous Interferon Beta 1A. *Mult Scler Int* 4986073. doi: 10.1155/2016/4986073
- Elián, M. and Dean, G. (1985). To tell or not to tell the diagnosis of multiple sclerosis. *The Lancet*, 326(8445), 27-28.

- European Commission (2014). The Pharmaceutical Industry: A Strategic Sector for the European Economy. Commission staff working document. Brussels: the European Commission.
- Faasse, K., Grey, A., Horne R. and Petrie KJ 2015 High perceived sensitivity to medicines is associated with higher medical care utilisation, increased symptom reporting and greater information-seeking about medication. See comment in *PubMed Commons below Pharmacoeconomics and Drug Safety* 24(6):592-9. doi: 10.1002/pds.3751.
- Frohman, E. M., Stuve, O., Havrdova, E. et al (2006). Therapeutic considerations for disease progression in multiple sclerosis: evidence, experience, and future expectations. *Archives of Neurology*, 62(10), 1519-1530. doi: 10.1001/archneur.62.10.1519
- Giovannoni G., Butzkueven H., Dhib-Jalbut S et al (2015) Brain health: time matters in multiple sclerosis. Oxford: Oxford Pharmagenesis Ltd
- Goldin, C. and Katz, L. (2002) The Power of the Pill: Oral Contraceptives and Women's Career and Marriage Decisions. *Journal of Political Economy* 110, 730-770.
- Gourraud P.A., Harbo H.F., Hauser S.L. and Baranzini S. E. (2012). The genetics of multiple sclerosis: an up-to-date review. *Immunol Rev* 248(1):87-103. doi: 10.1111/j.1600-065X.2012.01134.
- Gottberg, K., Gardulf, A. and Fredrikson, S. (2000). Interferon-beta treatment for patients with multiple sclerosis: the patients' perceptions of the side-effects. *Multiple Sclerosis Journal*, 6(5), 349-354.
- Hafler D. A. (2004). Multiple Sclerosis. *J Clin Invest* 113(6):788-94
- Handel, A. E., Williamson A. J. et al. (2010). An updated meta-analysis of risk of multiple sclerosis following infectious mononucleosis. *PLoS ONE* 5(9).
- Harbo H.F., Gold R. and Tintoré M. (2013). Sex and gender issues in Multiple Sclerosis. *Ther Adv Neurol Disord.* 6(4): 237 – 248
- Hauser S.L., Bar-Or G., Comi G. et al (2017) Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *N Engl J Med* 376:221-34 doi: 10.1056/NEJMoa1601277
- Hawker, K., O'Connor, P., Freedman, M.S. et al (2009). Rituximab in patients with primary progressive multiple sclerosis: Results of a randomized double-blind placebo-controlled multicenter trial. See comment in *PubMed Commons below Ann Neurol.* 66(4):460-71. doi: 10.1002/ana.21867
- Heesen, C., Böhm, J., Reich, C. et al (2008). Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable. *Multiple Sclerosis* 14(7):988-91. doi: 10.1177/1352458508088916.
- Heesen, C., Kasper, J., Segal, J. et al (2004). Decisional role preferences, risk knowledge and information interests in patients with multiple sclerosis. *Multiple Sclerosis Journal*, 10(6), 643-650.
- Heesen, C., Böhm, J., Reich, C. et al (2008). Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable. *Multiple Sclerosis*.
- Heesen, C., Kleiter, I., Nguyen, F. et al. (2010). Risk perception in natalizumab-treated multiple sclerosis patients and their neurologists. *Multiple Sclerosis Journal*, 16(12), 1507-1512.
- ICER (2017). Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value. Institute for Clinical and Economic Review
- Isaaksson, A. K. (2006). From symptom to diagnosis: illness experiences of multiple sclerosis patients. *The Journal of neuroscience nursing*, 38(4), 229.
- Janssens, A., De Boer, J., Van Doorn, P. et al (2003). Expectations of wheelchair dependency in recently diagnosed patients with multiple sclerosis and their partners. *European Journal of Neurology*, 10(3), 287-293.
- Janssens, A. C. J., van Doorn, P. A., de Boer, J. B. et al (2004). Perception of prognostic risk in patients with multiple sclerosis: the relationship with anxiety, depression, and disease-related distress. *Journal of Clinical Epidemiology*, 57(2), 180-186.
- Johnson, J. (2003). On receiving the diagnosis of multiple sclerosis: managing the transition. *Multiple Sclerosis*, 9(1), 82-88. doi: 10.1191/1352458503ms856oa
- Johnson, F. R., Van Houtven, G., Özdemir, S. et al (2009). Multiple sclerosis patients—benefit-risk preferences: serious adverse event risks versus treatment efficacy. *Journal of Neurology*, 256(4), 554.
- Kanavos P., Tinelli M., Efthymiadou O. et al (2016) The International MultiPIE Sclerosis Study (IMPRESS). London: The London School of Economics
- Kasper, J., Köpke, S., Mühlhauser, I. and Heesen, C. (2006). Evidence-based patient information about treatment of multiple sclerosis—a phase one study on comprehension and emotional responses. *Patient Education and Counseling*, 62(1), 56-63.
- Kobelt G., Thompson A., Berg J et al (2016). New insights into the burden and costs of multiple sclerosis in Europe. *Multiple Sclerosis* 23(8):1123-1136. doi: 10.1177/1352458517694432
- Koch-Henriksen N. and Soelberg Sorensen P. (2010) The changing demographic pattern of multiple sclerosis epidemiology. *Lancet Neurol* 9 520-532
- Köpke, S., Solari, A., Khan, F., Heesen, C., & Giordano, A. (2014). Information provision for people with multiple sclerosis. *The Cochrane Library*.
- Kumar D.R., Aslinia F., Yale S.H. and Mazza J.J. (2011) Jean-Martin Charcot: The Father of Neurology. *Clin Med Res* 9(1): 46 – 49.
- Lebrun, C., Le Page, E., Kantarci, O. et al (2012). Impact of pregnancy on conversion to clinically isolated syndrome in a radiologically isolated syndrome cohort. *Multiple Sclerosis Journal*, 18(9), 1297-1302.
- Lublin, F. D. and Reingold, S. C. (1996). Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology*, 46(4), 907-911.

- Lucchin, F. D., Reingold, S. C., Cohen, J. A. et al (2013) Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*, 83(3), 278-286. doi: 10.1212/WNL.0000000000000560
- Maslow A. H. (1943). A theory of human motivation. *Psychological Review*. **50** (4): 370 – 96. doi: 10.1037/h0054346
- Mehr S. R. and Zimmerman, M. P. (2015). Reviewing the Unmet Needs of Patients with Multiple Sclerosis. *Am Health Drug Benefits*, 8(8), 426-431.
- Messina, M. J., Dalla Costa, G., Rodegher, M. et al (2015). The Communication of Multiple Sclerosis Diagnosis: The Patients' Perspective. *Mult Scler Int*, 2015, 353828. doi: 10.1155/2015/353828
- Milner J.J. and Beck M.A. (2012) The impact of obesity on the immune response to infection. *Proc Nutr Soc* 71(2):298-306. doi: 10.1017/S0029665112000158
- Mitchell, A. J., Benito-León, J., González, J.-M. M. and Rivera-Navarro, J. (2005). Quality of life and its assessment in multiple sclerosis: integrating physical and psychological components of wellbeing. *The Lancet Neurology*, 4(9), 556-566.
- Mohr, D., Goodkin, D., Likosk, W. et al. (1996). Therapeutic expectations of patients with multiple sclerosis upon initiating interferon beta-1b: Relationship to adherence to treatment. *Multiple Sclerosis Journal*, 2(5), 222-226.
- Montalban X., Houser S.L. et al (2017). Ocrelizumab versus placebo in Primary Progressive Multiple Sclerosis. *N Engl J Med* 376:209-220 DOI: 10.1056/NEJMoa1606468
- Moutsianas, L., Jostins L. et al. (2015). Class II HLA interactions modulate genetic risk for multiple sclerosis. *Nat Genet* 47(10): 1107-1113.
- MSIF (2013). Atlas of Multiple Sclerosis. Available at <https://www.msif.org/about-us/advocacy/atlas/> Last accessed September 2017
- MST (2016) Risks of Developing Multiple Sclerosis. Available at <https://www.mstrust.org.uk/a-z/risk-developing-ms> Last accessed October 2017
- Munger K.L., Levin L.I et al (2011). Anti-Epstein-Barr virus antibodies as serological markers of multiple sclerosis: a prospective study among United States military personnel. *Mult Scler* 17(10):1185-93. doi: 10.1177/1352458511408991
- Munger K. L., Hongell K., Aivo J. et al (2017) 25-Hydroxyvitamin D deficiency and risk of MS among women in the Finnish Maternity Cohort. *Neurology* 89:1 – 6
- Münz, C., Lünemann J. D. et al. (2009). Antiviral immune responses: triggers of or triggered by autoimmunity? *Nat Rev Immunol* **9**(4): 246-258.
- Münz C. (2016). Personal communication
- Murphy Miller C. (1997). The lived experience of relapsing multiple sclerosis: a phenomenological study. *Journal of Neuroscience Nursing*, 29(5), 291-304
- Myhr K., Riise T., Vedeler C et al (2001). Disability and Prognosis in Multiple Sclerosis: demographic and clinical variables important for the ability to walk and awarding of disability pensions. *Multiple Sclerosis Journal* 7(1) 59-65
- National Multiple Sclerosis Society (2017). Functional Systems Scores (FSS) and Expanded Disability Status Scale (EDSS). Available at: [https://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Functional-Systems-Scores-\(FSS\)-and-Expanded-Disab](https://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Functional-Systems-Scores-(FSS)-and-Expanded-Disab) Last retrieved September 2017
- Naito, S., Namerow, N., Mickey, M.R. and Terasaki P.I.(1972). Multiple sclerosis: association with HL-A3. *Tissue Antigens* 2(1):1-4
- Nielsen T.R., Rostgaard K. et al (2007) "Multiple sclerosis after infectious mononucleosis." *Arch Neurol* **64**(1): 72-75
- Nielsen T., Rostgaard K. et al. (2009). Effects of infectious mononucleosis and HLA-DRB1*15 in multiple sclerosis. *Mult Scler* **15**(4):431-6.
- O'Connor P., Detsky A.S., Tansey C. and Kucharczyk W. (1994) Effect of diagnostic testing for multiple sclerosis on patient health perceptions. *Archives of Neurology* 51(1) 46-51
- OECD (2015). *Health at a Glance 2015: OECD Indicators*. Paris: OECD Publishing.
- OECD (2016). *Health at a Glance 2016: OECD Indicators*. Paris: OECD Publishing.
- Olsson, T., Barcellos L. F. et al. (2017). Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nat Rev Neurol* **13**(1): 25-36.
- O'Gorman C., Lucas R. and Taylor B. (2012) Environmental Risk Factors for Multiple Sclerosis: A Review with a Focus on Molecular Mechanisms. *Int Journal of Mol Science* 13, 11718-11752
- O'Rourke, K. E., & Hutchinson, M. (2005). Stopping beta-interferon therapy in multiple sclerosis: an analysis of stopping patterns. *Multiple Sclerosis Journal*, 11(1), 46-50.
- Pakenham, K. I. (1999). Adjustment to multiple sclerosis: Application of a stress and coping model. *Health Psychology*, 18(4), 383
- Pender, M.P. and Burrows, S.R. (2014) Epstein – Barr virus and multiple sclerosis: potential opportunities for immunotherapy. *Clin Trans Immunology* 31, 3(10) e27 doi: 10.1038/cti.2014.25
- Peterson, E. W., Cho, C. C., & Finlayson, M. L. (2007). Fear of falling and associated activity curtailment among middle aged and older adults with multiple sclerosis. *Multiple Sclerosis Journal*, 13(9), 1168-1175.
- Pietrangolo, A. and Higuera, V. (2015) Multiple Sclerosis by the Numbers: Facts, Statistics, and You. Healthline. <https://www.healthline.com/health/multiple-sclerosis/facts-statistics-infographic> Last accessed October 2017
- Polman, C. H., Reingold, S. C., Banwell, B. et al (2011). Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of Neurology*, 69(2), 292-302.

- Prosser L.A., Kuntz K.M., Bar-Or A. and Weinstein M.C. (2002). The relationship between risk attitude and treatment choice in patients with relapsing-remitting multiple sclerosis. *Med Decis Making* 22(6):506-13
- Rennie T. (2017) Personal communication
- Rothwell, P. M., McDowell, Z., Wong, C. and Dorman, P. (1997). Doctors and patients don't agree: cross sectional study of patients' and doctors' perceptions and assessments of disability in multiple sclerosis. *BMJ*, 314(7094), 1580.
- Rotstein D.L., Healy B.C., Malik M.T. et al (2015) Effect of vitamin D on MS activity by disease-modifying therapy class. See comment in PubMed Commons below *Neurol, Neuroimmunol and Neuroinflamm* 29;2(6):e167. doi: 10.1212/NXI.0000000000000167
- Russell, W. R. (1971). Multiple sclerosis: occupation and social group at onset. *The Lancet*, 298(7729), 832-834
- Salzer J., Svenningsson R., Alping P et al (2016). Rituximab in multiple sclerosis: A retrospective observational study on safety and efficacy. *Neurology* 15; 87(20): 2074-
- Saposnik G., Sempere A. P., Raptis R. et al (2016). Decision making under uncertainty, therapeutic inertia, and physicians' risk preferences in the management of multiple sclerosis (DIScUTIR MS). *BMC Neurology*, 16, 58. doi: 10.1186/s12883-016-0577-42081
- Sawcer S., Hellenthal G. et al. (2011). Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature* 476(7359): 214-219.
- Schreiner T.L. and Waubant E.L., 2015 Pediatric Multiple Sclerosis. *Medscape*
<http://emedicine.medscape.com/article/2091406-overview>
 Last retrieved September 2017
- Sellner, J., Kraus, J., Awad, A. et al (2011). The increasing incidence and prevalence of female multiple sclerosis—a critical analysis of potential environmental factors. *Autoimmunity reviews*, 10(8), 495-502.
- Simmons, R. D. (2010). Life issues in multiple sclerosis. *Nature Reviews Neurology*, 6(11), 603-610.
- Solari, A. (2014). Effective communication at the point of multiple sclerosis diagnosis. *Multiple Sclerosis Journal*, 20(4), 397-402.
- Soundy, A., Benson, J., Dawes, H. et al (2012). Understanding hope in patients with Multiple Sclerosis. *Physiotherapy*, 98(4), 344-350.
- Strautins, K., Tschochner M. et al. (2014). Combining HLA-DR risk alleles and anti-Epstein-Barr virus antibody profiles to stratify multiple sclerosis risk. *Mult Scler* 20(3): 286-294.
- Sundqvist, E., Sundstrom P. et al. (2012). Epstein-Barr virus and multiple sclerosis: interaction with HLA. *Genes Immun* 13(1): 14-20.
- Synnot, A. J., Hill, S. J., Garner, K. A. et al (2016). Online health information seeking: how people with multiple sclerosis find, assess and integrate treatment information to manage their health. *Health Expectations*, 19(3), 727-737.
- Taylor D.G. (2002) Funding Medicines for People with Multiple Sclerosis. *British Medical Journal* 2001; 322: 1379-80
- Taylor D.G (2016) Affording the Future? London: the UCL School of Pharmacy. Available at <https://www.ucl.ac.uk/pharmacy/departments/practice-policy/affording-the-future.pdf> Last retrieved September 2017
- Taylor D.G. (2017) The Reality of Economics for Oncologists. *Breast*. See comment in PubMed Commons below 33:183-190. doi: 10.1016/j.breast.2017.03.014
- Thorne S., Con, A., McGuinness, L., McPherson, G., & Harris, S. R. (2004). Health care communication issues in multiple sclerosis: an interpretive description. *Qualitative Health Research*, 14(1), 5-22.
- Tintore M., Rovira, A., Rio, J. et al (2015). Defining high, medium and low impact prognostic factors for developing multiple sclerosis. *Brain*, 138(Pt 7), 1863-1874. doi: 10.1093/brain/awv105
- Tintore M., Alexander, M., Costello, K. et al (2017). The state of multiple sclerosis: current insight into the patient/health care provider relationship, treatment challenges and satisfaction. *Patient Prefer Adherence* 11, 33-45. doi: 10.2147/ppa.s115090
- UNCRDP (2016) *Inquiry concerning the United Kingdom of Great Britain and Northern Ireland carried out by the Committee under article 6 of the Optional Protocol to the Convention: Report of the Committee*. Available at <http://www.ohchr.org/EN/HRBodies/CRPD/Pages/InquiryProcedure.aspx> Last retrieved September 2017
- Weinshenker, B. G., Bass, B. et al (1989). The natural history of multiple sclerosis: a geographically based study: I. Clinical course and disability. *Brain*, 112(1), 133-146.
- Whitehead L.C., Unahi K., Burrell B. and Crowe M.T. (2016). The Experience of Fatigue Across Long-Term Conditions: A Qualitative Meta-Synthesis. *Journal of Pain Symptom Management*. 52(1):131-143.e1. doi: 10.1016/j.jpainsymman.2016.02.013.
- Wilsden T., Barron A., Mitchell-Heggs A. and Ginoza S. (2014). Access to Medicines for Multiple Sclerosis: Challenges and Opportunities. London: Charles Rivers Associates
- Wood P (1980) The language of disablement: A glossary relating to disease and its consequences. *Int Rehabil Med* 2:86-92
- WHO (1980). International Classification of Impairments, Disabilities and Handicaps. Geneva: the World Health Organisation
- Zivadinov, R., Zorzon, M., Tommasi, M. A. et al (2003). A longitudinal study of quality of life and side effects in patients with multiple sclerosis treated with interferon beta-1a. *Journal of the Neurological Sciences*, 216(1), 113-118.

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