**Introduction**

Multiple sclerosis (MS) is a chronic inflammatory disease that is characterized by progressive demyelination and neuronal loss within the CNS, leading to numerous physical and mental symptoms [1,2]. The first clear description of the disease as "a remarkable lesion of the spinal cord accompanied with atrophy" was defined by the English physician and pathologist Robert Carswell in 1838 [3]. A more complete account was presented by the French neurologist Jean-Martin Charcot in an 1868 lecture when he described a young woman with an unusual tremor, slurred speech and abnormal eye movements. Her brain was examined post-mortem and multiple scars or 'plaques' were observed that are now characteristic of MS, and these symptoms were attributable to a loss of myelin. Charcot was baffled, however, by the cause of this demyelinating disease and was frustrated by its resistance to treatment attempts, which included electrical stimulation, strychnine administration and injections of both gold and silver [4].

Currently, the cause of MS remains unknown, but knowledge of the pathophysiology of this disease has increased substantially, leading to improvements in available pharmacotherapies. Progress in understanding the pathophysiology of MS and the prospects for new therapeutics are discussed in this review.

**Multiple sclerosis**

The global incidence and prevalence of MS is estimated to be 2.5 and 30 per 100,000 individuals, respectively [5]. The US National MS Society estimates that there are approximately 2.5 million individuals with MS worldwide [6] but, as there is no requirement for physicians to report new cases and because individuals with MS can be asymptomatic for a prolonged period, this total probably substantially underestimates the true number of individuals with MS. Furthermore, MS most commonly manifests in individuals in their late twenties, meaning that the magnitude of the disease burden, measured in terms of the number of working days lost, is high [7]. The disease is more than twice as common in females as it is in males; this gender selectivity has increased over the past five decades [8]. MS was historically considered more prevalent in high latitude countries, but more recent analyses suggest that this discrepancy is either declining [8] or has disappeared [9], possibly because of a reduction in the geographic variability of diagnostic acuity.

MS manifests itself through a variety of neurological symptoms and disabilities that follow different patterns of evolution and variable rates of accumulation. Initially, the symptoms are often transient, but become increasingly permanent with disease progression. Symptoms include changes in sensation (numbness and reduced sensitivity), muscle weakness, muscle spasms (anywhere throughout the body, but often in the limbs) or difficulty moving, difficulties with coordination and balance, problems with speech or swallowing, visual problems, fatigue and pain (both acute and chronic), and bladder and bowel difficulties. Other features of MS include cognitive impairment of varying extent, as well as depression, probably mainly in response to the uncertainties and restrictions imposed by a progressive, disabling illness [2]. The first clinical measure of disability progression and symptom severity, the Disability Status Scale (which includes 11 grades, from 0 to 10), was developed in 1955 [10]. This scale was further expanded in 1983, by dividing each grade into...
two to increase the sensitivity, to create the 21-grade Expanded Disability Status Scale (EDSS), which is currently the only scale recognized by regulatory agencies [11]; however, the EDSS has numerous disadvantages, including poor reproducibility [12] and a strong reliance upon ambulation, which means that the scale does not adequately assess upper limb function or cognitive decline [11].

In response to the shortcomings of the EDSS, the MS functional composite (MSFC) scale was developed by the National Multiple Sclerosis Society’s Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis in 1999 [13]. This scale encompasses functional measurements of the major clinical dimensions of arm, leg and cognition. The MSFC comprises three objective quantitative tests of neurological function that are easy to administer: a timed 25-foot walk (ambulation), a 9-hole peg test (arm function) and a paced auditory serial addition test (cognitive function). The MSFC has been suggested to be more sensitive than the EDSS, with a change in MSFC score over the first year of observation demonstrated to be predictive of subsequent changes in the EDSS [13]. Several other clinical outcome measures have also been proposed, including measures of visual function and health-related quality of life [11,14].

In the evaluation of MS, clinical data are necessary, but these data are not always sufficient for a diagnosis. The current paradigm for disease diagnosis is based on the McDonald criteria, which were agreed internationally in 2001, and require the dissemination of MS lesions over both time and space [15]. The most commonly used diagnostic tools are neuroimaging, analysis of CSF and evoked potentials. MRI of the brain and spine can reveal areas of demyelination (lesions or plaques), which can be enhanced by the intravenous administration of gadolinium that highlights areas of inflammation and breakdown of the blood-brain barrier. MRI visualizes focal or confluent abnormalities in the white matter of more than 95% of individuals with MS, as determined in a study to evaluate the use of MRI in diagnosing MS in individuals with suspected MS [16]. The McDonald criteria were further refined in 2005 to strengthen the role of MRI imaging in the diagnosis of MS [17].

The use of MRI has revolutionized the diagnosis and management of MS, and this test is now routinely used as the primary endpoint in proof-of-concept clinical trials evaluating potential new drugs for MS, and as the secondary endpoint in definitive phase III trials. MRI has yet to gain approval for use as a surrogate endpoint for the accumulation of physical disability, largely because plaque load correlates poorly with disability [18]. The poor correlation may be attributed to the limited specificity that MRI currently has for the underlying histopathology of MS or because many MS lesions are silent, meaning that these lesions do not cause clinically detectable symptoms. Advances in MRI methodology have provided more robust methods for the evaluation of disease status with improved sensitivity by combining assessment of MRI lesions with measures of brain atrophy [19]. Both brain and spinal cord atrophy is emerging as a useful measure of disease progression, particularly in secondary progressive MS (SP-MS) [19], leading to the prospect of new diagnostic scales that combine data on brain lesions using MRI with atrophy measures to better predict clinical progression in MS [20], in particular global and specific cognitive impairment [21], along with enhanced diagnostic accuracy and precision [22].

The earliest presentation of MS, which includes 80% of all patients, is the clinically isolated syndrome (CIS), in which MRI detects white matter abnormalities, but there is insufficient evidence for a definitive diagnosis [23]. Most patients with CIS progress to a full MS diagnosis: 80% of patients after 20 years [24,25]. The symptoms of MS usually appear in episodic acute periods (relapses or exacerbations), and most individuals in this relapsing-remitting stage (RR-MS) encounter a progressive deterioration of neurological function. A substantial minority of MS sufferers (20%) have no periods of remission and the disease worsens gradually from onset, known as primary progressive MS (PP-MS) [26]. Both PP-MS and SP-MS forms typically begin at approximately the age of 40 and often manifest as spinal disease (Figure 1) [27]. These different forms of MS likely reflect different clinical phenotypes of a unitary disease, with RR-MS reflecting a phenotype that has not had sufficient time for conversion to SP-MS [28].

Although the etiology of MS remains unknown, it is understood that MS must result from interactions between genetic and exogenous factors. While genetics shape the overall susceptibility of an individual to MS, observed epidemiological patterns suggest a role for the environment in the initiation and modulation of the disease. The MHC, the most gene-dense region of the mammalian genome, has a key role in immune function and autoimmunity, and is the only genomic region consistently associated with MS, particularly the HLA sub-region, specifically with SNP markers for the IL-2 and IL-7 receptors α chains [1,29]. Environmental factors that have been implicated include both infectious agents, such as the Epstein-Barr virus, and non-infectious agents, such as vitamin D [30-34].

A key event in the pathophysiology of MS is the increased migration of T-lymphocytes across the blood-brain barrier into the brain, spinal cord or both [35]. The process begins when endothelial adhesion molecules of the selectin family interact with carbohydrate motifs on lymphocytes; this interaction leads the lymphocytes to roll along the vascular wall, allowing the cells to be tethered via chemotactic factors on the endothelial surface. Chemokines then bind to serpentine receptors on the lymphocytes, which stimulates α4β1 integrin (very late antigen-4 [VLA-4]) and thus increases the avidity of α4β1 integrin for receptors, such as vascular cell adhesion molecule-1 (VCAM-1) and the CS-1 (alternative cell attachment) domain of fibronectin. Once securely anchored to the vascular endothelium, the lymphocytes can move through tiny spaces in the
endothelium into the CNS interstitial fluid [36,37]. The activation of these lymphocyte cells by MS auto-antigens leads to an error in the education of the lymphocytes, which renders these cells unable to distinguish self from non-self. Specifically, CD4+, CD8+ and CD25+ T-cells mistake molecules in the body’s own myelin for foreign antigens, beginning an immune response involving the release of B-lymphocytes, to rid the body of the perceived threat [38]. The B-lymphocytes begin to produce and release antibodies against myelin proteins, such as proteolipid protein and myelin basic protein (MBP), resulting in demyelination. This auto-antibody response is accompanied by the secretion of molecules, particularly cytokines and complement factors, that signal proteins and other immune cells to gather at the site of damage. The convergence of this immune response on the affected area causes the tissue to become inflamed. Under normal conditions, the inflammatory process is controlled and self-limiting, but in MS the process persists and damage occurs in the surrounding tissues. Important proinflammatory cytokines in MS appear to be TNFα, IL-12 and IFNγ, which are considered central to MS pathogenesis [39,40].

In addition to the breakdown of immune tolerance, and the subsequent self-directed inflammatory change leading to myelin loss, it is understood that neurodegenerative changes, principally the loss of neurons and their axons, also occur, causing a permanent, non-remitting loss of neurological function [41,42]. The temporal and causal relationships between the neuroinflammatory and neurodegenerative components of the disease are not yet clear [43].

Current drugs for multiple sclerosis
The current pharmacotherapy for MS is summarized in Tables 1 and 2, and is dominated by recombinant forms of β-interferon. Betaseron and Avonex were introduced in the mid-1990s, followed by Rebif in 2002 [44]. A review of clinical trial data from patients with RR-MS demonstrated that the clinical effect of β-interferons after the first year of treatment is unclear [45]. Similarly, a meta-analysis of glatiramer acetate (Copaxone), which is a random polymer composed of four amino acids that are present in MBP, demonstrated that this drug did not exhibit any beneficial effect on the main outcome measures in MS, nor did the drug substantially affect the risk of clinical relapses [46]. However, a further review of the clinical trial literature established that both the interferons and glatiramer acetate significantly delayed the conversion from CIS to clinically definite MS [47,48].

An additional review of clinical studies demonstrated that the immunosuppressant mitoxantrone (Novantrone) has clinical effectiveness in both worsening RR-MS and SP-MS [49,50]. However, toxic side effects have restricted the use of mitoxantrone to patients with evidence of worsening disability, and exposure has been carefully controlled and severely limited [49].

A more recently developed immunomodulatory drug is natalizumab (Tysabri), a humanized mAb targeted against α4β1 integrin, that blocks the endothelial transmigration of lymphocytes into the CNS [51]. In two phase III clinical trials, natalizumab reduced relapses to a similar, if not greater, extent as β-interferon and also slowed the progression of disability in individuals with RR-MS [52,53]. Natalizumab was approved in 2004 for the first-line treatment of patients with ‘aggressive’ MS (with frequent exacerbations) and for second-line treatment in other patients with MS after the failure of β-interferon therapies; however, since the launch of this drug, six patients who received natalizumab acquired a human polyomavirus JC infection and were diagnosed with progressive multifocal leukoencephalopathy (PML), a rare and usually fatal viral
disease (two of the six individuals subsequently died) that is characterized by progressive damage to the white matter of the brain [54]. These adverse events led to the voluntary withdrawal of natalizumab from the market in 2005, but because PML was only observed in patients receiving natalizumab in combination with Avonex, approval

<table>
<thead>
<tr>
<th>Table 1. Current drugs for the treatment of multiple sclerosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-interferon</strong></td>
</tr>
<tr>
<td>Molecule</td>
</tr>
<tr>
<td>Rate of relapse</td>
</tr>
<tr>
<td>Effect on disability progression</td>
</tr>
<tr>
<td>Change in MRI lesions</td>
</tr>
<tr>
<td>Side effects</td>
</tr>
<tr>
<td>Neutralizing antibodies detected</td>
</tr>
<tr>
<td>Target patient group</td>
</tr>
<tr>
<td>Effect on progressive MS</td>
</tr>
<tr>
<td>Reference</td>
</tr>
</tbody>
</table>

MS multiple sclerosis, RR-MS Relapsing-remitting MS, SP-MS secondary-progressive MS

<table>
<thead>
<tr>
<th>Table 2. FDA-approved drugs for the treatment of multiple sclerosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug (Trade name)</strong></td>
</tr>
<tr>
<td>β-interferon 1b (Betaseron)</td>
</tr>
<tr>
<td>β-interferon 1a (Avonex)</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)</td>
</tr>
<tr>
<td>Mitoxantrone (Novantron)</td>
</tr>
<tr>
<td>β-interferon (Rebif)</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
</tr>
</tbody>
</table>

Information for this table was obtained from reference [100]
was granted for the reintroduction of natalizumab as a monotherapy for highly active RR-MS in 2006. However, the subsequent emergence of new cases of PML in patients receiving natalizumab alone casts further doubt on the risk/benefit ratio of this antibody therapy [55]. Several small-molecule antagonists of α4β1 integrin are in development that inhibit leukocyte trafficking and may demonstrate a better risk/benefit profile than natalizumab [56].

Emerging drugs for multiple sclerosis
MS has become a major area of interest for pharmaceutical companies and there are a number of drug candidates in the pipeline [57-62], which are summarized in the following sections.

Anti-inflammatory approaches
There are many drug candidates that have attenuated the inflammatory response of MS in phase II and III clinical trials (Table 3). Targeting particular aspects of the inflammatory cascade using mAbs (an approach pioneered by natalizumab) is a prominent strategy, and mAb candidates are discussed in the following subsections.

Alemtuzumab
Alemtuzumab (Campath) is a recombinant humanized mAb that targets CD52, a glycoprotein present on the surface of mature lymphocytes and monocytes. Alemtuzumab reduced the rate of sustained accumulation of disability compared with β-interferon in a phase II clinical trial of patients with early RR-MS [63]. This therapy is currently being investigated by Bayer Schering Pharma AG and Genzyme Corp in two phase III trials for patients with MS (Clinicaltrials.gov identifiers: NCT00530348 and NCT00548405), and has been approved for use in patients with B-cell chronic lymphocytic leukemia [64].

Rituximab
Rituximab is murine/human chimeric anti-CD20 mAb that binds to the CD20 protein, which is widely expressed on B-cells, but is absent from terminally differentiated plasma cells. This drug has been demonstrated to reduce inflammatory brain lesions and clinical relapses in patients with RR-MS in phase I and II clinical trials by Genentech Inc [65,66] but, similar to natalizumab, has been associated with PML [54].

Daclizumab
Daclizumab is a humanized antibody targeting the α-subunit (CD25) of the IL-2 receptor, preventing normal IL-2 binding to this receptor, which is expressed on the surface of activated lymphocytes. Biogen Idec Inc and Facet Biotech Corp investigated daclizumab in a small phase II clinical trial. It was demonstrated that daclizumab reduced lesion load and improved clinical scores (including EDSS) in patients (n = 9) with active RR-MS not controlled by interferon therapy [67]. A second, small phase II trial also demonstrated efficacy in reducing the number of contrast-enhanced lesions detected with MRI, though systemic adverse effects were observed in two patients [68]. Daclizumab had been launched for the treatment of acute organ transplant rejection; however, Roche voluntarily withdrew its marketing authorization for the drug and, in June 2008, the European Commission withdrew marketing authorization for the drug for acute organ transplant rejection [69].

Targeting multiple sclerosis using NCEs
In addition to antibody therapies, there are a number of NCEs that target key points in the immunopathogenic cascade associated with MS.

Fingolimod
Fingolimod (FTY-720; Mitsubishi Tanabe Pharma Corp/Novartis AG) is a novel immunosuppressant drug that causes an abnormally low level of lymphocytes in the blood (lymphopenia) by preventing egress of lymphocytes from lymph nodes through modulation of the sphingosine-1-phosphate receptor 1 (SIP-1). Fingolimod is currently undergoing phase III clinical trials in patients with PP-MS and RR-MS (ClinicalTrials.gov identifiers: NCT00731692, NCT00340834, NCT00355134, NCT00340834 and NCT00289978), having demonstrated evidence of efficacy (measured as relapse rates and lesion activity visualized by MRI) in a phase II trial [70].

Laquinimod
Laquinimod (Active Biotech AB/Teva Pharmaceuticals Industries Ltd) is a once-daily, oral immunomodulator. In a phase II clinical trials, laquinimod reduced the formation of active lesions compared with placebo in patients with RR-MS, as assessed by MRI, in phase II clinical trials [71,72]. This drug is currently undergoing phase III trials in patients with RR-MS (ClinicalTrials identifiers: NCT00509145 and NCT00605215), and was awarded Fast Track status by the US FDA in February 2009 for RR-MS [73].

Dimethyl fumarate
Dimethyl fumarate (BG-00012, BG-12; Biogen Idec Inc) is a methylated tricarboxylic acid cycle intermediate that reduced the formation of new lesions in phase II clinical trials which was monitored using MRI of patients undergoing phase III clinical trials in patients with RR-MS when administered orally three times daily [74,75]. In January 2007, a phase III trial program consisting of two randomized, double-blind, dose-comparison, 2-year studies was initiated in patients with RR-MS (ClinicalTrials.gov identifiers: NCT00420212 and NCT00451451).

Teriflunomide
Teriflunomide (sanofi-aventis), a dihydroorotate dehydrogenase (an enzyme involved in the synthesis of pyrimidine) and tyrosine kinase inhibitor, was advanced to phase III clinical trials for RR-MS on the basis of efficacy in experimental autoimmune encephalomyelitis (EAE) models and phase II trials, in which significantly fewer patients receiving teriflunomide demonstrated an increase in disability compared with patients receiving placebo [76,77].

Cladribine
Cladribine (2-chlorodeoxyadenosine; Merck Serono SA) is a purine analog that inhibits the enzyme adenosine-
<table>
<thead>
<tr>
<th>Therapeutic</th>
<th>Developer for MS</th>
<th>Type of therapy</th>
<th>Development stage for MS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teriflunomide</td>
<td>sanofi-aventis</td>
<td>Orally active dihydroorotate dehydrogenase and tyrosine kinase inhibitor that acts by blocking pyrimidine synthesis.</td>
<td>Phase III</td>
<td>(ClinicalTrials.gov identifiers: NCT00662700, NCT00751881, NCT00803049 and NCT00883337)</td>
</tr>
<tr>
<td>Laquinimod</td>
<td>Active Biotech AB/ Teva Pharmaceutical Industries Ltd</td>
<td>A selective immunosuppressant.</td>
<td>Phase III</td>
<td>[71] (ClinicalTrials.gov identifiers: NCT00509145 and NCT00548405)</td>
</tr>
<tr>
<td>Dirucotide (MBP-8298)</td>
<td>BioMS Medical Corp/ Eli Lilly &amp; Co</td>
<td>A synthetic MBP peptide analog comprised of 17 amino acids.</td>
<td>Phase III</td>
<td>[86]</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Bayer Schering Pharma AG/Genzyme Corp</td>
<td>A humanized mAb that specifically binds to CD52 on the surface of most cells, leading the immune system to destroy malignant cells.</td>
<td>Phase III</td>
<td>(ClinicalTrials.gov identifiers: NCT00530348 and NCT00548405)</td>
</tr>
<tr>
<td>Dimethyl fumarate (BG-12/ BG-00012)</td>
<td>Biogen Idec Inc</td>
<td>Activates the Nrf2 transcriptional pathway, and is claimed to defend against oxidative-stress induced neuronal death, protect the blood-brain barrier and support myelin integrity in the CNS.</td>
<td>Phase III</td>
<td>(ClinicalTrials.gov identifiers: NCT00213135, NCT00641537 and NCT00725985)</td>
</tr>
<tr>
<td>Mylinax</td>
<td>Merck Serono SA</td>
<td>This drug contains cladribine, a chlorinated purine nucleoside analog, that is activated to 2-chlorodeoxyadenosine triphosphate by deoxycytidine kinase.</td>
<td>Phase III</td>
<td>(ClinicalTrials.gov identifiers: NCT00213135)</td>
</tr>
<tr>
<td>Trimesta</td>
<td>Effective Pharmaceuticals Inc</td>
<td>An oral formulation of estriol E3, an endogenous hormone produced in the placenta during pregnancy. This compound has multiple effects that lead to immunomodulation.</td>
<td>Phase III</td>
<td>[101]</td>
</tr>
<tr>
<td>Cladribine with Rebif</td>
<td>Merck Serono SA</td>
<td>A purine-analog that inhibits the enzyme adenosine deaminase, which interferes with the cell's ability to process DNA.</td>
<td>Phase III</td>
<td>(ClinicalTrials.gov identifier: NCT00213135)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Genentech Inc</td>
<td>A mAb that targets CD20, a receptor located on some B-cells; CD20 is expressed at all stages of B-cell development, excluding the first and last stages.</td>
<td>Phase II/III [65,66]</td>
<td>(ClinicalTrials.gov identifier: NCT00087529)</td>
</tr>
<tr>
<td>TV-1102 (ATL-1102)</td>
<td>Antisense Therapeutics Ltd/ Teva Pharmaceuticals Industries Ltd</td>
<td>Antisense inhibitor of CD49d, a subunit of the ( \alpha_4 \beta_1 ) integrin.</td>
<td>Phase II</td>
<td>[102]</td>
</tr>
<tr>
<td>BHT-3009</td>
<td>Bayhill Therapeutics Inc</td>
<td>DNA plasmid that contains the gene for MBP.</td>
<td>Phase II</td>
<td>[103]</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>Genentech Inc/ Roche Holding AG</td>
<td>A humanized anti-CD20 mAb.</td>
<td>Phase II</td>
<td>[104] (ClinicalTrials.gov identifier: NCT006767152)</td>
</tr>
<tr>
<td>CDP-323</td>
<td>UCB CellTech/Biogen Idec Inc</td>
<td>Small-molecule prodrug antagonist of VCAM-1 binding to ( \alpha_4 \beta_1 ) integrins.</td>
<td>Phase II</td>
<td>(ClinicalTrials.gov identifier: NCT00484536)</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Biogen Idec Inc/Facet Biotech Corp</td>
<td>Humanized antibody to the ( \alpha )-subunit (CD25) of the IL-2 receptor that blocks usual IL-2 binding to this receptor, which is expressed on the surface of activated lymphocytes.</td>
<td>Phase II</td>
<td>[67]</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>GlaxoSmithKline plc/ Genmab A/S</td>
<td>A fully human antibody targeting the CD20 antigen on B-cells.</td>
<td>Phase II</td>
<td>(ClinicalTrials.gov identifier: NCT00640328)</td>
</tr>
<tr>
<td>Atacicept</td>
<td>Merck Serono SA</td>
<td>Contains the soluble TACI receptor that binds to the cytokines BLYS and APRIL, which are members of the TNF family that promote B-cell survival and autoantibody production.</td>
<td>Phase II</td>
<td>(ClinicalTrials.gov identifier: NCT00642902)</td>
</tr>
<tr>
<td>Firategast</td>
<td>GlaxoSmithKline plc</td>
<td>A cell adhesion inhibitor that controls the infiltration of leukocytes into sites of inflammation by acting on integrin receptors (both ( \alpha_4 \beta_1 ) and ( \alpha_4 \beta_2 )).</td>
<td>Phase II</td>
<td>(ClinicalTrials.gov identifier: NCT00548769)</td>
</tr>
</tbody>
</table>
deaminase and thus interferes with DNA replication, which leads to cell death. By this mechanism, cladribine depletes lymphocyte levels in the blood. Clinical and MRI data from several trials with parenteral cladribine have demonstrated promise in RR-MS and SP-MS [78-81]. Cladribine tablets provide a convenient short-course dosing regimen: once daily for 5 days per course for a total of 10 or 20 days per year of treatment [81]. These findings have led to an ongoing phase III trial of RR-MS with oral cladribine over a 2-year period. The primary endpoint is relapse rate, and secondary objectives include the clinical endpoints of disability progression, MRI parameters and safety assessments [82-85].

**MBP-8298**

Dirucotide (MBP-8298; BioMS Medical Corp/Eli Lilly & Co) is a synthetic peptide with a sequence corresponding to amino acid residues 82 to 98 of human MBP. The drug suppresses anti-MBP autoantibodies and is currently in phase III clinical trials for SP-MS and phase II for RR-MS [86]. This compound may be the vanguard of antigen-specific tolerance-based therapies for the treatment of MS [87].

**Non-anti-inflammatory approaches**

Non-anti-inflammatory approaches to the treatment of MS are summarized in Table 4. Such compounds are either neuroprotective or palliative.

**The search for neuroprotective therapies**

Strategies to protect neurons from degeneration have been investigated for stroke and traumatic brain injury without success [88-90]. The prospect of a neuroprotective therapy for MS emerged with the realization, mainly through MRI studies, that neurodegenerative changes in patients may occur independently from inflammation [43]. The blockade of sodium channels is the area of greatest focus of research, largely because sodium channel blockers have been demonstrated to protect both gray and white matter [41,42], with both phenytoin and lamotrigine demonstrating efficacy in mouse EAE models [92,93]. Lamotrigine is currently being assessed in a phase II clinical trial [94].

**Symptomatic therapies**

No drug has gained approval for the treatment of the symptoms of MS, except for the limited approval of an extract of cannabis (nabiximols; Sativex) containing tetrahydrocannabinol (THC) and synthetic THC (dronabinol). This drug has utility in the relief of pain, spasms and spasticity, and also offers the potential to provide neuroprotective efficacy [95-97]. A phase III clinical trial to assess the neuroprotective efficacy of cannabis in progressive MS is currently ongoing [98].

The most notable palliative therapy in clinical development is the potassium channel blocker 4-aminopyridine (fampridine). Positive results from two phase III clinical trials of a sustained-release formulation (fampridine-SR; Acorda Therapeutics Inc) suggest that this compound could be approved as a drug to improve both walking speed and lower extremity strength in patients with MS [99].

**Conclusion**

The understanding of MS has progressed substantially since Charcot’s first description of a creeping paralysis, and treatment has moved far beyond the injection of precious...
metals. Blockbuster biologics are currently the mainstay for MS therapy and rank among some of the world’s most expensive therapeutic agents, despite these compounds having only a modest effect on disease progression. This observation highlights that the market for MS drugs is highly lucrative even though it is currently under-served, and suggests that any agent able to make an impact on disease progression would have blockbuster potential. Relatively little attention has been directed toward drugs targeting the various symptoms of MS, but the progress of fampridine-SR along the regulatory pathway should emphasize the importance and commercial potential of this neglected area of pharmacotherapy for MS.

Acknowledgements
The author should like to thank Paul Rompani from the Multiple Sclerosis International Federation, and Lee Dunster and David Potter, both from the UK MS Society, for providing useful information. He should also like to thank Steven Palmer for the preparation of Figure 1 and Jennifer Scattereggia, from Thomson Reuters (Scientific) Ltd, for her editorial input.

References


Table 4. Non-immunomodulatory compounds in phase II or III clinical trials for MS.

<table>
<thead>
<tr>
<th>Therapeutic</th>
<th>Company</th>
<th>Action</th>
<th>Type of therapy</th>
<th>Development status</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fampridine</td>
<td>Accorda Therapeutics Inc</td>
<td>Symptomatic</td>
<td>Small-molecule potassium channel blocker.</td>
<td>Two phase III clinical trials have demonstrated a consistent improvement in walking speed compared with placebo.</td>
<td>[99]</td>
</tr>
<tr>
<td>Nabiximols</td>
<td>GW Pharmaceuticals plc</td>
<td>Analgesic and antispastic</td>
<td>A plant medicinal cannabis extract containing tetranabinex and nabidiolex (cannabidiol) as the principal components; these agents are CB1 receptor agonists.</td>
<td>Phase II clinical trials in the US, phase III trials in Europe and approved in Canada for the treatment of neuropathic pain in MS.</td>
<td>[108] (ClinicalTrials.gov identifiers: NCT00682929 and NCT00702468)</td>
</tr>
<tr>
<td>MCT-125</td>
<td>MultiCell Technologies Inc</td>
<td>Antifatigue</td>
<td>A combination of an atypical antidepressant and an amino acid.</td>
<td>In a phase II clinical trial, the compound reduced fatigue levels in patients with moderate-to-severe MS (n = 138).</td>
<td>[109,110]</td>
</tr>
<tr>
<td>Nerispridine</td>
<td>sanofi-aventis</td>
<td>Visual function</td>
<td>An acetylcholine release stimulator, and sodium and potassium ion channels inhibitor.</td>
<td>Undergoing phase II clinical trials in patients with multiple sclerosis.</td>
<td>(ClinicalTrials.gov identifiers: NCT00772525 and NCT00811902)</td>
</tr>
<tr>
<td>Modafinil</td>
<td>–</td>
<td>Antifatigue</td>
<td>Small molecule.</td>
<td>Approved by the FDA for the treatment of narcolepsy and shift work sleep disorder. This compound is being investigated for the treatment of fatigue associated with MS.</td>
<td>[111,112]</td>
</tr>
</tbody>
</table>

CB1 cannabinoid receptor CB2, MS multiple sclerosis


Suggests that early initiation of treatment with β-interferon is more efficacious than delayed treatment in RR-MS.
   • Reviews neuroprotective studies in stroke, with a perceptive analysis of what went wrong in this research.
   • Demonstrates the neuroprotective efficacy of phenyltoin in a mouse experimental autoimmune encephalomyelitis model of MS, and that this action is mediated by the blockade of sodium channels.