Repurposing multiple sclerosis drugs: a review of studies in neurological and psychiatric conditions

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Treatment options for multiple sclerosis (MS) have improved in the past 20 years, with new oral disease-modifying drugs and monoclonal antibodies becoming available. The success seen with these drugs in MS, and their various mechanisms of action, has led to them being investigated in other neurological and psychiatric disorders. This review article summarises the ongoing and completed studies of MS drugs in neurological and psychiatric conditions other than MS. The most promising results are for interferon beta in human T cell leukaemia virus 1 associated myelopathy/tropical spastic paraparesis and glioma, and for fingolimod in acute ischaemic stroke and intracerebral haemorrhage. The coming years could see the arrival of exciting new therapies for disorders that neurologists have historically found difficult to treat and that represent a significant unmet clinical need.

Introduction

The treatment of multiple sclerosis (MS) has seen major advances in the past 20 years [1,2]. As well as the older treatments [interferon beta (IFN-β) and glatiramer acetate (GA)], new oral disease-modifying treatments [teriflunomide, mitoxantrone, dimethyl fumarate (DMF), fingolimod, cladribine] and monoclonal antibodies (natalizumab, alemtuzumab and ocrelizumab) have become available, and rituximab is commonly used off-label [3]. As a result, treatment options have improved and a significant number of MS patients now achieve 'no evidence of disease activity' status [4,5].

MS is an autoimmune condition in which the myelin surrounding nerve fibres in the brain and spinal cord are damaged by inflammation. It is characterised by the presence of focal and diffuse inflammatory and degenerative lesions in the central nervous system (CNS). Most of the drugs used to treat MS mainly have anti-inflammatory effects [6]; Table 1 describes their mechanisms of action. The success seen with these drugs in MS, and their various mechanisms of action, has led to them being investigated in other neurological and psychiatric conditions. These include conditions with an underlying immunological and inflammatory pathology [e.g., chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)] and those with a nonimmunological pathology but in which inflammation has a role (e.g., RETT syndrome, stroke). This review article provides an overview of recent and ongoing clinical trials of MS drugs in other neurological and psychiatric indications; and summarises the rationale for their potential future use in these conditions so that practising neurologists can be aware of this ongoing research and development work.

Methods

The search strategy is summarised in Fig. 1. A search of ClinicalTrials.gov was conducted using the name of each of the MS drugs listed in Table 1 (IFN-β, GA, teriflunomide, mitoxantrone, DMF, fingolimod, cladribine, natalizumab, alemtuzumab, ocrelizumab), and all ongoing or completed studies in neurological and psychiatric indications other than MS were identified. For completed studies, PubMed was searched for published results. Additional PubMed searches for clinical studies of each drug published in the past 10 years were conducted, and the titles were examined for any non-MS indications. For each study found, the rationale for the use of the drug in the particular indication was examined, and clinical results were summarised where available.

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TABLE 1

Mechanism of action of drugs used to treat multiple sclerosis [6,56–58]

Drug	Mechanism of action in MS
Interferon beta	• Inhibits T lymphocyte proliferation • Shifts cytokine response from an proinflammatory response to an anti-inflammatory profile • Reduces migration of inflammatory cells across the blood–brain barrier
Glatiramer acetate	• Promotes Th2 deviation under the development of Th2 glatiramer-acetate-reactive $CD4^+$ T cells, which can accumulate in the CNS • Promotes bystander suppression by releasing anti-inflammatory cytokines
Teriflunomide	• Inhibits the mitochondrial enzyme dihydroorotate dehydrogenase, leading to reduced proliferation of dividing cells that need *de novo* synthesis of pyrimidine to expand, and reducing the number of circulating lymphocytes
Mitoxantrone	• Synthetic anthracenedione derivative mostly used in treating various malignancies • Interacts with nuclear DNA and is a potent immunosuppressive agent targeting proliferating immune cells, inhibiting proliferation and inducing apoptosis of T lymphocytes, B lymphocytes, macrophages and other antigen-presenting cells
Dimethyl fumarate	• Activates the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway and upregulates Nrf2-dependent antioxidant genes • Reduces memory T cells and shifts balance towards less proinflammatory Th1/Th17 cells and more anti-inflammatory Th2 cells • Protects neural stem cells from oxidative damage via the Nrf2/ERK1/2 MAPK pathway
Fingolimod	• Oral sphingosine 1 phosphate receptor (S1PR) modulator • Causes internalisation and degradation of the receptor in lymphocytes and thus inhibits the ability of autoreactive lymphocytes to egress from the lymph nodes towards the CNS, without suppression of systemic immune responses
Cladribine	• Nucleoside analogue that is cytotoxic particularly to lymphocytes and monocytes, inhibiting DNA synthesis and repair. Its effect on B and T lymphocytes is thought to interrupt the cascade of immune events central to MS
Natalizumab	• Monoclonal antibody against α4-integrin, which has a central role in endothelial transmigration of lymphocytes into the CNS • Blocks interaction of α4-integrin with its ligands and prevents adherence of activated leucocytes to inflamed endothelium, thus inhibiting the migration of inflammatory cells into the CNS
Alemtuzumab	• Monoclonal antibody against CD52, a cell surface antigen present at high levels on T and B lymphocytes • Antibody-dependent cellular cytolysis and complement-mediated lysis probably lead to depletion and repopulation of lymphocytes
Ocrelizumab	• Anti-CD20 monoclonal antibody that depletes circulating immature and mature B cells but spares CD20-negative plasma cells

Abbreviations: CNS, central nervous system; MS, multiple sclerosis.

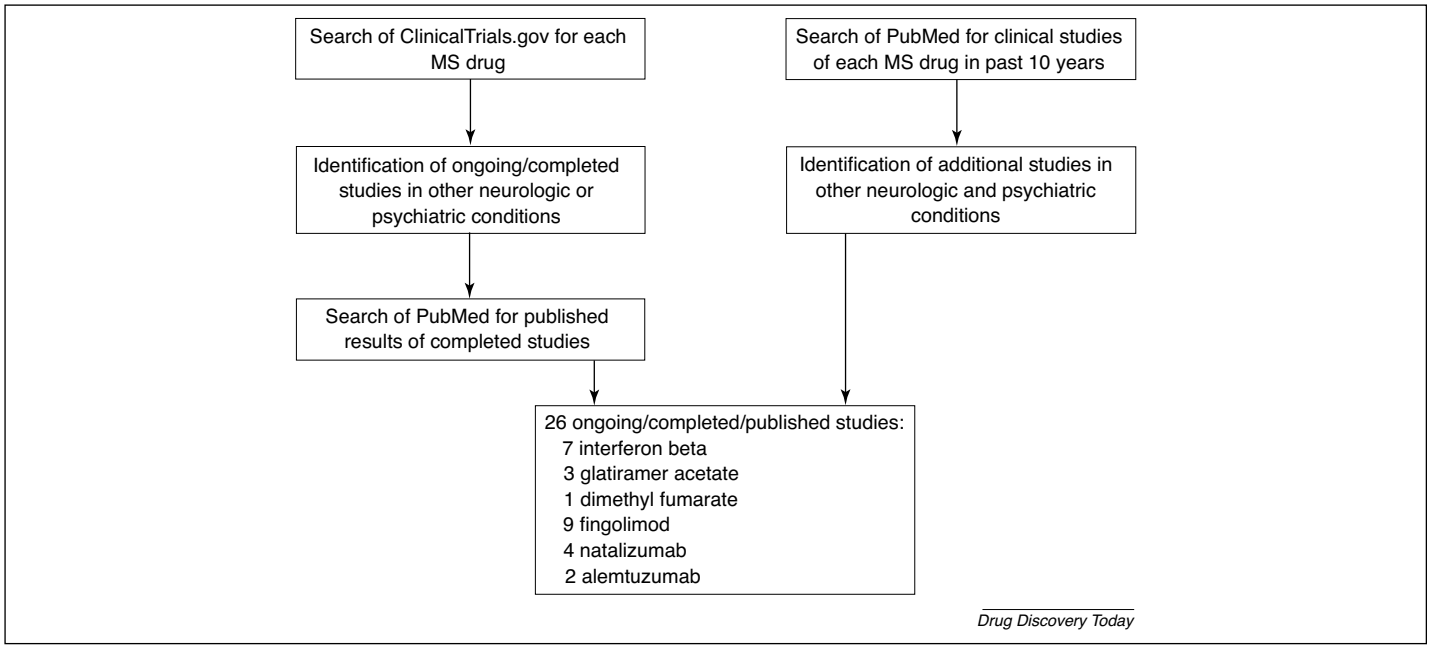

FIGURE 1

Flowchart of search strategy. ClinicalTrials.gov and PubMed have been reviewed for studies outside multiple sclerosis.

Details

The searches identified 26 studies for inclusion, nine for fingolimod, seven for IFN-β, four for natalizumab, three for GA, two for alemtuzumab and one for DMF. No studies of teriflunomide, mitoxantrone, cladribine or ocrelizumab in non-MS neurological and psychiatric conditions were found.

IFN-β

Results of a pilot study of IFN-β1a in 42 patients with early Alzheimer's disease (AD) were published in 2014 [7]. The rationale for this study was based on the similarity of some of the immunopathological pathways shared by AD and MS, the similar alteration of the blood–brain barrier and the positive effects of IFN-β

on cognition in MS patients. Like MS, AD is associated with expression of proinflammatory cytokines including interleukin (IL)-1β and IL-6, as well as tumour necrosis factor alpha (TNFα). Although a reduction in disease progression (Alzheimer's Disease Assessment Scale) was observed following 24 weeks' IFN-β1a treatment, there was no statistically significant difference versus placebo [7]. However, significant improvements were seen in the Instrumental Activities of Daily Living and Physical Self-maintenance Scale. The authors suggest that the strategy should be further investigated in larger studies targeting patients in early-stage AD where inflammatory-mediated facilitation of misfolded-protein accumulation is more likely to occur. No ongoing studies are registered on ClinicalTrials.gov.

IFN-β1a has also been investigated in human T cell leukaemia virus 1 (HTLV-1)-associated myelopathy (HAM)/tropical spastic paraparesis (TSP), which results from a viral-induced immunopathological process involving increased spontaneous T cell proliferation. The rationale for the use of IFN-β includes its antiviral and cytostatic effects, as well as its efficacy in MS, which is at least in part caused by a T-cell-mediated immunopathological process. Results of a study of IFN-β1a in 12 patients with HAM/TSP were published in 2005 [8]. IFN-β1a therapy reduced the HTLV-1 tax messenger RNA load and the frequency of potentially pathogenic HTLV-1-specific $CD8^+$ cells, as well as spontaneous lymphoproliferation, a marker of T cell activation in HAM/TSP. Some measures of motor function were improved, and no significant clinical progression occurred during therapy [8]. More recently, individual cases of HAM/TSP successfully treated with IFN-β1a have been reported [9,10].

Another condition in which IFN-β1a treatment has been explored is CIDP, an acquired peripheral neuropathy of unknown origin with a presumed immunological aetiology. The immune mechanisms responsible for CIDP resemble those implicated in MS, thus making CIDP the peripheral counterpart of MS. A randomised trial in ten CIPD patients published in 1999 found IFN not to be efficacious [11]. However, subsequent reports suggested successful treatment of CIPD with IFN-β1a in a few individual cases [12,13]. Another randomised trial ($n = 67$) published in 2010 also found no significant benefit of IFN-β1a versus placebo when added to intravenous immunoglobulin in CIDP [14], and a Cochrane systematic review concluded that low-quality evidence from randomised trials does not show significant benefit from IFN-β1a in CIDP [15].

Two studies have investigated the use of IFN-β in combination with standard temozolomide-based chemotherapy and radiotherapy in patients with glioma, suggesting a prolongation of survival [16,17]. The authors suggested that a Phase II study was warranted, but no such studies appear to be ongoing. Previous studies had reported promising results with IFN-β in combination with other chemotherapy regimens in glioma [18,19].

An open-label study of IFN-β1a as adjuvant therapy in three patients with multifocal motor neuropathy showed increased intravenous immunoglobulin infusion intervals in two of the patients but concluded that further trials were not supported [20]. Finally, two studies were registered on ClinicalTrials.gov and marked as completed, but the results have not been posted on ClinicalTrials.gov and do not appear to have been published. The first (NCT00004450, completed in 2000) evaluated the efficacy of IFN-β and thalidomide in male patients with adrenoleukodystrophy who showed evidence of brain inflammatory response and were receiving concurrent glyceryl trierucate and glyceryl trioleate (Lorenzo's oil). The other (NCT00097318, completed in 2011) examined the safety of IFN-β1a in 60 patients with acute ischaemic stroke, based on its actions in inhibiting proinflammatory cytokines and preventing blood–brain barrier disruption.

GA

GA has been investigated for the treatment of Rett syndrome – an X-linked dominant neurodevelopmental disorder that manifests with severe intellectual disability in girls and is caused by various mutations in the MECP2 gene. Brain-derived neurotrophic factor (BDNF) is one of the main proteins regulated by the MECP2 protein, and drugs that lead to increased BDNF in individuals with Rett syndrome are expected to have a positive effect. GA increases BDNF levels in animal models of MS and patients responding to treatment, as well as in Rett mouse models. An open-label study in ten patients with Rett syndrome showed significant improvements in gait velocity, memory and the breath-holding index after 32 weeks' treatment with GA [21]. There was also a nonsignificant trend towards improved quality of life. However, a second open-label study, which aimed to recruit 20 participants, had to be terminated after four of the 14 patients recruited developed an exaggerated immediate post-injection response to GA, which was considered life-threatening in three of the cases [22].

A condition in which GA has previously been investigated owing to its anti-inflammatory and neuroprotective effects is amyotrophic lateral sclerosis (ALS) – a degenerative disorder primarily affecting motor neurons, which results in progressive wasting and paralysis of voluntary muscles. At a higher dose than is used in MS (40 mg/day), GA did not show any beneficial effect versus placebo in a randomised trial in 363 ALS patients [23].

DMF

DMF has been shown to reduce the proliferation rate, generate cell lysis, decrease the expression of nuclear factor (NF)-κB and restrict the growth of CD133 cells in mouse gliomas and human glioblastoma cells [24]. It also enhances the cytotoxicity of the standard-of-care brain tumour therapeutics temozolomide and ionising radiation [25]. An open-label study that began in 2015 is looking at combining DMF with concurrent temozolomide and radiotherapy in 12 patients with newly diagnosed glioblastoma multiforme (NCT02337426). The study has been completed, but no results have been reported so far.

Fingolimod

There have been several studies of the use of fingolimod to treat stroke, with reduction of intralesional lymphocytic infiltration, amelioration of blood–brain barrier disruption and reperfusion injury and putative direct neuroprotective effects being suggested as possible mechanisms of action [26]. A meta-analysis of nine studies of the efficacy of fingolimod in animal models in 2013 concluded that it was a candidate drug for stroke, reducing infarct volume and improving clinical outcomes in all but one study [27]. In a single-centre, open-label pilot trial ($n = 22$), patients who received fingolimod >4.5 h after the onset of acute ischaemic

stroke had lower circulating lymphocyte counts, milder neurologic deficits and better recovery of neurologic functions, compared with matched patients who received standard management alone [28]. Another (multicentre) pilot study randomised 57 patients with hemispheric ischaemic stroke stemming from anterior or middle cerebral arterial occlusion to receive alteplase alone or alteplase plus fingolimod for three consecutive days within 4.5 h of onset. The addition of fingolimod attenuated reperfusion injury and improved clinical outcomes compared with alteplase alone [29]. Following on from these studies, a randomised, open-label study began in 2016 to investigate whether the addition of fingolimod, administered within 6 h after the onset of symptoms in patients receiving alteplase bridging with mechanical thrombectomy, improves radiological and clinical outcomes compared with standard care [30]. This study, which plans to enrol 96 participants, recruitment status is unknown (NCT02956200). In addition, an open-label proof-of-concept study ($n = 23$) examined the use of fingolimod within 72 h of symptom onset in patients with intracerebral haemorrhage. Compared with standard care alone, use of fingolimod reduced perihaematomal oedema, attenuated neurologic deficits and promoted recovery [31]. Further analysis demonstrated that fingolimod effectively prevented the entry of immune cells into circulating pools, affected the plasma concentration of mediators of inflammation and protected the vascular permeability in these patients [32].

Neuroinflammation is increasingly implicated in the pathogenesis of ALS and increasing the number and function of regulatory T cells is known to slow the progression of neuroinflammation. This provides a rationale for using a focused immunomodulatory agent that spares regulatory immune function, such as fingolimod, and the latter has been shown to be protective in an ALS mouse model [33]. A randomised controlled trial of fingolimod versus placebo in 28 ALS patients showed fingolimod to be safe and well tolerated; circulating lymphocytes decreased significantly in the fingolimod arm [34]. No Phase III trials of fingolimod in ALS have yet been registered on ClinicalTrials.gov.

A randomised controlled trial ($n = 106$) of fingolimod vs placebo for the treatment of CIDP started in 2012 (NCT01625182). Results have been posted on ClinicalTrials.gov and were presented at the American Academy of Neurology Annual Meeting in 2017 [35]. In a pre-planned interim analysis, the time to first confirmed worsening on the Adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Scale was 721 days with fingolimod versus 540 days with placebo, but the difference was not significant ($P = 0.984$). Because this analysis showed that it would be unlikely for the study to show significant benefit of fingolimod versus placebo at the time of completion, the study was discontinued for futility [35]. In line with this, a study in a mouse model of CIDP found no beneficial effects of fingolimod therapy; the authors suggest that it could interfere with remyelination after peripheral nerve injury [36].

Like GA, fingolimod is being investigated for the treatment of Rett syndrome. It has been shown to increase BDNF levels and improve symptoms in mice lacking the MECP2 gene – a model for Rett syndrome [37]. On the basis of this, an open-label study of fingolimod in six children with Rett syndrome began in 2013 (NCT02061137). The study was completed in April 2018 but no results have yet been released. Other preclinical work in cell cultures and animal models suggests a possible role for fingolimod in Parkinson's disease, AD, Huntington's disease and Guillain–Barré syndrome [26,38,39].

There is also a rationale for using fingolimod in patients with glioma, because it has shown inhibitory effects against cancer cells and crosses the blood–brain barrier [40]. It has been shown to induce apoptosis of brain cell tumour cells derived from human glioblastoma tissue (synergistically with temozolomide, the standard chemotherapeutic agent for glioblastoma) [40], reduce migration and invasion of human glioblastoma cell lines via inhibiting the PI3K/AKT/mTOR/p70S6K signalling pathway [41] and delay tumour growth and improve survival in a xenograft glioma mouse model [42]. An open-label study of fingolimod with radiation and temozolomide in five patients with newly diagnosed high-grade glioma was registered on ClinicalTrials.gov in 2015 (NCT02490930). The study was completed in September 2017, but no results have yet been posted.

Finally, a study of fingolimod in schizophrenia was registered on ClinicalTrials.gov in 2013 (NCT01779700); the estimated completion date was December 2017, but the study is described as 'active, not recruiting'. The rationale for investigating fingolimod in schizophrenia was the possibility of the integrity of cortical white matter tracts contributing to the pathophysiology of this illness, the association of numerous myelin-related genes and their functional expression with schizophrenia, quantitative and qualitative abnormalities in prefrontal cortical oligodendrocytes being found in post-mortem studies, and MRI-determined volumetric reductions in prefrontal white matter being reported in schizophrenia.

Natalizumab

Natalizumab has been studied in patients with acute ischaemic stroke. ACTION randomised 161 patients to natalizumab or placebo within 9 h of stroke onset [43]. No difference was seen between natalizumab and placebo in terms of change in infarct volume, although some benefits of natalizumab on functional outcomes were noted and were maintained to day 90. ACTION-2, which began in 2016 and recruited 270 participants, assessed the clinical effects of two doses of natalizumab versus placebo (<9 h or 9–24 h after onset) on clinical measures of functional independence and activities of daily living in patients with acute ischaemic stroke (NCT02730455). The study was completed in November 2017, but primary and secondary outcomes were reported to be negative [44].

Neuroinflammation appears to have a role in schizophrenia, and specifically overactivity of microglia; however, it is unclear whether activated microglia play a primary part in schizophrenia or whether this is a secondary phenomenon of no pathophysiological significance. This provides a rationale for the investigation of natalizumab in the treatment of schizophrenia. A study described as 'active, not recruiting' aims to provide a mechanistic understanding of neuroinflammation in schizophrenia by investigating response to natalizumab (NCT03093064). The study, which plans to enrol 60 participants, started in April 2017 with an estimated completion date of 2022. Patients with a first psychotic episode will be randomised to natalizumab or placebo, with a primary outcome measure of change in translocator protein

availability; secondary outcome measures include correlation of blood and cerebrospinal fluid inflammatory markers with brain functional measures.

Natalizumab is also being investigated as adjunctive therapy in patients with drug-resistant focal epilepsy (NCT03283371). There is a rationale for using immunomodulatory treatments in epilepsy, because immunity and inflammation appear to be an integral part of the pathogenic processes associated with some seizures, particularly with refractory epilepsy [45]. Seizures can occur in MS patients, and the risk of epilepsy appears to be higher than in the general population. In 2010, a case report described a patient who manifested abrupt tonic–clonic generalised seizures at disease onset of MS; although the MS was successfully treated with GA, the patient went on to develop severe refractory epilepsy [46]. Following worsening of MS, the patient was treated with natalizumab and, along with an improvement in MS, the seizure frequency was dramatically reduced. The authors suggested that inhibition of leukocyte adhesion could represent a new potential therapeutic approach in epilepsy and complement the traditional therapy with antiepileptic drugs [46]. The ongoing natalizumab study began in January 2018 and is currently recruiting participants (NCT03283371). The plan is to randomise 70 patients with drug-resistant focal epilepsy to natalizumab or placebo for 6 months, followed by a 6-month open-label phase during which all participants will receive natalizumab. The primary outcome measure is change from baseline in seizure frequency during weeks 8–24 of treatment, and the estimated study completion date is April 2022.

Alemtuzumab

A case report published in 2006 suggested some potential for the use of alemtuzumab to treat CIDP, although the patient experienced two relapses after alemtuzumab therapy [47]. This was followed by a case series reported in 2010, in which seven patients with CIDP who had failed to respond to conventional immunosuppression received nine courses of alemtuzumab [48]. Following treatment, mean monthly intravenous immunoglobulin use and administration frequency both decreased. Two patients had prolonged remission, two patients had a partial response and no clear benefit was observed in the remaining three patients; three patients developed autoimmune disease following treatment [48]. An open-label, multicentre study of alemtuzumab in CIDP was registered on ClinicalTrials.gov in 2012 (NCT01757574) but was later withdrawn without any participants being enrolled.

Discussion

Several of the drugs used to treat MS have been, or are being, investigated for use in other neurologic and psychiatric conditions in which inflammation is thought to play a part. Table 2 summarises the ongoing and completed studies for each drug. The drugs investigated in the greatest number of conditions are IFN-β and fingolimod. Both have been studied in CIDP, glioma and acute ischaemic stroke. Neither showed any benefit in CIDP, and research on the use of alemtuzumab in CIDP has stopped owing to development of autoimmune disease in some patients. CIDP thus remains an area of unmet need, with only intravenous immunoglobulin, plasma exchange and corticosteroids as treatment options, although subcutaneous immunoglobulin (Hizentra®) has recently been approved by the FDA and European Medicines Agency. IFN-β has demonstrated improved survival in patients with glioma, and there is a good rationale for the use of fingolimod. DMF is also being investigated in glioma. Fingolimod has shown promising results in acute ischaemic stroke, either given alone >4.5 h after onset or in addition to alteplase within 4.5 h. A Phase II study is underway in which fingolimod is administered within 6 h after the onset of symptoms in patients receiving alteplase bridging with mechanical thrombectomy. Fingolimod has also shown promise in the treatment of intracranial haemorrhage. A study of IFN-β in acute ischaemic stroke has not yet reported, and studies with natalizumab have been largely unsuccessful.

IFN-β has shown some benefit in HAM/TSP, as well as functional improvements but no reduction in disease progression in AD, and no benefit in multifocal motor neuropathy; a study in adrenoleukodystrophy has yet to report results. Two conditions in which fingolimod and GA have been investigated are Rett syndrome and ALS. The study of fingolimod in Rett syndrome has not yet reported; GA led to significant improvements in one study but a second was terminated owing to an exaggerated immediate post-injection response in some patients. No beneficial effect of GA was seen in ALS, whereas fingolimod reduced circulating lymphocytes compared with placebo. Finally, studies of fingolimod and natalizumab in schizophrenia are described on ClinicalTrials.gov as 'active, not recruiting', and a study of natalizumab in focal epilepsy is ongoing.

Some of the drugs used to treat MS were repurposed from other indications. For example, DMF in combination with monoethyl fumarate salts (Fumaderm®) was approved in Germany for the systemic treatment of severe psoriasis in 1994 [49]. Cladribine and mitoxantrone have been used to treat certain types of cancer. Alemtuzumab, under the name Campath®, was approved for the treatment of B cell chronic lymphocytic leukaemia (CLL) in 2001; it has also been widely studied in organ transplantation and sickle cell disease. Rituximab, which is used off-label to treat MS, is licensed for the treatment of non-Hodgkin's lymphoma, CLL, rheumatoid arthritis and granulomatosis with polyangiitis and microscopic polyangiitis. In addition to the neurologic and psychiatric conditions discussed above, some of the MS drugs have also been investigated in other disease areas. For example, IFN-β1a has been studied in inflammatory bowel disease [50,51] and asthma (NCT02491684), and a study in chronic obstructive pulmonary disease has recently started (NCT03570359). DMF was shown to partially ameliorate the severity of obstructive sleep apnoea [52] and is being studied in relapsed/refractory patients with CLL/small lymphocytic lymphoma (NCT02784834) and systemic sclerosis-associated pulmonary arterial hypertension (NCT02981082). Fingolimod has been investigated in renal transplantation but did not show any advantage over standard agents [53,54]. Two studies of natalizumab in acute graft-versus-host disease are ongoing (NCT02176031, NCT02133924) but studies in rheumatoid arthritis (NCT00831649) and Crohn's disease (NCT00707512) have been terminated. Studies of ocrelizumab in rheumatoid arthritis (NCT02720120) and systemic lupus erythematosus (NCT00539838) have also been terminated; but the drug showed activity in patients with relapsed/refractory follicular lymphoma following prior rituximab treatment [55].

TABLE 2

Studies of multiple sclerosis drugs in other neurologic and psychiatric conditions

Drug	Neurologic and psychiatric condition	Status and/or outcome
Interferon beta	Alzheimer's disease	No reduction in disease progression vs placebo; some functional improvements [7]
	HAM/TSP	Some improvement in motor function; no significant clinical progression [8]
	CIDP	No significant benefit [15]
	Glioma	Prolongation of survival as adjuvant therapy [17]
	Multifocal motor neuropathy	No support for further trials [20]
	Adrenoleukodystrophy	Completed, not reported (NCT00004450)
	Acute ischaemic stroke	Completed, not reported (NCT00097318)
Glatiramer acetate	Rett syndrome	Significant improvements in one study [21]; exaggerated immediate post-injection response in some patients led to termination of another [22]
	Amyotrophic lateral sclerosis	No beneficial effect [23]
Dimethyl fumarate	Glioma	Estimated completion date September 2018 (NCT02337426)
Fingolimod	Acute ischaemic stoke	Improved outcomes in two pilot studies [28,29]; Phase II study estimated to complete in December 2018 (NCT02956200)
	Intracerebral haemorrhage	Improved outcomes vs standard care [31]
	Amyotrophic lateral sclerosis	Decreased circulating lymphocytes vs placebo [34]
	CIDP	Study discontinued because interim analysis showed significant benefits unlikely [35]
	Rett syndrome	Completed, not reported (NCT02061137)
	Glioma	Completed, not reported (NCT02490930)
	Schizophrenia	Active, not recruiting (NCT01779700)
Natalizumab	Acute ischaemic stroke	Possible benefits on functional outcomes in ACTION [43]; negative outcomes in ACTION-2 [44]
	Schizophrenia	Active, not recruiting (NCT03093064)
	Focal epilepsy	Estimated completion date April 2022 (NCT03283371)
Alemtuzumab	CIDP	Some success, but some patients developed autoimmune disease [48]; multicentre study withdrawn with no enrolment (NCT01757574)

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; HAM/TSP, human T cell leukaemia virus 1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis.

Concluding remarks

In recent years, the role of inflammation in many neurologic and psychiatric conditions has become better understood, and immunological pathways are being targeted in the treatment of many neurologic and psychiatric conditions. The MS treatment landscape has changed dramatically in the past 20 years and some of the drugs used in MS are now being investigated in other neurologic and psychiatric indications. The next few years could see the arrival of exciting new therapies for various disorders that neurologists have historically found difficult to treat and that represent significant unmet clinical need.

Conflicts of interest

PSR Speaker or consultancy from Biogen, Celgene, Daiichi Sankyo, Merck, Novartis, Sanofi Genzyme, Roche. Research Grants to institution from Biogen, Merck, Roche. JS Speaker or consultancy from Biogen, Celgene, Gerot-Lannach, Merck, Novartis, Roche, Sanofi, Teva. Research support to institution from Biogen, Merck, Roche, Teva. Medical monitor for an Immunic Therapeutics trial.'

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