PCORI Topic Brief: Treatment of Symptoms in Multiple Sclerosis

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Introduction

Multiple sclerosis (MS) is a neurologic condition typically affecting young adults. MS is characterized by an autoimmune disorder that causes damage of neural pathways within the central nervous system (CNS) by damaging the myelin sheaths that surround many neurons or tracks (demyelination). Patients may have one of three classic types of MS at any given time:[1]

1) Relapsing-remitting:
    - Patients with relapsing-remitting MS experience symptom flare-ups or relapses. During these relapses the patient may either experience new symptoms or increases in existing symptoms. These relapses usually persist for a short time (a few days to a few months) and then afterwards the patient may remain symptom-free (i.e., be in remission) for a period of months or even years.
2) Secondary progressive:
    - Patients with secondary progressive MS do not have the dramatic variations in symptoms characteristic of relapsing-remitting MS, but instead have a slow, steady progression. Although patients in this category also have flare-ups, if they occur the symptoms from those flare-ups normally persist.
3) Primary progressive:
    - Patients with primary progressive MS experience a steady worsening of symptoms from the beginning and do not have periodic relapses or remissions.

Relapsing-remitting MS is the most common type, affecting 85% to 90% of patients.[2] In addition, patients may transition across the three types over time. For example, most patients

with relapsing-remitting MS will eventually enter a secondary progressive phase, in which progression of disability occurs gradually with or without relapses.[3]

Patients with MS have episodes of CNS dysfunction, lasting at least 24 hours, which partially resolve over time. CNS dysfunction most commonly shows up first as sensory disturbances or visual loss, often due to optic neuritis (inflammation of the optic nerve), but also as motor weakness, diplopia (double vision), gait disturbances, or other neurologic symptoms. Some symptoms, such as fatigue, may be chronic.

Symptoms commonly associated with MS are categorized as primary, secondary, or tertiary. Primary symptoms are believed to be the direct result of damage to the myelin and nerve fibers in the CNS. Secondary symptoms arise from complications of the primary symptoms. For example, the primary symptom of bladder dysfunction may cause urinary tract infections, and immobility can result in the secondary symptom of loss of muscle tone, decreased bone density, or shallow breathing. Tertiary symptoms refer to societal, psychological, vocational, etc. effects that are at least indirectly related to having MS.

The standard of care for patients with MS normally involves both standardized treatment with a disease-modifying therapy (DMT), and individualized treatment as indicated to alleviate specific symptoms commonly associated with MS. The effectiveness of DMTs in slowing disease progression and minimizing disability has been well demonstrated, and there is a large body of evidence that supports the use of a wide variety of treatments for specific symptoms that are commonly experienced by people with MS. However, clinical trials of DMTs have historically not assessed symptom-specific outcomes, and much of the evidence in support of symptomatic treatments is derived from clinical trials and experience in patients who do not have

MS. There is also a lack of information about the preferences that patients with MS may have regarding the relative advantages and disadvantages of various DMTs and symptomatic treatments in MS.[4-7]

The objective of this report is to summarize recent relevant literature on treatments for symptoms of MS, with a focus on the four following specific questions:

1) What is the comparative effectiveness of DMTs on symptoms in MS?
2) What is the comparative effectiveness of symptomatic treatments in MS?
3) What are the most important subgroups of MS patients to consider, in terms of symptoms and disease course for comparative effectiveness research of symptom management?
4) How do patient preferences influence the trade-offs between symptom relief and other treatment goals in MS?

To answer these questions, we reviewed current systematic reviews and evidence-based guidelines for treatment of MS and its related symptoms, and explored ongoing research through ClinicalTrials.gov. Throughout this report, we highlight research gaps where future targeted research funded by the Patient-Centered Outcomes Research Institute (PCORI) might address existing uncertainties.

Burden on Society

Incidence and Prevalence

More than 200 cases of MS are diagnosed weekly in the United States.[8] Incidence generally occurs between 20 and 50 years of age, peaking at about 30 years of age but is occasionally diagnosed in children and older adults.[9] In total, approximately 400,000 adults currently have

MS in the United States, with worldwide prevalence estimated at 2.5 million adults.[8] The highest prevalence occurs among women, white people of Nordic origin, in areas with moderate climates, and among people with higher incomes.[9] The prevalence of MS is increasing as incidence increases, and as more effective treatments are extending the survival of patients with MS. Currently prevalence peaks at about 50 years of age.[9]

Relapses and Disease Progression

Most randomized controlled trials (RCTs) of DMTs for MS use relapse rates or disease progression (or both) as primary outcome measures. A relapse is defined as the development of new symptoms related to MS, or worsening of existing symptoms, for a period lasting at least 24 hours. The rate of relapse that is most commonly reported in RCTs is the annualized relapse rate, which is calculated by dividing the total number of relapses by the total time that patients are at risk of a relapse. Some recent trials also include time to first relapse as a primary outcome. Disease progression is defined in many different ways, including conversion to a different more advanced stage of MS, increased disability as measured by the Expanded Disability Status Scale (EDSS) (see below), or radiologic imaging evidence of brain atrophy or shrinkage.[10] RCTs of DMTs also commonly report surrogate outcomes (i.e., markers of treatment effect that are believed—but not necessarily known—to correlate with the clinical outcomes described above) such as magnetic resonance imaging (MRI) findings. These findings include lesion counts, "black hole" formation, T2 lesion volume, or brain volume.[11] Although slowing/reversing disease progression is important to patients, it is unclear how these outcomes balance against their other MS-related symptoms and how they trade off the risks and benefits of the different treatments to manage these different types of outcomes.

Disability, Impairment, and Functional Status

The most commonly used instrument for assessing and following disability in patients with MS is the 11-point EDSS,[12] according to which a score of 0 indicates no impairment due to MS, 4.0 indicates the onset of significant walking impairment, 7.5 indicates wheelchair dependence, and 10.0 represents death due to MS.[13] The EDSS, the MS Functional Composite, the Functional Assessment Multiple Sclerosis scale, and other measures of disability, impairment, or functional status commonly used in research or clinical practice for MS incorporate in their total scores both findings from physical examinations by healthcare professionals and patient self-report of selected symptoms. These measures, however, are neither purely measures of health-related quality of life nor reliable assessments of the impact that specific (and potentially treatable) MS-related symptoms have on patients' quality of life.

Productivity

Based on a 2009 insurance claims database study, employees with MS had 29.8 disability days per year compared to 4.5 days for employees without MS.[14] Employees with MS also had significantly higher annual disability costs ($3868 versus $414).[14] Absenteeism costs ($1901 versus $1003) and total indirect costs ($5769 versus $1417) were also increased in employees with MS versus those without MS.[14]

Mortality

MS is associated with increased mortality relative to the general population, with a mean age of death of 58 years.[15] The most common causes of MS-related death involve respiratory failure, which may in turn lead to bronchopneumonia.[16] Suicide rates are also relatively high among

patients with MS, leading some researchers to argue that suicides among patients with MS should be considered an MS-related cause of death.[17]

Costs

Total direct medical costs for all patients with MS in the United States is estimated to be more than $10 billion per year, with a lifetime financial cost estimated at $1.2 million per MS patient.[18]

MS Symptoms and Effect on Patient Quality of Life

MS affects patients' health-related quality of life by causing disability (e.g., impairment in ability to walk) and by causing a wide variety of symptoms. As discussed above, MS-related symptoms can be categorized as primary, secondary, or tertiary, depending on whether the symptoms are considered as a direct result of the underlying disease (primary symptoms), complications from the primary symptoms (secondary symptoms), or indirectly related to having the chronic and progressive condition of MS (tertiary symptoms). According to the National Multiple Sclerosis Society, primary symptoms can be further categorized as "more common" or "less common."[19] More common primary symptoms often occurring in 80% of more of MS patients include: fatigue; walking difficulties; numbness or tingling; spasticity; weakness; vision problems; dizziness or vertigo; bladder problems; sexual problems; bowel problems; pain; cognitive changes; emotional changes; and depression. Less common symptoms include: speech problems; swallowing problems; tremor; seizures; breathing problems; itching, headache, and hearing loss. Brief descriptions of the more common symptoms and currently used options based on informed expert judgment for treating those symptoms are provided in Table 1. DMTs do not feature prominently in Table 1 because clinical trials that evaluate the effectiveness and safety of

DMTs do not typically report symptom-specific outcomes. In this report, we focus on the more common primary symptoms, the existing evidence for treatment of these symptoms, and future research needs.

Table 1. More Common Primary MS Symptoms and Commonly Used Treatment Options

Symptom	Commonly Used Treatment Options
Fatigue	Pharmacologic: Amantadine, methylphenidate, natalizumab, SSRIs, aspirin, modafinil, dextroamphetamine salts , lisdexamfetamine Nonpharmacologic: Multidisciplinary rehabilitation programs, physical therapy, exercise training, yoga
Walking difficulties	Pharmacologic: Dalfampridine Nonpharmacologic: Physical therapy
Numbness or tingling	Pharmacologic: No medications have been proven effective for numbness. For tingling, gabapentin, pregabalin, carbamazepine, oxcarbamazepine, duloxetine, tricyclic antidepressants, lidoderm patches, capsaicin cream
Spasticity	Pharmacologic: Baclofen, tizanidine, dantrolene, clonazepam, gabapentin, levetiracetam, clonidine, intrathecal baclofen. Nonpharmacologic: Botulinum toxin, physical therapy, exercise, transcranial magnetic stimulation, electromagnetic therapy, TENS, cannabinoids
Weakness	Nonpharmacologic: Exercise, assistive devices, medication, physical therapy, occupational therapy (OT), Pilates training
Vision problems	Pharmacologic: Corticosteroids Nonpharmacologic: Eye rest, special prisms
Dizziness or vertigo	Pharmacologic: Motion-sickness or anti-nausea drugs (e.g., meclizine, scopolamine, ondansetron), diazepam, valium (benzodiazepines)
Bladder problems	Pharmacologic: Onobatulinumtoxin A, desmopressin, tolterodine, oxybutynin, darifenacin, tamsulosin, terazosin, prazosin, propantheline, trospium chloride, imipramine, solifenacine succinate, capsaicin Nonpharmacologic: Intermittent catheterization, physical therapy, pelvic floor training, bladder stimluators
Sexual problems	Pharmacologic: Pro-erective medications for men Nonpharmacologic: Vaginal lubricants for women
Bowel problems	Nonpharmacologic: Dietary and lifestyle approaches, enemas, suppositories, laxatives for constipation
Pain	Pharmacologic: Gabapentin, pregabalin, carbamazepine, oxcarbamazepine, duloxetine, tricyclic antidepressants, lidoderm patches, capsaicin cream Nonpharmacologic: Cannabinoids, marijuana, massage therapy, acupuncture, various treatments for pain depending on location, quality, severity, chronicity, etc.

Symptom	Commonly Used Treatment Options
Cognitive changes	Pharmacologic: Interferon, donepezil, galantamine, modafanil, amphetamines Nonpharmacologic: Multidisciplinary rehabilitation programs, exercise training, behavioral training
Emotional changes	Nonpharmacologic: Physical therapy, exercise training, yoga, mindfulness-based interventions
Depression	Pharmacologic: Pharmacologic management as evaluated in non-MS populations Nonpharmacologic: Psychotherapy, yoga, exercise training, acupuncture

Abbreviations: MS=multiple sclerosis; OT=occupational therapy; SSRIs=selective serotonin reuptake inhibitors; TENS=transcutaneous electrical nerve stimulation

Options for Addressing the Issue

Available Management or Treatment Options for MS Symptoms

As discussed, current standard of care for MS patients is dominated by the use of DMTs for reducing disease progression and then symptom-specific treatment for MS-related symptoms. We summarize here the limited evidence for using DMTs for treating MS symptoms and then highlight the additional categories of treatments for specific symptoms and the evidence of their effectiveness in MS populations.

Disease-Modifying Therapies (DMTs)

Ten pharmacologic interventions have been approved by the U.S. Food and Drug Administration (FDA) as DMTs. These 10 DMTs are comprised of 5 injectable therapies (4 different interferon-beta preparations and glatiramer acetate), 3 oral therapies (fingolimod, teriflunomide, and dimethyl fumarate), and 2 infusions (mitoxantrone and natalizumab). DMTs are typically administered soon after diagnosis, with the goal of decreasing the rate of relapse and slowing the accumulation of brain lesions that are seen on MRI. DMTs work primarily by altering a patient's autoimmune response, which is in turn responsible for damaging the myelin

sheaths that envelop the axons of many nerves or nerve bundles in the CNS. DMTs have been shown to reduce annualized relapse rates and decrease the risk of sustained disability progression relative to placebo in patients with relapsing-remitting MS.[20] Select DMTs have also been shown to improve MRI findings. Systematic reviews and meta-analyses of DMTs, however, provide very limited evidence in support of DMTs' effectiveness in improving health-related quality of life,[20] and they provide essentially no evidence to inform the potential effectiveness of DMTs in alleviating symptoms commonly associated with MS (with the exception of those neurological symptoms whose recurrence define a relapse). For example, a review of outcomes reported in 19 RCTs of DMTs for relapsing-remitting MS in adults published in 2014 found that none of the studies used quality-of-life measures or modifications of symptoms as primary or secondary outcomes.[11] Second, a review by our team of the 30 RCTs included in the recent Canadian Agency for Drugs and Technologies in Health (CADTH) review[20] confirms that only 2 studies included primary or secondary outcomes which can be considered related to quality of life (as assessed using the EDSS disability scale), and that although several studies evaluated symptoms such as fatigue and pain, these outcomes were categorized as adverse events from the treatment or placebo arms and not evaluated in terms of the treatment's efficacy. CADTH confirms that their review was "limited by the paucity of data related to quality of life and many of the outcomes of importance to patients."

Complementary and Alternative Treatments

In March 2014, the American Academy of Neurology (AAN) published a summary of the evidence for complementary and alternative medicine (CAM) in MS.[21] The guideline was also endorsed by the Consortium of Multiple Sclerosis Centers and the International Organization of

Multiple Sclerosis Nurses. This guideline focused on whether CAM therapies reduce specific symptoms and prevent relapses or disability, whether CAM use worsens MS or causes serious adverse effects, and whether CAM can interfere with MS DMTs. Because needed studies were unavailable or, when available, had a high risk of bias, were inconsistent, or lacked statistical power/precision, the AAN analysis determined that evidence was insufficient to support/refute the effectiveness of the following CAM therapies in MS (Table 2):

Table 2. CAM Therapies with Insufficient Evidence to Support/Refute Effectiveness in MS

acetyl-l-carnitine	glucosamine sulfate	naturopathic medicine
acupuncture	hippotherapy	neural therapy
biofeedback	hyperbaric oxygen	Padma 28
carnitine	inosine	progressive muscle
chelation therapy	linoleic acid	relaxation therapy
Chinese medicine	low-dose naltrexone	tai chi
chiropractic medicine	massage therapy	threonine
creatine monohydrate	mindfulness training	transdermal histamine
dental amalgam replacement	music therapy	yoga

Data were also insufficient to determine whether any of the CAM therapies worsened MS or interfered with DMTs.

Those CAM therapies where evidence was able to support a recommendation are summarized in Table 3.

Table 3. CAM Therapies with Sufficient Evidence to Support Practice Recommendations in MS*

CAM Intervention	Number of Studies	MS Types Studied	Outcome	AAN Recommendation
Cannabinoids				
Oral cannabis extract (OCE)	4	RRMS, SPMS, PPMS, MSU	Symptoms of spasticity, pain	Established effective
	1	RRMS, SPMS, PPMS	Signs of spasticity (short-term), tremor (short-term)	Probably ineffective
	1	MSU	Signs and symptoms of spasticity (long-term)	Possibly effective
	3	RRMS, SPMS, PPMS, MSU	Bladder symptoms, urge incontinence	Insufficient evidence
Synthetic THC	2	RRMS, SPMS, PPMS	Symptoms of spasticity, pain	Probably effective
	1	RRMS, SPMS, PPMS	Signs of spasticity (short-term), tremor (short-term)	Probably ineffective
	1	MSU	Signs and symptoms of spasticity (long-term)	Possibly effective
	3	RRMS, SPMS, PPMS, MSU	Bladder symptoms, urge incontinence, central neuropathic pain	Insufficient evidence
Sativex oromucosal spray	8	MSU	Symptoms of spasticity, pain, urinary frequency	Probably effective
			Signs of spasticity, incontinence episodes	Probably ineffective
			Tremor	Possibly Ineffective

CAM Intervention	Number of Studies	MS Types Studied	Outcome	AAN Recommendation
			Anxiety/sleep, cognition, QOL, fatigue	Insufficient evidence
Smoked cannabis	2	RRMS, SPMS, MSU	Spasticity, pain, balance and posture, cognition	Insufficient evidence
Other CAM				
Ginkgo biloba	4	RRMS, SPMS, PPMS	Fatigue Cognitive function	Possibly effective Established ineffective
Lofepramine plus phenylalanine with B12	1	RRMS, SPMS, PPMS	Disability, symptoms, depression, fatigue	Possibly ineffective
Reflexology	4	MSU	Paresthesia	Possibly effective
			Pain, HRQOL, disability, spasticity, fatigue, cognition, bowel/bladder function, depression, anxiety, insomnia	Insufficient evidence
Bee venom	1	RRMS, SPMS	MRI lesion number and volume, relapses, disability, fatigue, HRQOL	Possibly ineffective
Magnetic therapy	5	RRMS, SPMS, PPMS	Fatigue Depression	Probably effective Probably ineffective
Low-fat diet with omea-3 supplementation	3	RRMS	Relapses, disability, MRI lesions, fatigue, QOL	Probably ineffective

* Adapted from Table 2 in Yadav, 2014.[21]

Abbreviations: AAN=American Academy of Neurology; CAM=complementary and alternative medicine; HRQOL=health-related quality of life; MRI=magnetic resonance imaging; MS=multiple sclerosis; MSU=multiple sclerosis type unspecified; OCE=oral cannabis extract; PPMS=primary progressive multiple sclerosis; QOL=quality of life; RRMS=relapsing-remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis; THC=tetrahydrocannabinol

Exercise Therapy and Physical Therapy

A Cochrane systematic review of exercise therapy for MS published in 2004 identified 9 eligible, high-quality RCTs representing 260 patients.[22] Six of these trials included a no exercise comparator. The systematic review concluded that there is strong evidence in support of exercise therapy's effectiveness for improving muscle weakness, exercise tolerance, and mobility-related activities, and moderate evidence in support for improving mood, compared with no exercise. Exercise therapy was not found to be effective for fatigue. A more recent meta-analysis of 17

studies did find a small but statistically significant reduction in fatigue associated with exercise training compared with no exercise training among patients with MS.[23] Finally, a recent systematic review and meta-analysis of 13 studies (published in 2 different journals)[24,25] demonstrated that exercise training is associated with a small but statistically significant effect in improving depressive symptoms in people with MS compared with no exercise training. A systematic review published in 2014 qualitatively described 4 clinical trials involving a total of 269 patients of physical therapy interventions for non-spastic and non-trigeminal pain management in MS.[26] Sample sizes within these studies ranged from 31 to 111, and treatment duration ranged from 3 weeks to 18 months. The included studies suggested that outpatient rehabilitation, physiotherapy, and robotic-assisted gait training are associated with a modest decrease in self-reported pain over time.

Non-DMT Pharmacological and Dietary Treatments

There is a very large body literature that evaluates the effectiveness of interventions for each of the symptoms that are commonly experienced by patients with MS. Most of this evidence, however, was not derived from MS patient populations. Below we summarize findings from identified systematic reviews that evaluated the effectiveness of (non-DMT) pharmacologic treatments for symptomatic treatment in patients with MS.

Fatigue: One drug and one nutritional supplement have been evaluated by systematic reviews for the treatment of MS-related fatigue. Amantadine is an orally administered medication that inhibits replication of influenza A viruses; it also appears to improve symptoms of Parkinson's disease[27] and is often prescribed to treat MS-related fatigue. A Cochrane systematic review published in 2007 identified 5 RCTs involving a total of 272 patients that evaluated the

effectiveness of amantadine for fatigue in patients with MS.[28] Although the studies demonstrated a small improvement in fatigue associated with amantadine, the authors of the systematic review concluded that there is insufficient evidence in support of amantadine's effectiveness for MS-related fatigue. Acetyl L-carnitine is nutritional supplement that has been found to be effective in the treatment of chronic fatigue syndrome[29] and fatigue in elderly persons.[30] A Cochrane systematic review of carnitine for the treatment of MS-related fatigue updated in 2011 identified a single randomized cross-over trial that compared a 3-month course of 2 grams daily of carnitine with amantadine 200 mg daily (36 patients).[31] There was a small but statistically significant improvement in fatigue symptoms in favor of carnitine. The authors of the systematic review, however, concluded that this one study represents insufficient evidence for carnitine in the treatment of MS-related fatigue.

Walking difficulties: Difficulty walking is one of the more common symptoms associated with MS. Ataxia (diminished muscle control) often contributes to MS-related walking difficulty. A Cochrane systematic review published in 2007 identified 6 placebo-controlled RCTs of pharmacologic treatments for ataxia in MS patients.[32] The interventions studied were isoniazid plus pyridoxine (2 studies), cannabis-based medicine (3 studies), and baclofen (1 study). The authors of the systematic review however concluded that there is insufficient evidence in support of the effectiveness of pharmacologic approaches for the treatment of ataxia in patients with MS.

Spasticity: A Cochrane systematic review published in 2003 identified 26 placebo-controlled trials and 13 comparative RCTs involving one or more pharmacologic agents in the treatment of MS-related spasticity.[33] The authors concluded that the evidence from these studies is too poorly documented and the results too inconsistent to support a recommendation to prescribe these

drugs for MS-related spasticity. The authors emphasized that the lack of a validated assessment tool for spasticity is an important contributor to this inconclusive evidence.

Sexual problems: A Cochrane systematic review published in 2012 identified 2 placebo controlled randomized trials involving a total of 420 male patients that evaluated the effectiveness of the phosphodiesterase 5 inhibitor sildenafil for erective dysfunction in patients with MS.[34] These two trials demonstrated that sildenafil was associated with an improvement in the ability to achieve and maintain an erection and achieve vaginal penetration.

Bladder problems: Anticholinergic medications have been used for the past several decades to manage of symptoms due to an overactive bladder. These medications are associated with a relative high rate of adverse effects, especially in elderly persons. A Cochrane systematic review of anticholinergics for MS patients with urinary symptoms published in 2009 identified 3 pertinent RCTs that compared 2-week treatment regimens that included an anticholinergic with no treatment and an active comparator.[35] The authors of the systematic review concluded that there is insufficient evidence in support of the effectiveness of anticholinergics for urinary symptoms in patients with MS.

Cognitive changes: A Cochrane systematic review published in 2013 included 7 RCTs involving 625 patients evaluated the effectiveness of pharmacologic treatment for memory disorder in MS.[36] The cholinesterase inhibitors donepezil and rivastigmine, the herbal treatment ginkgo biloba, and the N-methyl D-aspartate receptor antagonist memantine were compared with placebo. The authors of the systematic review concluded that that there is inconclusive evidence in support of the effectiveness of pharmacologic treatment for MS-related memory disorder. Another Cochrane systematic review first published in 2011 and updated in 2014[37] identified 20

studies involving 966 patients with MS that evaluated neuropsychological rehabilitation interventions for MS. The authors of the systematic review concluded that there is low-level evidence for positive effects of neuropsychological rehabilitation for improving cognitive deficits such as memory span and working memory.

Depression: A Cochrane systematic review published in 2011 identified 2 RCTs involving a total of 70 patients that compared a pharmacologic treatment to placebo for the treatment of major depressive disorder in patients with MS.[38] Neither the trial that evaluated a 5-week course of the tricyclic antidepressant desipramine nor the trial that evaluated a 12-week course of the selective serotonin reuptake inhibitor paroxetine demonstrated statistically significant improvement in depressive symptoms relative to placebo, but paroxetine was associated with a higher rate of nausea and headache compared with placebo. An evidence-based guideline published in 2014 by the AAN for the assessment and management of psychiatric disorders in individuals with MS concluded: "Although pharmacologic and nonpharmacologic therapies are widely used to treat depressive and anxiety disorders in individuals with MS, evidence is insufficient to support/refute the use of the antidepressants and individual and group therapies reviewed herein."[39]

Recent Innovations

As discussed above, quality-of-life and symptom-specific outcomes were historically rarely included as outcome measures in clinical trials that evaluated the efficacy of DMTs in the treatment of MS.[11] A recent innovation, as indicated by outcomes being assessed in ongoing clinical trials reported on the ClinicalTrials.gov website is that ongoing clinical trials of DMTs—as well as those that target symptom-specific therapies—are increasingly reporting these

outcomes, thereby providing some (future) evidence to evaluate the effects that these therapies have on important patient-reported outcomes (see Table 4).

Variations in Care

There is significant variability in the content of the many MS clinical practice guidelines sponsored by organizations in the United States, Canada, and Europe.[40] Also, recommendations for the treatment of MS have been known to change relatively rapidly. Given that there is insufficient and inconsistent evidence to inform the treatment and management of MS-related symptoms, variation in care across populations, subpopulations, medical specialties, healthcare settings, and geographic location is expected.

Ongoing Research

As discussed above, clinical trials of potentially therapeutic interventions for MS have historically focused primarily or entirely on signs of disease progression. In the past few years, however, there has been a marked increase in the number of clinical trials of symptomatic treatments in for MS-related symptoms and clinical trials that include symptom-specific clinical outcomes in MS patient populations. To explore this trend in clinical trial design and reporting, we conducted a search of the ClinicalTrials.gov website (www.clinicaltrials.gov) using the term "multiple sclerosis" and using filters to include only open trials (Phase 2, 3, or 4). We identified 120 ongoing or completed clinical trials. Of these, 37 (33 percent) report that quality of life or one or more of the "more common" MS symptoms are included as outcome measures (Table 4). Twenty-one trials include quality of life measures, 14 assess fatigue, 10 assess depression, 4 assess pain, 3 assess cognitive function, 3 assess muscle spasms, and 3 assess anxiety. Walking speed, mobility, gastrointestinal symptoms, and bladder symptoms are each listed as outcomes in

1 trial each. These 37 studies include 30 RCTs and 7 observational studies. One or more DMTs are evaluated in 5 of the RCTs and 5 of the observational studies. Of the 5 RCTs that include a DMT as an intervention, 5 include a quality of life measure, 3 assess fatigue, 1 assesses depression, and 1 compares anxiety and depressive symptoms associated with a morning versus evening administration of interferon beta 1a. Target sample size ranges from 8 to 711 in the RCTs and from 15 to 1080 in the observational studies. Planned follow up range from 24 days to 5.5 years. Twelve studies included at least two active interventions and these studies are highlighted in yellow in Table 4.

Table 4. Clinical Trials Registered in ClinicalTrials.gov with Quality of Life or Common MS Symptoms as Outcome Measures.
Comparative studies with more than one active intervention are highlighted in yellow.

NCT #	Title	Objective	Design/ Recruitment Phase	N	Interventions	QoL or Symptom-Specific Outcome Measure(s)	~Com-pletion Date	Follow Up
RCTs (30, arranged by anticipated completion date)								
NCT02012439	Comparison of the Efficacy and Mechanisms for MBCT and CT for Multiple Sclerosis (MS) Chronic Pain	Study to examine MBCT, as additional psychosocial treatment option for patients with chronic MS pain	RCT/ Recruiting	32	Mindfulness Based Cognitive Therapy, Cognitive Therapy	Pain intensity	09/01/14	5 weeks
NCT01879202	Methylphenidate as Treatment Option of Fatigue in Multiple Sclerosis	Determine whether MS-associated fatigue improves after 6 weeks of methylphenidate therapy	RCT/ Recruiting	96	Methylphenidate modified release, Maltodextrin	Fatigue as measured by Fatigue Severity Scale and as measured by Modified Fatigue Impact Scale (MFIS)	02/01/15	6 weeks
NCT02143167	Resistance Training and Amino Pyridine in Multiple Sclerosis	Study of the Effect of the Combination of Resistance Training and Prolonged Release Fampridine in Patients With Multiple Sclerosis	RCT/ Recruiting	50	SR-fampridine, Placebo, Resistance Training	Muscle power in the lower limbs; Activity; Walking capacity; Walking speed; Functional capacity in the lower limbs; Self rated walking capacity	01/01/15	26 weeks
NCT01411514	Oral Prednisone Taper Versus Placebo for the Treatment of Acute Relapses in Multiple Sclerosis	The primary analysis will test whether placebo is equivalent to oral prednisone taper on the recovery status as measured by EDSS change from baseline to 3 months after baseline	RCT/ Recruiting	40	Prednisone Taper, Placebo	Euroqol-5D (EQ-5D; Functional Assessment Multiple Sclerosis (FAMS); Beck Depression Inventory Second edition (BDI-II); Fatigue Scale for Motor and Cognitive functions (FSMC)	03/01/15	9 months
NCT02146534	Prolonged-release Fampridine as Adjunct Therapy to Active Motor Training in MS Patients	Demonstrate that prolonged-release fampridine will show greater benefit from active motor training	RCT/ Recruiting	50	SR-fampridine, Placebo, Motor Training	Change in mobility; Quality of life	03/01/15	14 weeks

NCT #	Title	Objective	Design/ Recruitment Phase	N	Interventions	QoL or Symptom-Specific Outcome Measure(s)	~Com-pletion Date	Follow Up
NCT02133664	Lipoic Acid and Omega-3 Fatty Acids for Cognitive Impairment in Multiple Sclerosis	Determine if lipoic acid and omega-3 fatty acids can improve cognitive function in MS patients	RCT/ Not yet recruiting	53	Alpha lipoic acid and omega-3 fatty acids, Placebo	Cognitive Test	05/01/15	12 weeks
NCT02096133	Vitamin D3 and the Stress-axis in MS	Effect of high vitamin D levels on the risk of depression in MS	RCT/ Recruiting	80	Cholecalciferol (D3), Placebo	Clinical outcomes on depression	07/01/15	16 weeks
NCT02217982	Pilot Study to Assess Dimethyl Fumarate Related GI Symptom Mitigation	Assess Dimethyl Fumarate (Tecfidera) Related GI Symptom Mitigation Via Food Bolus Alteration and Simethicone/Loperamide Administration	RCT/ Recruiting	100	Simethicone, Loperamid, Peanut Butter	Reported GI Symptoms|Diarrhea Reduction	07/01/15	7 weeks
NCT02280096	Efficacy and Safety of 4-aminopyridine on Cognitive Performance and Motor Function of Patients With Multiple Sclerosis	Efficacy and Safety of 4-aminopyridine on Cognitive and Motor Function	RCT/ Recruiting	24	4-Aminopyridine, Placebo	Fatigue; Walk; Spasticity	07/01/15	9 months
NCT01986998	Study to Compare the Clinical and Radiological Efficacy of 625 mg Versus 1250 mg of Oral Methylprednisolone in Patients With Multiple Sclerosis in Relapse	MRI study of high-dose oMP versus lower-high dose oMP for efficacy and safety treating acute relapse of multiple sclerosis	RCT/ Recruiting	28	Methylprednisolone (1250 mg/24h x3 days), Methylprednisolone (625 mg/24h x3 days)	MSQOL-54	07/01/15	91 days

NCT #	Title	Objective	Design/ Recruitment Phase	N	Interventions	QoL or Symptom-Specific Outcome Measure(s)	~Com-pletion Date	Follow Up
NCT02286557	Testing the Effects of Methylphenidate on Multiple Sclerosis	Test whether methylphenidate (MP), a well-known psychostimulant, can effective treat fatigue experienced by individuals with MS	RCT/ Not yet recruiting	36	Methylpheni-date, Placebo	Fatigue - Modified Fatigue Impact Scale	09/01/15	10 weeks
NCT02059096	Analgesic Effect of Repetitive Transcranial Magnetic Stimulation (rTMS) for Central Neuropathic Pain in Multiple Sclerosis	Evaluate the effect of repetitive Transcranial Magnetic Stimulation (rTMS) in the resolution of chronic pain	RCT/ Recruiting	66	Repetitive Transcranial Magnetic Stimulation (rTMS)	Brief pain inventory	10/01/15	4 weeks
NCT01848327	Caprylic Triglyceride for Treatment of Cognitive Impairments in Multiple Sclerosis	To evaluate the therapeutic effects of 90 days of caprylic triglyceride on cognitive impairment in multiple sclerosis	RCT/ Recruiting	158	Caprylic Triglyceride (dietary supplement), Placebo	Beck Depression Inventory -2nd edition (BDI-II); Multiple Sclerosis Quality of Life Inventory (MSQOL-54); Modified Fatigue Impact Scale (MFIS)	11/01/15	90 days
NCT02019550	Rebif® Rebidose® Versus Rebiject II® Ease-of-Use	Evaluate ease-of-use with Rebif® Rebidose® and Rebiject II® autoinjectors in subjects with relapsing remitting multiple sclerosis (RRMS)	RCT/ Recruiting	90	Rebif®, Rebidose®, Rebiject II®	Multiple Sclerosis International Quality of Life (MusiQoL)	11/01/15	8 weeks

NCT #	Title	Objective	Design/ Recruitment Phase	N	Interventions	QoL or Symptom-Specific Outcome Measure(s)	~Com-pletion Date	Follow Up
NCT02090348	Study to Evaluate Fatigue in Participants With Relapsing Remitting Multiple Sclerosis When Treated With BG00012 or Standard of Care	Determine whether BG00012 (dimethyl fumarate, DMF, Tecfidera™) taken over 12 months is effective in reducing Multiple Sclerosis-related fatigue, as measured by changes in the Fatigue Scale for Motor and Cognitive Functions (FSMC)	RCT/ Not yet recruiting	320	Dimethyl Fumarate, Standard of Care (SOC)	MS-related fatigue as measured by changes in the Fatigue Scale for Motor and Cognitive Functions (FSMC); Quality of life as measured by the 15-dimensional health-related quality of life questionnaire (15D HRQoL); Depression as measured by the Beck Depression Inventory-Fast Screen (BDI-FS) BG00012; Fatigue (measured by the Fatigue Scale for Motor and Cognitive Functions [FSMC] and the Fatigue Severity Scale [FSS]); Patient reported outcomes (PROs)	11/01/15	12 months
NCT02064816	A Study of Rebif® in Subjects With Relapsing Multiple Sclerosis	Assess whether the morning administration of interferon beta 1a (Rebif®) leads to a lower severity of flu-like symptoms (FLS) as compared to the evening administration	RCT/ Recruiting	218	Rebif® (am), Rebif® (pm)	Hospital Anxiety and Depression Scale (HADS); Fatigue Severity Scale (FSS); Multiple Sclerosis International Quality of Life (MusiQoL)	12/01/15	12 weeks
NCT02027025	Action of Baclofen Capsules in Spasticity Due to Multiple Sclerosis	Evaluate duration of action of Baclofen ER capsules (GRS) compared with placebo in subjects with spasticity due to Multiple sclerosis	RCT/ Recruiting	135	Baclofen(dose 1), Baclofen (dose 2), Placebo	Spasm frequency	12/01/15	24 days

NCT #	Title	Objective	Design/ Recruitment Phase	N	Interventions	QoL or Symptom-Specific Outcome Measure(s)	~Com-pletion Date	Follow Up
NCT02035514	Phase I-II Clinical Trial With Autologous Bone Marrow Derived Mesenchymal Stem Cells for the Therapy of Multiple Sclerosis	Proposed trial will enable us to ascertain whether autologous BM-MSC transplantation is a feasible and safe procedure, and whether BM-MSC can establish an environment of immune tolerance and through the local production of neurotrophic/growth factors, might induce neuroprotection and improvement in CNS function	RCT/ Recruiting	8	Bone marrow autologous mesenchymal stem cells transplantation	Quality of life	12/01/15	12 months
NCT01896700	Methylphenidate to Improve Balance and Walking in MS	Methylphenidate may also improve imbalance and walking deficits in MS by improving concentration and central integration	RCT/ Recruiting	24	Methylpheni-date, Placebo	Modified Fatigue Index Scale score	12/01/15	6 weeks
NCT01911377	Botulinum Toxin Type A for Treating Allodynic Pain in SCI and MS	Efficacy of Botulinum Toxin Type A ("Botox") in treating Allodynic-type neuropathic pain in people with spinal cord injury or multiple sclerosis	RCT/ Recruiting	12	Botulinum Toxin Type A, Normal Saline	Brief Pain Inventory; Neuropathic Pain Symptom Inventory;The Hospital Anxiety and Depression Scale	01/01/16	13 weeks
NCT02090413	Phase 4 Study of Effect of Aspirin on Flushing in Dimethyl Fumarate (DMF)-Treated Participants With Relapsing-Remitting Multiple Sclerosis (RRMS)	Evaluate whether ASA reduces the incidence and/or severity of flushing events in subjects with relapsing-remitting multiple sclerosis (RRMS)	RCT/ Recruiting	240	Dimethyl fumarate, ASA, ASA-Placebo	Quality of Life Measurements as Assessed by the Short Form 36 (SF-36) and European Quality of Life - 5 Dimensions - 5 Levels (EQ-5D-5L) Questionnaires	04/01/16	48 weeks

NCT #	Title	Objective	Design/ Recruitment Phase	N	Interventions	QoL or Symptom-Specific Outcome Measure(s)	~Com-pletion Date	Follow Up
NCT01466114	Estriol Treatment in Multiple Sclerosis (MS): Effect on Cognition	Ascertain whether treatment with an estrogen pill, used in combination with standard MS anti-inflammatory drugs, can improve cognitive testing as compared to treatment with a placebo pill in combination with standard anti-inflammatory drugs in women with MS	RCT/ Recruiting	64	Estriol, Norethindrone Progestin Placebo	Cognitive function as assessed by a brief battery of cognitive tests.	04/01/16	1 year
NCT01490502	Vitamin D Supplementation in Multiple Sclerosis	Effect of high-dose vitamin D supplementation on the rate of MS attacks and on the number of new lesions and change in brain volume on MRI will be determined	RCT/ Recruiting	172	High and Low dose Vitamin D3	MS Functional Composite Score; Health-related quality of life	12/01/16	2 years
NCT02340754	Mindfulness-based Stress Reduction for Multiple Sclerosis	Assess the feasibility of mindfulness-based stress reduction (MBSR) for adults with any type of multiple sclerosis	RCT/Not yet recruiting	60	Mindfulness-based Stress Reduction, MS Education Control	Perceived Stress Scale; Short Form-36 Mental Health Subscale; Patient Reported Outcomes Measurement Information System (PROMIS) Anxiety; PROMIS Depression Score; PROMIS Fatigue Score; PROMIS Pain Score	03/01/17	12 months

NCT #	Title	Objective	Design/ Recruitment Phase	N	Interventions	QoL or Symptom-Specific Outcome Measure(s)	~Com-pletion Date	Follow Up
NCT02273635	Efficacy, Safety and Tolerability of Andrographolides Versus Placebo in Patients With Progressive Forms of MS	Compare the efficacy and safety of andrographolide versus a placebo in patients with the progressive forms of MS	RCT/ Recruiting	68	Andrographolides, Placebo	Quality of life Multiple Sclerosis Impact Scale (MSIS 29); Depression by Beck scale; Fatigue by Krupp scale	04/01/17	24 months
NCT02086188	Study of Behavioral Modification Program and Mirabegron to Improve Urinary Urgency in Multiple Sclerosis	Determine if treatment with Mirabegron will improve urinary urgency control beyond that achieved with pelvic floor exercises alone	RCT/ Recruiting	40	Mirabegron, Placebo	Overactive Bladder Symptom Composite Score (OAB-SCS); Mean # of micturitions/day based on voiding diaries; Mean # of incontinence episodes/day; Qualiveen Questionnaire; Bladder Management Difficulties Questionnaire - Short Form (SCI-QOL v1.0)	05/01/17	3 years
NCT01817166	Efficacy of Cholecalciferol (Vitamin D3) for Delaying the Diagnosis of MS After a Clinically Isolated Syndrome	Evaluate the efficacy and tolerance of 2 years of treatment with cholecalciferol (vitamin D3) in patients with a clinically isolated syndrome at high risk for MS (CIS)	RCT/ Recruiting	316	Vitamin D3, Placebo	EQ5D questionnaire; SF36 questionnaire; FSMC fatigue scale	07/01/17	2 years
NCT02315872	ACTH for Fatigue in Multiple Sclerosis Patients	Effect of ACTH (Acthar) on Measures of Chronic Fatigue in Patients With Relapsing Multiple Sclerosis	RCT/ Recruiting	90	ACTH, Placebo	Fatigue; Depression; Quality of life	12/01/17	28 weeks

NCT #	Title	Objective	Design/ Recruitment Phase	N	Interventions	QoL or Symptom-Specific Outcome Measure(s)	~Com-pletion Date	Follow Up
NCT02283853	Phase 3 Efficacy and Safety Study of BG00012 in Pediatric Subjects With Relapsing-remitting Multiple Sclerosis (RRMS)	To evaluate the safety, tolerability, and effect on the disease course of BG00012 (dimethyl fumarate) in pediatric participants with RRMS as compared with a disease-modifying treatment	RCT/ Recruiting	142	dimethyl fumarate, Interferon Î²-1a	Fatigue as measured by the Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale scores; Quality of Life as measured by the PedsQL|Change	09/01/20	96 weeks
NCT01868048	Phase 3, 28-week, Randomized, Double-blind, Placebo-controlled Safety and Efficacy Study of Nabiximols as an add-on Therapy in Subjects With Spasticity Due to Multiple Sclerosis.	Determine the effective dose range of Sativex compared with placebo in relieving symptoms of spasticity	RCT/ Not yet recruiting	711	Sativex, Placebo	Mean spasm frequency (number of spasms per day)	Not Reported	28 weeks
OBSERVATIONAL STUDIES (7, arranged by anticipated completion date)								
NCT01578330	A 12 -Month, Open-label, Multi-center Study to Explore the Health Outcomes of FTY720	Assess the patients' satisfaction of treatment after 12 months treatment with fingolimod	Observational/ Recruiting	50	Fingolimod	Patient-reported health-related quality-of-life with Fingolimod	03/01/15	12 months
NCT02076841	SFERA Study: Prospective, Single-arm, Open-label, Multi-center, Interventional Phase IV Study	Assess the overall change in injection site tolerability from treatment switch to intramuscular interferon beta 1a Autoinjector (Avonex Pen)	Observational/ Recruiting	50	Interferon-beta-1a	Quality of Life as assessed by the change in Short Form (SF) Health Survey, SF-36; Fatigue Scale for Motor and Cognitive functions (FSMC)	06/01/15	12 months

NCT #	Title	Objective	Design/ Recruitment Phase	N	Interventions	QoL or Symptom-Specific Outcome Measure(s)	~Com-pletion Date	Follow Up
NCT01930708	A Study Evaluating the Effectiveness of Tecfidera™ (Dimethyl Fumarate) on Multiple Sclerosis (MS) Disease Activity and Patient-Reported Outcomes	Estimate the annualized relapse rate (ARR) in subjects with Relapsing Remitting Multiple Sclerosis (RRMS) who are treated with dimethyl fumarate (DMF) over a 12-month period	Observational/ Recruiting	1080	Dimethyl fumarate (DMF)	Modified Fatigue Impact Scale-5 Item (MFIS-5) score; EQ-5D 5 level version (EQ-5D-5L; Beck Depression Inventory-Fast Screen (BDI-Fast Screen)	03/01/16	12 months
NCT01883661	Safety and Efficacy of BMMNC in Multiple Sclerosis (MS)	Autologous Bone Marrow Derived Mono Nuclear Stem Cell (MNCs) to control symptoms and help to maintain a normal quality of life	Observational/ Recruiting	15	Autologous Bone Marrow Derived Mono Nuclear Stem Cell (MNCs)	Quality Of life	12/01/16	6 months
NCT02117050	RESOunD: REbif Satisfaction On Discontinuing Oral Dimethyl Fumarate	Assess treatment satisfaction in patients with relapsing MS who are currently being treated with, but are considering discontinuing, Tecfidera™	Observational/ Recruiting	90	Dimethyl fumarate (RebifÂ®)	Multiple Sclerosis Quality of Life-54 (MSQoL-54)	01/01/17	24 weeks
NCT02308137	Domperidone in Secondary Progressive Multiple Sclerosis (SPMS)	Determine if Domperidone in a dose of 40 mg daily can prevent worsening of walking ability in people secondary progressive MS	Observational/ Not yet recruiting	62	Domperidone	Modified Fatigue Impact Scale (MFIS)|Multiple Sclerosis Quality of Life Scale 54 item version	01/01/19	12 months
NCT02255656	Phase IIIB-IV Long-Term Follow-up Study for Patients Who Participated in CAMMS03409	Evaluate long-term safety of alemtuzumab	Observational/ Recruiting	812	Alemtuzumab GZ402673	Self-reported quality of life (QoL) as assessed by the Medical Outcome Study (MOS) 36-Item Short-Form Health Survey (SF-36) Version 2; Functional Assessment of Multiple Sclerosis (FAMS); EuroQoL in 5 Dimensions (EQ-5D)	01/01/20	5.5 years

Abbreviations: 15D-HRQoL=15-dimensional health-related quality of life questionnaire; ACTH=adrenocorticotropic hormone; ARR=annualized relapse rate; ASA=aspirin; BDI-FS=Beck Depression Inventory-Fast Screen; BDI-II=Beck Depression Inventory, 2nd edition; BG00012=dimethyl fumarate; BMMNC=bone marrow derived mono nuclear stem cell transplantation; BM-MSC=bone marrow derived mesenchymal stem cell; CIS=clinically isolated syndrome; CNS=central nervous system; CT=cognitive therapy; DMF=dimethyl fumarate; EDSS=Expanded Disability Status Scale; EQ-5D=European Quality of Life-5 Dimensions; EQ-5D-5L=European Quality of Life-5 Dimensions-5 Levels; FAMS=Functional Assessment of Multiple Sclerosis; FLS=flu-like symptoms; FSMC=Fatigue Scale for Motor and Cognitive Functions; FSS=Fatigue Severity Scale; FTY720=oral fingolimod; GI=gastrointestinal; GRS=gastric release system; HADS=Hospital Anxiety and Depression Scale; MBCT=mindfulness-based cognitive therapy; MBSR=mindfulness-based stress reduction; MEP=motor evoked potential; MFIS=Modified Fatigue Impact Scale; MFIS-5=Modified Fatigue Impact Scale-5 Item; MNCs=mono nuclear stem cells; MOS=Medical Outcome Study; MP=methylphenidate; MRI=magnetic resonance imaging; MS=multiple sclerosis; MSIS-29=Multiple Sclerosis Impact Scale; MSQOL-54=Multiple Sclerosis Quality of Life Inventory; MusiQoL=Multiple Sclerosis International Quality of Life questionnaire; N=number of participants; NCT=National Clinical Trial; OAB-SCS=Overactive Bladder Symptom Composite Score; oMP=oral methylprednisolone; QoL=quality-of-life; PedsQL=Pediatric Quality of Life Inventory; PROMIS=Patient Reported Outcomes Measurement Information System; PROs=patient-reported outcomes; RCT(s)=randomized controlled trial(s); RRMS=relapsing-remitting multiple sclerosis; rTMS=repetitive transcranial magnetic stimulation; SCI=spinal cord injury; SCI-QOL v1.0=Bladder Management Difficulties Questionnaire-Short Form; SF-36=Medical Outcome Study 36-Item Short-Form Health Survey; SPMS=secondary progressive multiple sclerosis

Potential of New Research to Increase Certainty About Treatment of MS-Related Symptoms

Given that there is limited evidence on the effectiveness of DMTs or other treatment options for alleviating the symptoms of MS and improving health-related quality of life for patients with MS, most stakeholders (e.g., patients, providers, payers) are likely to be interested in new information about MS and in implementing new findings that might lead to improvement outcomes that are most meaningful to patients, including treatment options for MS-related symptoms.

Potential for New Information to Rapidly Improve Care and Patient-Centered Outcomes

Facilitators and Barriers That May Affect Implementation of New Findings in Practice

Facilitators that might affect the implementation of new findings in practice include the observation that there is an increasing interest among stakeholders in patient-centered outcomes in general, and for MS specifically. In the case of MS, new findings could be disseminated readily via the National Multiple Sclerosis Society website (http://www.nationalmssociety.org), which is used by patients, families, and providers, as well as through relevant professional societies and other patient advocacy groups. As for potential barriers, rapid changes in the available treatments and their supporting may complicate efforts to update MS-specific guidelines and to therefore provide stakeholders with timely and accurate information.

Likelihood That Results of New Research Would Be Immediately Implemented in Practice

The historical focus of research developing DMTs has left MS symptom research and

treatment under-represented or unexamined. Furthermore, no apparent concerted effort has been made yet to characterize the enduring symptoms MS patients suffer as a result of their disease, especially nonfocal symptoms like fatigue, cognitive decline, and depression. These observations increase the likelihood that new research on common primary MS-related symptoms will be immediately implemented in practice by providers or patients or both.

Durability of Information

Likelihood That Information from New Comparative Effectiveness Research (CER) Would Remain Current

A systematic review published in October 2013 focused on the comparative efficacy, safety, and cost-effectiveness of both individual DMTs and combination therapy for relapsing-remitting MS.[20] Currently a number of new DMTs are in development for the treatment of MS,[20] and as new drug treatments continue to be approved, any CER that compares current drug treatments may quickly become outdated. Information from CER on the topics of patient-centered outcome measures is, however, likely to remain current for several years because this does not now appear to be an area of very active research. Research on ways to help patients make informed decisions regarding their available treatment options, incorporating their patient preferences and characteristics, is likely to remain currently for several years, and to be potentially generalizable to other clinical domains.

Opportunities for PCORI to Fund Comparative Effectiveness Studies

Based on our review of the literature and informed expert judgment, key uncertainties in research related to treatment of MS symptoms—and which may be opportunities for PCORI

targeted funding—include the following questions:

- What are the most important patient-centered and family-centered outcomes for patients with MS and their families?
- What is the comparative effectiveness of DMTs on MS-related symptoms in patients with MS? Does this effectiveness differ for different subgroups of MS patients (i.e. those with relapsing, remitting MS, those with secondary progressive MS, or those with primary progressive MS)?
- What is the comparative effectiveness of therapies other than DMTs (e.g., exercise therapy, CAM therapies, non-DMT pharmacologic therapies) on MS-related symptoms in patients with MS? Does this effectiveness differ for different subgroups of MS patients (i.e. those with relapsing, remitting MS, those with secondary progressive MS, or those with primary progressive MS)?
- Are there DMTs, non-DMT pharmacologic treatments, or nonpharmacologic interventions that can prevent the development of MS-related symptoms?
- How does the use of therapies other than DMTs for patients with MS impact the effectiveness of DMTs in patients with MS?
- How do the most frequently used MS outcomes (e.g., annualized relapse rate, disease progression, and disability) correlate with symptom severity, health-related quality of life, and other patient-centered outcomes that are meaningful to patients?
- What considerations are most important to patients and providers in deciding between various DMTs and/or other symptomatic treatment options?
- What existing tools, or as-yet not developed tools, effectively measure MS-related

symptoms? How can these tools be used to identify best practices to mitigate the impact of these symptoms on patients' quality of life?

- Do DMTs or symptomatic treatments differ in effectiveness or safety by patient characteristics, MS type or other disease characteristics, genetic differences, or other patient subgroups?
- What are the comparative safety and effectiveness of strategies to help patients engage in key self-management behaviors for managing MS or MS-related symptoms?
- How do people with MS find, assess, and integrate treatment information to manage their health?
- What kind of information do people with MS seek to inform their self-care or shared decision making with their healthcare providers?
- How do patient preferences influence the trade-offs between symptom relief and other treatment goals in MS?

Summary

Multiple sclerosis is characterized by the presence of a wide variety of symptoms, many of which can have a very significant negative impact on health-related quality of life. There are 10 drugs approved by the FDA as DMTs for MS that have been shown to slow disease progression There is little evidence, however, that any of these DMTs ameliorate MS-related symptoms. Similarly, there is a very large body of literature that evaluates a wide variety of treatment options for symptoms that are commonly experienced by persons with MS, but there is limited evidence of the effectiveness and safety of these interventions in MS patient populations, specifically. There is a clear and urgent need for research that can inform clinical care for

patients who seek treatment and/or prevention of symptoms caused by MS.

Acronyms and Abbreviations

AAN	American Academy of Neurology
CADTH	Canadian Agency for Drugs and Technologies in Health
CAM	complementary and alternative medicine
CER	comparative effectiveness research
CNS	central nervous system
DMT(s)	disease-modifying therapy/therapies
EDSS	Expanded Disability Status Scale
FDA	U.S. Food and Drug Administration
MRI	magnetic resonance imaging
MS	multiple sclerosis
PCORI	Patient-Centered Outcomes Research Institute
RCTs	randomized controlled trials

References

1. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014;83(3):278-86. PMID: 24871874.
2. Richards RG, Sampson FC, Beard SM, Tappenden P. A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models. Health Technol Assess. 2002;6(10):1-73. PMID: 12022938.
3. Olek MJ. Treatment of relapsing-remitting multiple sclerosis in adults. UpToDate. Feb 10, 2015. Available at: http://www.uptodate.com/contents/treatment-of-relapsing-remitting-multiple-sclerosis-in-adults. Accessed: March 11, 2015.
4. Utz KS, Hoog J, Wentrup A, et al. Patient preferences for disease-modifying drugs in multiple sclerosis therapy: a choice-based conjoint analysis. Ther Adv Neurol Disord. 2014;7(6):263-75. PMID: 25371708.
5. Wilson L, Loucks A, Bui C, et al. Patient centered decision making: use of conjoint analysis to determine risk-benefit trade-offs for preference sensitive treatment choices. J Neurol Sci. 2014;344(1-2):80-7. PMID: 25037284.
6. Knaster ES, Yorkston KM, Johnson K, McMullen KA, Ehde DM. Perspectives on self-management in multiple sclerosis: a focus group study. Int J MS Care. 2011;13(3):146-52. PMID: 24453718.
7. Heesen C, Kasper J, Segal J, Kopke S, Muhlhauser I. Decisional role preferences, risk knowledge and information interests in patients with multiple sclerosis. Mult Scler. 2004;10(6):643-50. PMID: 15584489.

8. Tullman MJ. Overview of the epidemiology, diagnosis, and disease progression associated with multiple sclerosis. Am J Manag Care. 2013;19(2 Suppl):S15-20. PMID: 23544716.

9. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol. 2010;9(5):520-32. PMID: 20398859.

10. MS Progression. MS ActiveSource website. Available at: http://www.msactivesource.com/ms-progression.xml. Accessed March 10, 2015.

11. Lavery AM, Verhey LH, Waldman AT. Outcome measures in relapsing-remitting multiple sclerosis: capturing disability and disease progression in clinical trials. Mult Scler Int. 2014;2014:262350. PMID: 24883205.

12. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-52. PMID: 6685237.

13. Socie MJ, Sosnoff JJ. Gait variability and multiple sclerosis. Mult Scler Int. 2013;2013:645197. PMID: 23533759.

14. Ivanova JI, Birnbaum HG, Samuels S, et al. The cost of disability and medically related absenteeism among employees with multiple sclerosis in the US. Pharmacoeconomics. 2009;27(8):681-91. PMID: 19712010.

15. Olek MJ. Epidemiology and clinical features of multiple sclerosis in adults. UpToDate. Nov 4, 2013. Available at: www.uptodate.com/contents/epidemiology-and-clinical-features-of-multiple-sclerosis-in-adults?source=search_result&search=multiple+sclerosis&selectedTitle=2%7E150. Accessed: March 5, 2015

16. Phadke JG. Survival pattern and cause of death in patients with multiple sclerosis: results from an epidemiological survey in north east Scotland. J Neurol Neurosurg Psychiatry. 1987;50(5):523-31. PMID: 3495637.

17. Scalfari A, Neuhaus A, Daumer M, et al. Early relapses, onset of progression, and late outcome in multiple sclerosis. JAMA Neurol. 2013;70(2):214-22. PMID: 23407713.

18. Mathis AS. Managed care aspects of managing multiple sclerosis. Am J Manag Care. 2013;19(2 Suppl):S28-34. PMID: 23544718.

19. National Multiple Sclerosis Society (NMSS). Symptoms. NMSS website. Available at: http://www.nationalmssociety.org/Symptoms-Diagnosis/MS-Symptoms. Accessed March 10, 2015.

20. Canadian Agency for Drugs and Technologies in Health (CADTH). Recommendations for Drug Therapies for Relapsing-Remitting Multiple Sclerosis. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health (CADTH); 2013 Oct. (CADTH Therapeutic Review, Volume 1, Issue 2C). Available at: www.cadth.ca/media/pdf/TR0004_RRMS_RecsReport_TR_e.pdf. Accessed: March 5, 2015.

21. Yadav V, Bever C, Jr., Bowen J, et al. Summary of evidence-based guideline: complementary and alternative medicine in multiple sclerosis: report of the guideline development subcommittee of the American Academy of Neurology. Neurology. 2014;82(12):1083-92. PMID: 24663230.

22. Rietberg MB, Brooks D, Uitdehaag BM, Kwakkel G. Exercise therapy for multiple sclerosis. Cochrane Database Syst Rev. 2005(1):Cd003980. PMID: 15674920.

23. Pilutti LA, Greenlee TA, Motl RW, Nickrent MS, Petruzzello SJ. Effects of exercise training on fatigue in multiple sclerosis: a meta-analysis. Psychosom Med. 2013;75(6):575-80. PMID: 23788693.

24. Ensari I, Motl RW, Pilutti LA. Exercise training improves depressive symptoms in people with multiple sclerosis: results of a meta-analysis. J Psychosom Res. 2014;76(6):465-71. PMID: 24840141.

25. Adamson BC, Ensari I, Motl RW. Effect of exercise on depressive symptoms in adults with neurologic disorders: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2015. PMID: 25596001.

26. Jawahar R, Oh U, Yang S, Lapane KL. Alternative approach: a systematic review of non-pharmacological non-spastic and non-trigeminal pain management in multiple sclerosis. Eur J Phys Rehabil Med. 2014;50(5):567-77. PMID: 24621986.

27. Schwab RS, Poskanzer DC, England AC, Jr., Young RR. Amantadine in Parkinson's disease. Review of more than two years' experience. JAMA. 1972;222(7):792-5. PMID: 4677928.

28. Pucci E, Branas P, D'Amico R, et al. Amantadine for fatigue in multiple sclerosis. Cochrane Database Syst Rev. 2007(1):CD002818. PMID: 17253480.

29. Plioplys AV, Plioplys S. Amantadine and L-carnitine treatment of Chronic Fatigue Syndrome. Neuropsychobiology. 1997;35(1):16-23. PMID: 9018019.

30. Pistone G, Marino A, Leotta C, et al. Levocarnitine administration in elderly subjects with rapid muscle fatigue: effect on body composition, lipid profile and fatigue. Drugs & Aging. 2003;20(10):761-7. PMID: 12875611.

31. Tejani AM, Wasdell M, Spiwak R, Rowell G, Nathwani S. Carnitine for fatigue in multiple sclerosis. Cochrane Database Syst Rev. 2012;5:Cd007280. PMID: 22592719.

32. Mills RJ, Yap L, Young CA. Treatment for ataxia in multiple sclerosis. Cochrane Database Syst Rev. 2007(1):CD005029. PMID: 17253537.

33. Shakespeare DT, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis. Cochrane Database Syst Rev. 2003(4):CD001332. PMID: 14583932.

34. Xiao Y, Wang J, Luo H. Sildenafil citrate for erectile dysfunction in patients with multiple sclerosis. Cochrane Database Syst Rev. 2012;4:CD009427. PMID: 22513975.

35. Nicholas RS, Friede T, Hollis S, Young CA. Anticholinergics for urinary symptoms in multiple sclerosis. Cochrane Database Syst Rev. 2009(1):CD004193. PMID: 19160231.

36. He D, Zhang Y, Dong S, et al. Pharmacological treatment for memory disorder in multiple sclerosis. Cochrane Database Syst Rev. 2013;12:Cd008876. PMID: 24343792.

37. Rosti-Otajarvi EM, Hamalainen PI. Neuropsychological rehabilitation for multiple sclerosis. Cochrane Database Syst Rev. 2014;2:CD009131. PMID: 24515630.

38. Koch MW, Glazenborg A, Uyttenboogaart M, Mostert J, De Keyser J. Pharmacologic treatment of depression in multiple sclerosis. Cochrane Database Syst Rev. 2011(2):CD007295. PMID: 21328292.

39. Minden SL, Feinstein A, Kalb RC, et al. Evidence-based guideline: assessment and management of psychiatric disorders in individuals with MS: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014;82(2):174-81. PMID: 24376275.

40. Trisolini MG. Comparison of Multiple Sclerosis Guidelines Underscores Need for Collaboration. December 8, 2008. Available at: http://guidelines.gov/expert/expert-commentary.aspx?id=16443. Accessed: March 5, 2015.