Multiple Sclerosis Therapeutics

Fourth Edition
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## Abbreviations list

This list includes abbreviations that were utilized in multiple chapters.

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<th>Abbreviation</th>
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<tr>
<td>9HPT</td>
<td>Nine-Hole Peg Test</td>
<td>Ig</td>
<td>immunoglobulin</td>
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<td>AA</td>
<td>African American</td>
<td>IL-2</td>
<td>interleukin, e.g. IL-2</td>
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<td>AE</td>
<td>adverse event</td>
<td>IM</td>
<td>intramuscular</td>
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<td>APC</td>
<td>antigen presenting cell</td>
<td>IMD</td>
<td>immunomodulatory drug</td>
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<td>AQP4</td>
<td>aquaporin-4</td>
<td>IRIS</td>
<td>immune reconstitution inflammatory</td>
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<td>ARR</td>
<td>annualized relapse rate</td>
<td>i.v.</td>
<td>intravenous</td>
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<td>B-cell</td>
<td>B lymphocyte</td>
<td>IVIg</td>
<td>intravenous immunoglobulin</td>
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<tr>
<td>BBB</td>
<td>blood–brain barrier</td>
<td>MBP</td>
<td>myelin basic protein</td>
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<td>BDNF</td>
<td>brain-derived neurotrophic factor</td>
<td>MHC</td>
<td>major histocompatibility complex</td>
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<td>BPF</td>
<td>brain parenchymal fraction</td>
<td>MMP</td>
<td>matrix metalloproteinase</td>
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<tr>
<td>CD</td>
<td>clinically definite</td>
<td>MOG</td>
<td>myelin oligodendrocytes glycoprotein</td>
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<td>CDMS</td>
<td>clinically definite multiple sclerosis</td>
<td>MP</td>
<td>methylprednisolone</td>
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<td>confidence interval</td>
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<td>magnetic resonance imaging</td>
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<td>clinically isolated syndrome</td>
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<td>conventional magnetic resonance imaging</td>
<td>MS</td>
<td>multiple sclerosis</td>
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<td>CNS</td>
<td>central nervous system</td>
<td>MSFC</td>
<td>Multiple Sclerosis Functional Composite</td>
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<td>CSF</td>
<td>cerebrospinal fluid</td>
<td>MSQLI</td>
<td>Multiple Sclerosis Quality of Life Inventory</td>
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<td>DMT</td>
<td>disease-modifying therapy</td>
<td>MSSS</td>
<td>Multiple Sclerosis Severity Scale</td>
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<tr>
<td>DTI</td>
<td>diffusion tensor imaging</td>
<td>MxA</td>
<td>Myxovirus resistance protein A</td>
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<tr>
<td>EAE</td>
<td>experimental autoimmune encephalomyelitis</td>
<td>NAA</td>
<td>N-acetyl aspartate</td>
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<td>EBV</td>
<td>Epstein Barr virus</td>
<td>NAb</td>
<td>neutralizing antibody</td>
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<tr>
<td>EDSS</td>
<td>Expanded Disability Status Scale</td>
<td>NABT</td>
<td>normal-appearing brain tissue</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
<td>NAWM</td>
<td>normal-appearing white matter</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
<td>NMO</td>
<td>neuromyelitis optica</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
<td>NP</td>
<td>neuropsychological</td>
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<tr>
<td>FSS</td>
<td>Functional System Score</td>
<td>OCT</td>
<td>optical coherence tomography</td>
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<tr>
<td>GA</td>
<td>glatiramer acetate, Copaxone</td>
<td>ON</td>
<td>optic neuritis</td>
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<tr>
<td>GABA</td>
<td>gamma-aminobutyric acid</td>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>Gd-enhancing</td>
<td>gadolinium-enhancing</td>
<td>PASAT</td>
<td>Paced Auditory Serial Addition Test</td>
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<td>GM</td>
<td>gray matter</td>
<td>PLEX</td>
<td>plasma exchange</td>
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<tr>
<td>HLA</td>
<td>human leukocyte antigen</td>
<td>PLP</td>
<td>proteolipid protein</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
<td>PML</td>
<td>progressive multifocal leukoencephalopathy</td>
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<tr>
<td>HRQoL</td>
<td>health-related quality of life</td>
<td>PP</td>
<td>primary progressive</td>
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<tr>
<td>IFNβ</td>
<td>interferon beta</td>
<td>PPMS</td>
<td>primary progressive multiple sclerosis</td>
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<tr>
<td>IFNβ-1b</td>
<td>interferon beta-1b</td>
<td>QoL</td>
<td>quality of life</td>
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<tr>
<td>IFNβ-1a(IM)</td>
<td>interferon beta-1a by intramuscular injection</td>
<td>RCT</td>
<td>randomized controlled trial</td>
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<tr>
<td>IFNβ-1a(SC)</td>
<td>interferon beta-1a by subcutaneous injection</td>
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### List of abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>RNFL</td>
<td>retinal nerve fiber layer</td>
<td>SP</td>
<td>secondary progressive</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver operating characteristic</td>
<td>SPMS</td>
<td>secondary progressive multiple sclerosis</td>
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<tr>
<td>RR</td>
<td>relapsing–remitting</td>
<td>T25FW</td>
<td>Timed 25-Foot Walk</td>
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<td>RRMS</td>
<td>relapsing–remitting multiple sclerosis</td>
<td>T-cell</td>
<td>T lymphocyte</td>
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<td>SAE</td>
<td>serious adverse event</td>
<td>TCR</td>
<td>T-cell receptor</td>
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<tr>
<td>s.c.</td>
<td>subcutaneous</td>
<td>TGFβ</td>
<td>transforming growth factor-beta</td>
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<td>SDMT</td>
<td>Symbol Digits Modalities Test</td>
<td>TNFα</td>
<td>tumor necrosis factor-alpha</td>
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<td>SNP</td>
<td>single nucleotide polymorphism</td>
<td>WM</td>
<td>white matter</td>
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Foreword

Multiple Sclerosis Therapeutics is now in its fourth edition and remains the definitive source of information about the theory and art of clinical trials for this complex disorder. The first edition of the book appeared in 1999, only a few years after regulatory approval of the first agents to modify the multiple sclerosis (MS) disease course. Subsequent editions have appeared every 3 to 5 years, attesting to the rapid progress that has been made over the past decade. However, this fourth edition serves as a reminder that we still have only partially effective therapies for only some forms of the disease, that available therapies have problematic side effects and remain extremely expensive, and that there remains a strong demand for safer, more effective, more tolerable, and more affordable therapeutic agents for all forms of MS. An interesting irony to the progress that has been made is that our past success has created new problems in clinical trial theory, design, and conduct. The availability of multiple relatively safe and effective immunomodulatory therapies stresses the need to identify new biological modes of action that might be useful for MS, thus underscoring the problem that we still do not know entirely what causes the disease. And, with many patients worldwide having access to available therapy, the practical and ethical challenges of testing the next generation(s) of therapies require entirely new ways of thinking about trial design and interpretation.

Compared with prior editions, the current volume contains expansive chapters on the biology and demographics of MS, including separate chapters on disease pathology, immunology, genetics, and epidemiology. New MS treatments will require our ability to better target the etiopathology of the disease. Thus, this emphasis on the fundamentals of the disease process helps to chart progress in disease pathology that will surely result in new therapeutic modalities.

An extensive treatment of clinical trial methodology is provided in 19 chapters, providing updated information on clinical assessment, imaging outcomes, biological markers, and evolving developments in regulatory review. New information about cortical lesions in MS – previously a relatively underappreciated locus of disease pathology – points to modalities such as double inversion recovery imaging and other measures of cortical pathology that should be in the “mix” of assessments done to track changes in the brain by MRI. A review of data on neutralizing antibodies that often develop in subjects using interferon therapy has been moved from the prior edition’s section on specific therapeutic modalities to the current section on trial design considerations, a reflection perhaps of the need to pay attention to the complexities of evaluating long-term efficacy and of combining new experimental therapies with available therapies which may no longer be effective in some subjects.

The fourth edition contains 27 separate chapters devoted to specific available or experimental therapies for MS, a significant increase over the prior edition. Significantly, there are new chapters on therapies that were not particularly visible at the time of the prior edition 5 years ago: cladribine, fingolimod, fumarate, laquinimod, and teriflunomide, all represent a new era of oral therapy for MS; and alemtuzumab and daclizumab may represent the next steps for monoclonal antibody therapy. A new chapter on mesenchymal and neural stem cell transplantation represents a “brave new world” for MS therapeutics and would not have been possible to include previously. Finally, no discussion of MS therapies today would be complete without a review of the current knowledge and controversy about chronic cerebrospinal venous insufficiency, its detection, prevalence, relevance, and treatment.

Of highly practical impact is the final section of the volume, on “Therapy in Clinical Practice.” Recent therapeutic achievements dictate the need for practical advice to practitioners around the world and the expansion of treatment-focus fellowship programs for MS physicians and allied health professionals is an indication of the need for “texts” like Multiple Sclerosis Therapeutics. Diagnosis and treatment of neuromyelitis optica (NMO) is given a new chapter, emphasizing both the recent development of a biological marker for the disease (the aquaporin 4 autoantibody assay) and the prominent role that NMO and NMO spectrum disorders play in the differential diagnosis for MS. Many clinicians are newly focused on diagnosis, treatment, and management of pediatric-onset MS and this topic as well is given a new chapter in the present edition. Also previously not addressed is the topic of comorbidities in patients with MS, which highlights the need to consider and treat non-MS pathologies as well as MS itself, whether these be associated with the underlying autoimmune nature of the disease, a symptomatic consequence of the disease or its treatments, or are simply coincidental.

This will not be the final edition of Multiple Sclerosis Therapeutics. Fundamental and applied research related to MS is burgeoning and will result in new, especially
Foreword

non-immunomodulatory, interventions with novel modes of action that may be used to combine with, or replace, current therapies. Ongoing clinical studies described in this fourth edition will be completed in the next few years and some, at least, will be added to our mix of available therapies with the consequent need for new perspectives on patient management for relapsing and likely progressive forms of MS. Increased focus on biomarkers – cellular, biochemical and imaging – and their potential as valid clinical surrogates will alter the outcomes that we monitor in MS trials. A better understanding of the genetic basis for MS and its subtypes and a better, biologically based definition of MS phenotypes and more efficient and accurate diagnostic procedures will result in more targeted clinical trial recruitment based on rational objective data and might well usher in an era of “personalized medicine.” Regulatory agencies worldwide have already begun to stress the importance of head-to-head comparisons of new agents against available agents to provide a sense of relative safety and efficacy to guide physicians, patients, and third-party payers. And regulators are on the cusp of providing formal guidance for adaptive trial design in an effort to streamline current trial and statistical protocols and guidelines for the development of biosimilar agents, creating the possibility of “generic” products for MS with all of their challenges.

For any practitioner, clinical investigator, or fundamental or applied scientist who hopes his or her work will have an impact on new treatments for MS, *Multiple Sclerosis Therapeutics* is an invaluable resource. Its regular updating has provided an ongoing MS history for more than a decade and will serve to guide and prepare us all for the exciting developments to come.

*Stephen C. Reingold, PhD*

*President, Scientific and Clinical Review Associates, LLC Salisbury, Connecticut and New York City, NY, USA*
Preface

The field of multiple sclerosis therapeutics is rapidly changing. Understanding of the disease is improving, leading to new concepts with major diagnostic and therapeutic implications. Clinical trial methodology is evolving, and there are numerous ongoing or recently completed clinical trials for novel therapeutic strategies in all categories of the disease. As a result, a variety of new therapeutic options are emerging. Multiple sclerosis therapy is now proactive – there is general consensus that early diagnosis and initiation of disease-modifying drug therapy, and active monitoring of patients during therapy are essential to delay or prevent neurological disability. For all these reasons, we felt a single text, providing a comprehensive summary of the dynamic field of multiple sclerosis therapeutics, would be valuable.

This book has been substantially updated from the prior edition: over 50% of the material is new, including new chapters on pathology, epidemiology, gray matter imaging, neuromyelitis optica, pediatric multiple sclerosis, medical comorbidities, chronic cerebrospinal venous insufficiency, and a wide range of emerging therapies. All chapters have been substantially revised to provide current information, particularly on rapidly evolving topics such as genetics, magnetic resonance imaging and other endpoints, drug mechanism of action and potential adverse effects, and neuroprotection and repair strategies. The current status of recently approved disease-modifying and symptomatic drugs for multiple sclerosis is summarized. Experts provide overviews on disease and symptom management. This book will be an essential reference for practitioners caring for patients with multiple sclerosis, investigators planning or conducting clinical trials, clinical and research trainees, and clinical trial sponsors.

We thank the authors and co-authors who provided current and comprehensive chapters. We also gratefully acknowledge Cassandra Talerico, PhD for expert assistance in compiling the book. Finally, we dedicate this book to our wives and families for their patience and support.

J. A. Cohen and R. A. Rudick