How to S.E.A.R.C.H.™ for the Right MS Therapy for You!

Second Edition

MSAA
Multiple Sclerosis Association of America
Improving Lives Today!™

How to S.E.A.R.C.H.™ for the Right MS Therapy for You!

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MSAA strives to provide useful, up-to-date information on matters of concern to MS patients and their families. This material is intended for general informational purposes only, and it does not constitute medical advice. You should not use the information presented as a means of diagnosis or for determining treatment. For diagnosis and treatment options, you are urged to consult your physician.

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Introduction

MSAA's S.E.A.R.C.H.™ program is just one of several programs designed as tools for individuals with MS and their families to play a more active role in the successful management of their MS. In addition, these programs assist patients and care partners with working more productively with their healthcare team.

Other tools developed include My MS Manager,™ a free application for mobile phones that helps individuals to track and record their symptoms and create reports for their healthcare professionals. MSAA's My MS Resource Locator® enables individuals to find nearby professionals and resources aimed at helping the MS community.

With MSAA's SEARCH program, individuals with MS and their care partners learn about the FDA-approved disease-modifying therapies for MS. They are given the questions to ask about these drugs when discussing them with their doctor. Overall, our SEARCH program can assist individuals with relapsing forms of MS to find the MS therapy that is right for them.

Readers should note that as of the time of this booklet's printing, long-term treatments have only been approved for individuals with relapsing forms of MS. No long-term treatments (at this time) have been approved for individuals with progressive forms of MS. However, several clinical trials are presently studying the effectiveness and safety of different medications with progressive forms of MS, and some medications are making progress toward FDA approval. Please visit **mymsaa.org/types-of-ms** for information on the different forms of MS, or visit **mymsaa.org/ppms** for specific information on PPMS.

For an overview of MS and the approved treatments, as well as a listing of drug-assistance programs, please refer to the appendices at the end of this booklet. For additional information on MS, approved treatments, symptom-management therapies, plus MSAA's programs and services, please visit MSAA's website at **mymsaa.org** or contact MSAA at **(800) 532-7667**. Inquiries may also be emailed to **MSquestions@mymsaa.org**.

The Changing Landscape

The first treatment for relapsing-remitting multiple sclerosis (RRMS) was approved by the United States Food and Drug Administration (FDA) in 1993. This forever changed the landscape of how MS could be managed. The approval of Betaseron® (interferon beta-1b) for RRMS ushered in a remarkable surge of MS treatments designed to reduce the number and severity of exacerbations and help lessen disease progression. Throughout the past two decades, more than a dozen medications for MS have become available, giving neurologists and patients a variety of treatment options for slowing disease activity.

Along with these treatments, known as disease-modifying therapies (DMTs), came the expanded use and improved technology of magnetic resonance imaging (MRI). Through diagnostic and follow-up MRI scans of the brain and spinal cord, physicians could now better diagnose, treat, track, and manage the ever-changing course of MS in a more definitive and proactive manner.

Advances in MRI techniques, along with years of consistent research data, have demonstrated that most patients who begin and maintain a DMT will experience fewer active lesions on the brain and spinal cord, fewer and less severe exacerbations, a reduction in symptoms, and potentially a delay in disease progression and disability. In addition, more recent clinical trials have found that many of these DMTs also delay time to a second MS-like event, in cases of clinically isolated syndrome (CIS). CIS refers to the first presenting symptom of MS, prior to a confirmed diagnosis.

These impressive results led the MS medical community to universally adopt and support the position of treating relapsing forms of MS with approved DMTs as early as possible and for patients to maintain adherence. Since the mid-2000s, the issue of treatment adherence has been aggressively advocated by leaders in the MS medical and healthcare communities, including MSAA.

Framing the Discussion

While the issue of treatment adherence continues to gain awareness and momentum, MSAA also recognizes the complexity of the situation. Healthcare providers continue to encourage their patients to become more health-literate and to take an active, decision-making role in selecting a treatment. In doing so, an extraordinary number of factors need to be considered when choosing an appropriate MS therapy or switching from one DMT to another.

Among the numerous questions to consider include: What are the therapies? Am I a candidate? What should I know about each one? How will my body react to taking one of these medications? How are the different medications administered? What about the costs or insurance? Once I have begun taking a DMT, how do I know if the one I am prescribed is working?

These and other important considerations require ongoing conversations with your doctor and other healthcare professionals. The treatment decision for each patient is unique and must be addressed individually between the person and his or her healthcare team. Additionally, patients must recognize the need to prioritize their issues, questions, and concerns in order to maximize the time with their doctor and healthcare team.

With so much information to remember, organize, and prioritize, MSAA recognized the need to help frame these important discussions and created "S.E.A.R.C.H.™"

What is S.E.A.R.C.H.™?

Designed as a memory aid, the SEARCH acronym represents the key areas that should be considered when "searching" for the most appropriate MS treatment. Each letter represents an important topic to be addressed by patients, physicians, and other healthcare and social service professionals. SEARCH stands for:

Safety
Effectiveness
Access
Risks
Convenience
Health Outcomes
(overall wellness and quality of life)

The SEARCH acronym is not only a useful tool to help frame and remember these important issues, but gives patients a way to start the conversation with their healthcare team. MSAA's goal is to foster a positive doctor-patient relationship and allow the dialog to take its own course, recognizing that MS is a uniquely individual disease that affects each person differently. MSAA is not advocating any one treatment or approach, but is rather looking to help guide the conversation between patients and their medical team toward issues that matter most.

To assist with this conversation, MSAA has prepared a sampling of key questions within each aspect of SEARCH. These questions represent a broad overview of many different factors to consider and investigate. They also allow the flexibility for patients to adapt their specific medical history, current disease state, experiences and other physical, emotional, and financial aspects into the decision-making process.

The S.E.A.R.C.H.™ Questions

MSAA has developed the following SEARCH questions to serve as a sample, or guide, for you to consider when evaluating your own healthcare needs. These SEARCH questions merely reflect a starting point to help you think about your own medical situation, issues to prioritize, and ways to develop questions which address your specific healthcare needs.

Safety

- What are the long-term safety profiles of these FDA-approved MS disease-modifying therapies (DMTs)?
- What tests are required prior to taking DMTs? What tests are required while receiving DMTs?
- How will DMTs interact with my current medical treatments, other medical conditions, and any complementary and alternative medicines?

Effectiveness

- How effective are these DMTs in reducing MS relapses, reducing disease activity (as shown on an MRI), and delaying disability?
- What are my realistic expectations regarding the effectiveness of these DMTs?
- How can I tell if my DMT is working?

Access

Access to DMT medications and the ability to switch from one therapy to another can vary greatly depending on your insurance provider, coverage levels, and additional restrictions such as step-therapy requirements. Please see below for a few sample questions, with additional information on page 12.

1. Which MS DMT medications are covered by my insurance carrier?
2. What are their Tier Levels and how does that affect the cost?
3. If I needed to change my MS medication, what alternative DMTs are available to me?

Risks

- What are the risks of side effects associated with these DMTs?
- How frequent and severe are the side effects? How soon do they subside?
- Can these side effects be managed, and if so, how?

Convenience

- How are the DMTs administered?
- How often do I take these DMTs?
- Must I have regular tests or visits to other healthcare providers to monitor the effects of my treatment?

Health Outcomes

- How will my general health and quality of life be affected by these DMTs?
- Will taking a DMT lower my immune system and cause other problems?
- Can these DMTs assist with my mobility, cognition, and other health factors?

When using the SEARCH model, it is also important to recognize that reviewing key topics and questions will likely require more than one office visit with members of your healthcare team. The SEARCH framework can also be helpful when conducting your own research before or after visiting your healthcare provider.

Treatment Chart

This easy-to-follow reference chart shows those medications that have been approved by the FDA and are available for the long-term treatment of relapsing forms of MS. This chart does not address the issues of efficacy, safety, and risk.

All of these disease-modifying therapies (DMTs) for MS have different benefits and risks. The effectiveness and side effects of each medication may vary from one person to another. Additionally, individuals who do not respond well to one DMT may benefit by switching to a different treatment.

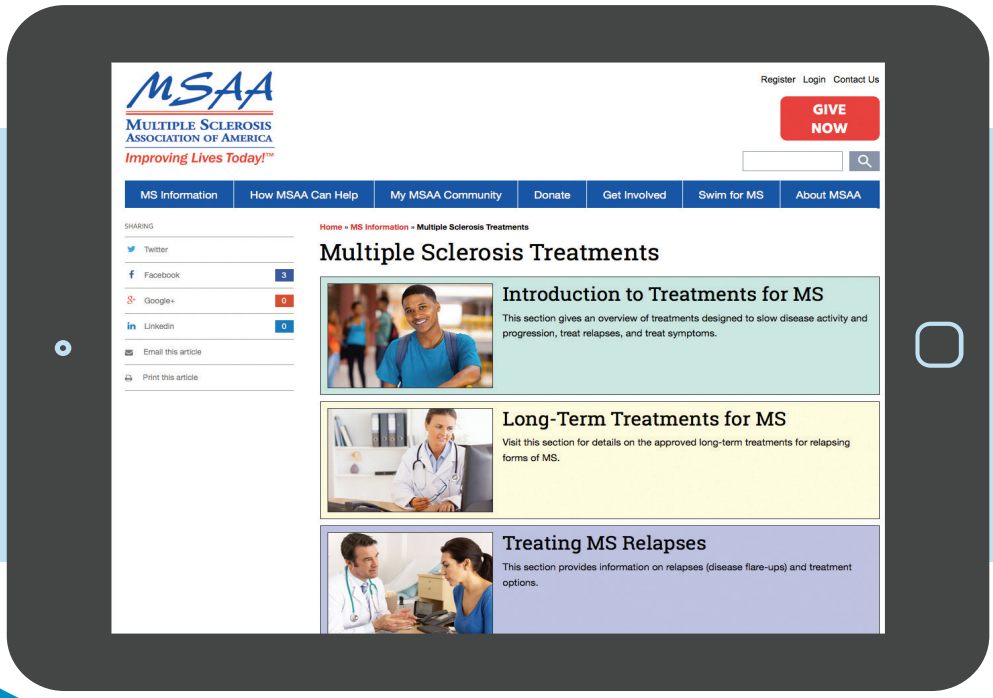
Individuals need to consult with their healthcare team to determine which treatment might be the best option for them. For additional information on the specific treatments, administration, and side effects, please refer to Appendix #2 at the end of this booklet.

Self-Injected Medications

MEDICATION NAME	TYPE OF DRUG	HOW ADMINISTERED
Avonex® (Interferon beta-1a)	Immune system modulator with antiviral properties	30 micrograms taken via weekly intermuscular injection
Betaseron® (Interferon beta-1b)	Immune system modulator with antiviral properties	250 micrograms taken via subcutaneous injection every other day
Copaxone® (glatiramer acetate)	Synthetic chain of four amino acids found in myelin (immune system modulator that blocks attacks on myelin)	20 (daily) or 40 (three times weekly) milligrams taken via subcutaneous injection
Extavia® (Interferon beta-1b)	Immune system modulator with antiviral properties	250 micrograms taken via subcutaneous injection every other day
Glatopa™ (glatiramer acetate)	As a generic version of Copaxone, Glatopa is a synthetic chain of four amino acids found in myelin (immune system modulator that blocks attacks on myelin)	20 milligrams taken daily via subcutaneous injection
Plegridy® (Interferon beta-1a)	Immune system modulator with antiviral properties	125 micrograms taken via subcutaneous injection once every two weeks
Rebif® (Interferon beta-1a)	Immune system modulator with antiviral properties	44 micrograms taken via subcutaneous injection three times weekly

Infused Medications

MEDICATION NAME	TYPE OF DRUG	HOW ADMINISTERED
Lemtrada® (alemtuzumab)	Humanized monoclonal antibody that rapidly depletes or suppresses immune system cells (T and B cells), which can damage the myelin and nerves of the central nervous system (CNS).	Lemtrada is given for a course of five days via intravenous (IV) infusion and followed one year later by a second three-day course
Novantrone® (mitoxantrone)	Antineoplastic agent (immune system modulator and suppressor)	IV infusion once every three months (for two to three years maximum)
Tysabri® (natalizumab)	Humanized monoclonal antibody (inhibits adhesion molecules; thought to prevent damaging immune cells from crossing the blood-brain barrier)	IV infusion every four weeks



Oral Medications

MEDICATION NAME	TYPE OF DRUG	HOW ADMINISTERED
Aubagio® (teriflunomide)	Immunomodulator (affecting the production of T and B cells; may also inhibit nerve degeneration)	7- or 14-milligram tablet taken orally, once per day
Gilenya® (fingolimod, FTY720)	S1P-receptor modulator (blocks potentially damaging T cells from leaving lymph nodes)	0.5-milligram capsule taken orally once per day
Tecfidera® (dimethyl fumarate)	Immunomodulator with anti-inflammatory properties; may have neuroprotective effects, potentially protecting the nerves and myelin covering from damage	240-milligram tablet taken twice daily

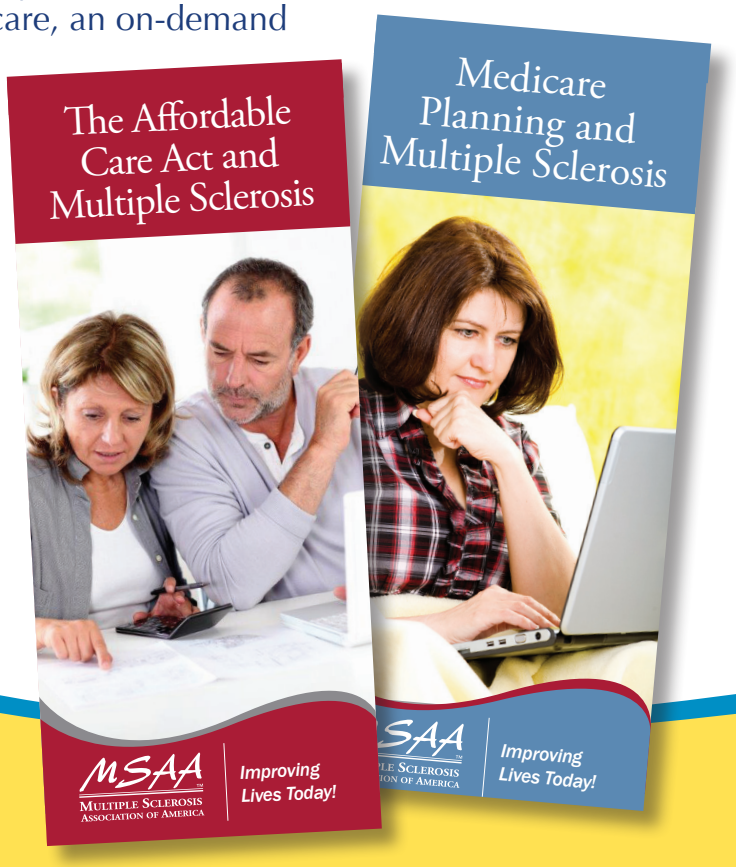
As a reminder, the 13 disease-modifying therapies (DMTs) for MS shown in this chart are limited to those approved by the FDA as of the printing of this booklet. At any time, more long-term treatments may become available as new medications complete the clinical-trial process and are submitted to the FDA for approval. To learn more about these approved treatments as well as new medications as they become approved, please visit MSAA's website at ***mymsaa.org*** *and select "Treatments" under "MS Information." The image to the left is a screenshot from MSAA's website, showing the treatments landing page.*

SEARCH-ing for Insurance Coverage

As mentioned earlier in this booklet, healthcare professionals and organizations including MSAA recommend early and continuous treatment of multiple sclerosis through FDA-approved DMTs, if deemed appropriate by one's doctor. However, MSAA also recognizes that MS is a very expensive disease to manage and having health insurance coverage for doctor's visits, medications, MRIs, etc. is paramount.

With the passage of the Affordable Care Act (ACA) in 2014, private health insurance coverage should continue to become more accessible for the MS community and allow people to qualify for certain premium subsidies, which are based on family income. For those with Medicare, the ACA is also helping to close the Part D "Donut Hole," which refers to a temporary limit on prescription drug coverage.

To help the MS community better understand and utilize health insurance, MSAA developed an online resource center titled: My Health Insurance Guide. This easy-to-use website section accessed at **mymsaa.org/healthinsurance** features a useful glossary of common insurance terms, downloadable brochures on the ACA and Medicare, an on-demand video and two archived webinars, helpful questions to ask when looking at insurance coverage or appealing a denial, and many other resources.



The S.E.A.R.C.H.™ Toolkit

MSAA has produced a variety of informational tools to help people maximize their success with SEARCH. In addition to this booklet, MSAA has produced a wallet-size reference card that includes the six key elements of SEARCH. A SEARCH reference card has been included on the inside-back cover of this booklet.

As a secondary and more comprehensive tool to help organize and manage the many aspects of SEARCH, MSAA has created a very useful patient workbook. The SEARCH Patient Workbook includes an easy-to-follow chart which organizes and provides current MS treatment options; a comprehensive listing of suggested questions within each aspect of SEARCH; ample writing space to develop questions and take comprehensive notes; an extensive resource guide; and an office-visit questionnaire to help prioritize questions for the doctor. You can download your free copy of the MSAA SEARCH Patient Workbook online at **mymsaa.org/search** or you can request a copy be mailed to you by calling **(800) 532-7667**.

Details of MSAA's SEARCH program may also be viewed online through an informative webinar that was presented live and recorded for on-demand viewing at any time. To access this webinar – which may be viewed as an online video or in a written, slide format – please go to **mymsaa.org/programs/videos** and select the "How to SEARCH for the Right MS Therapy for You!" webinar from among the many educational video selections.

As the SEARCH campaign expands, MSAA will continue to organize and host national, public education programs through our network of regional offices. Additional SEARCH tools MSAA seeks to develop include support materials for healthcare professionals to help patients and their doctors work together to make informed decisions.

Remaining Adherent

Once a DMT is initiated, evidence suggests that treatment needs to be ongoing for benefits to persist. Non-adherence and gaps in treatment have been associated with an increased rate of relapses and progression of disability.

Rather than discontinuing the medication, it is essential for individuals to talk with their doctor about recent changes in their MS and explore options to make adjustments with their current medication or switch to another DMT. The SEARCH model can be helpful in recalculating a treatment decision.

MSAA also recognizes that adhering to an MS medication can present certain challenges over time, which may cause people to limit or discontinue prescribed usage. Fortunately, many of these challenges can be managed to help keep you on course with your therapy. Some helpful strategies include:

Managing Side Effects
Each of the approved treatments has side effects that are usually manageable. Initial side effects to some of the DMTs include headache and flu-like symptoms. These often dissipate after several weeks and can be easily managed with over-the-counter medications. Individuals using injectable medications can manage pain or skin reactions at the injection site by icing the area, rotating injection sites, taking over-the-counter pain relievers, and using an auto injector.

For individuals taking an oral medication, common side effects include headache, nausea, and diarrhea. These are usually mild, dissipate over time, and can often be managed by taking over-the-counter medications, as prescribed by your doctor. Taking an oral DMT while having a full stomach may also assist with reducing side effects, if advised by your doctor.

Understanding Expectations
Individuals must allow six months to one year for their prescribed medication to have an effect on their disease course. This also necessitates that patients are taking their medication as prescribed on a consistent basis and not skipping or altering doses. People often think that in order for the medication to be working they must "see" results. In fact, the opposite is true for MS. It is important to realize that if patients are not seeing an increase in relapses and/or not experiencing additional symptoms, then, most likely, their DMT is effectively treating their MS. However, individuals need to consult their neurologist and/or healthcare team to help determine the success of their current long-term treatment.

Learning to Adjust
Even with the best intentions, people can forget to take their medication. A few simple suggestions to help remember include setting a schedule and abiding to it as much as possible, utilizing memory aids such as print and electronic calendars and reminder notes, recording your dosage in a journal or mobile phone app such as **My MS Manager™**, and involving family members in the treatment plan.

In addition to forgetfulness, fear or anxiety related to injections has often been a concern shared by the MS community. Receiving proper training from a healthcare professional on administering the injection and using an auto injector are effective strategies in building self-confidence and reducing fear.

Staying on Course
The effectiveness of any disease-modifying therapy for MS can vary greatly from person-to-person and even change within the same individual as the disease progresses over time. All DMT's have potential risks and some of the newer therapies require tests before and during treatment to help determine if the medication would be considered an appropriate option for the individual, and whether or not he or she can manage the potential side effects. It is important for individuals with MS to work together with their neurologist to explore new treatment options and remain committed to finding a therapy that works for them.

APPENDIX # 1: MS OVERVIEW

What is MS?

Multiple sclerosis (MS) is a neurological disorder affecting the nerves of the **central nervous system (CNS)**, which consists of the brain, optic nerves, and spinal cord. Most individuals with MS experience their first symptoms as a young adult and are often diagnosed in the prime of their life. Although MS is not contagious, a cause and cure have yet to be discovered. As discussed later in this booklet, several effective treatment choices are available for most individuals with MS to help reduce disease activity.

Caucasians have the greatest incidence of MS and about three times as many women are diagnosed with MS than men. MS does not usually occur with populations living in warm areas near the equator; in general, the further people live from the equator (north or south), the greater their risk of developing the disease.

With MS, nerve fibers (or "**axons"**) and their fatty-rich protective covering (known as "**myelin**") become damaged. As a result, nerve impulses along these nerve fibers are interrupted; causing the symptoms of MS. MS is believed to be an **autoimmune disease**, where the body's own immune system is sending disease-fighting cells to destroy specific elements within the body. Examples of other autoimmune diseases include lupus and rheumatoid arthritis.

The symptoms of MS include a wide range of physical, mental, and emotional difficulties. Examples include: visual problems, spasticity (spasms and tightening of muscles), weakness, tremor, numbness, and dizziness; bladder, bowel, and sexual dysfunction; mobility issues; chronic, aching pain; fatigue, depression, and memory problems.

Types of MS

On average, 80 percent of people with MS begin with the **relapsing-remitting form of MS (RRMS)**. This type of MS has temporary symptom flare-ups or "relapses" (also referred to as exacerbations, attacks, or bouts), which may last from a few days to a few months. These are followed by a complete or partial recovery **("remission").** Women are more likely to be diagnosed with RRMS than men.

Between relapses, many people may go into remission for a year or more. During this time, they may remain symptom-free, or only experience mild changes with symptoms that did not fully remit following the exacerbation.

This remission can be deceptive, however, because of the **clinically silent** aspect of MS. While symptoms may not appear or worsen between MS attacks, changes do continue within the CNS. **Lesions** (areas of inflammation along the nerves in the brain and spinal cord) can flare up within the CNS at least 10 times as often as clinical attacks (those with visible symptoms).

If untreated, more than 90 percent of individuals with RRMS may eventually enter a second phase of RRMS, known as **secondary-progressive MS (SPMS)**, within 25 years of their diagnosis. This phase is reached when an individual experiences a progressive worsening of symptoms. SPMS may occur with or without superimposed relapses.

While approximately 80 percent of individuals with MS are initially diagnosed with RRMS, the majority of the other 20 percent are diagnosed with **primary-progressive MS (PPMS)**. This form of MS presents a gradual but steady accumulation of neurological problems from the onset, without the presence of relapses and remissions. Unlike RRMS, PPMS is equally divided between the genders.

Other types of MS exist, but these are not as common. These include **benign MS** (with little or no change after 20 years), **progressive-relapsing MS** (PRMS) (a progressive course from the onset with acute relapses), and **malignant** or **fulminant MS** (a rapidly progressive disease course).

APPENDIX # 2: MS TREATMENT OVERVIEW

What drugs are approved for the long-term treatment of MS?
At the time of this publication, **13 disease-modifying treatments** have been approved by the United States Food and Drug Administration (FDA), each shown to help slow disease activity for individuals with relapsing forms of MS. Since inflammation appears to be a major component in the relapsing forms of MS, these treatments are believed to reduce the inflammation within the CNS, thereby reducing the number and severity of active lesions (and also reducing the number of clinically silent flare-ups). Other immunological changes are also thought to occur with these disease-modifying therapies (DMTs).

Many experts now recommend treatment as early as possible with one of these approved DMTs. Research has shown that treating after the first attack can significantly delay the amount of time to the second attack. Early treatment is also thought to possibly limit axonal (nerve) injury, which may be irreversible, and later lead to a progressive form of MS.

The 13 FDA-approved, long-term disease-modifying therapies (DMTs) for MS (as of the printing of this booklet) are listed on pages 8 through 11. An individual with MS is usually prescribed only one of these medications during any one time period, although trials with combinations of these treatments are being conducted.

When switching from one therapy to another, doctors will often allow time between treatments for the former medication to be completely out of one's system. This is known as a "wash-out" period. Results from several large clinical trials have found that all of these medications reduce the number and severity of relapses, as well as the development of new areas of inflammation as seen on MRI. These studies also showed some evidence of delaying disease progression.

What are the side effects of these medications?
Similar to most any medication, these DMTs are accompanied by certain side effects and/or adverse events, most of which may be managed or avoided through various precautionary actions. For instance, the interferons may cause flu-like symptoms and injection-site reactions, especially when first starting the

medication. Strategies put in place by the pharmaceutical companies, such as smaller needles and gradually increasing from a small dose to the full dose (dose titration), can greatly help to avoid the potential side effects mentioned. Liver function is also monitored while taking an interferon. Injection-site reactions can occur with Copaxone, and for a small percentage of patients, a brief systemic reaction (such as flushing, dizziness, palpations, and/or shortness of breath) may occur following an injection.

Novantrone poses additional risks to the heart and for developing leukemia. For this reason, this medication is typically reserved for severe cases of MS that are not responding to any of the other DMTs. To avoid these adverse events, Novantrone may not be taken for more than two to three years.

Approximately 0.1 percent (or one in one thousand) of patients taking Tysabri develop a condition known as progressive multifocal leukoencephalopathy (PML), which is a potentially fatal brain infection with the JC virus (JCV), in people with weakened immune systems. About 55 percent of individuals with MS have this virus, which normally stays dormant, unless a suppressed immune system allows it to become activated. New guidelines to minimize the risk have been identified, and safety monitoring programs have been put in place for early detection and treatment, as well as to track any occurrences of this condition. A new blood test shows if a person has been exposed to the JC virus and if he or she could be at risk of developing PML if taking Tysabri.

Gilenya may cause certain heart-related issues when first starting the medication. For this reason, patients are screened in advance for heart problems and are monitored during the first six to 24 hours following the initial treatment at a treatment center.

Please note that all of these MS medications have been approved by the FDA. This agency has determined that the benefits of these medications outweigh any risks – many of which are rare. Other side effects (not listed in this booklet) may occur with these drugs. For more information on potential benefits and risks, individuals are advised to speak with their physician.

APPENDIX # 3: ASSISTANCE PROGRAMS

The following pharmaceutical companies offer patient programs to provide information, instruction, and resources for advocacy and financial assistance (listed alphabetically).

Aubagio - MS One to One
(855) 676-6326; www.aubagio.com

Avonex - Above MS
(800) 456-2255; www.avonex.com

Betaseron - BetaPlus
(800) 788-1467; www.betaseron.com

Copaxone - Shared Solutions
(800) 887-8100; www.copaxone.com

Extavia - Patient Services Program
(866) 398-2842; www.extavia.com

Gilenya - Patient Services Program
(800) 445-3692; www.gilenya.com

Glatopa - GlatopaCare
(855) GLATOPA (855-452-8672); www.glatopa.com

Lemtrada - MS One to One
(855) 676-6326; www.lemtrada.com

Plegridy - Above MS
(800) 456-2255; www.plegridy.com

Rebif - MS Lifelines
(877) 447-3243; www.rebif.com

Tecfidera - Above MS
(800) 456-2255; www.tecfidera.com

Tysabri - Above MS
(800) 456-2255; www.tysabri.com

Here is Your S.E.A.R.C.H.™ Reference Card!

MSAA

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