MS

Multiple symptoms

Multiple types

Multiple treatment options

Disclaimers

- ZERO

Goals

- The goals of this discussion will be an overview:
  - types of multiple sclerosis
  - symptoms of multiple sclerosis
  - various treatment options
  - and to improve understanding of the disease process.

- This is not a comprehensive lecture obviously as we would be here for several days.

MS types Clinically isolated syndrome

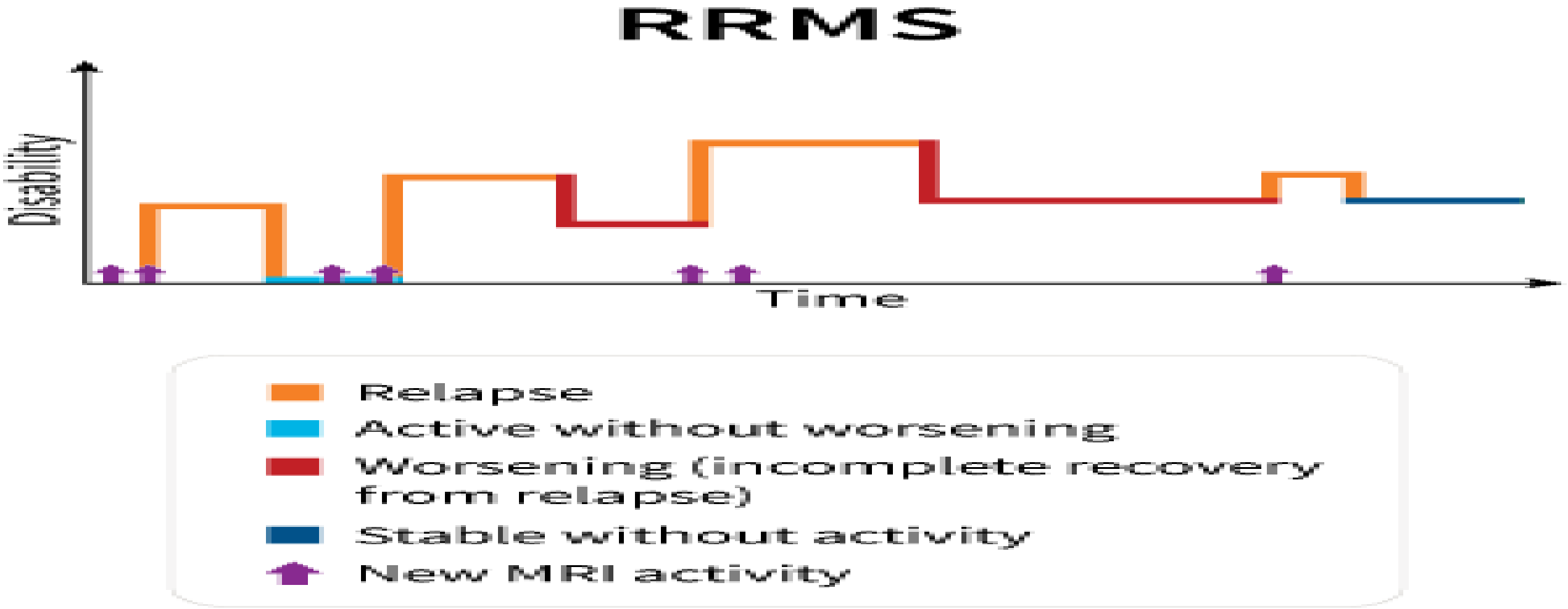
- Clinically isolated syndrome is strongly correlated with multiple sclerosis
- If the patient has an **abnormal MRI at presentation-> 60-80% chance of achieving the diagnosis of multiple sclerosis within 2 years**
- If the patient does not have an abnormal MRI presentation the risk of multiple sclerosis decreases to 20%.
- 50% will go on to develop secondary progressive multiple sclerosis

- National MS Society & Lancet Neurology

Relapsing remitting multiple sclerosis

- 85% of all multiple sclerosis patients have this time
- More commonly diagnosed around age 20-30
- Women are affected 2-3 times more than men
- This is the most studied form of multiple sclerosis
- Fatigue is a significant component

Relapsing remitting multiple sclerosis



Source: Lublin et al., 2014.

MS types Primary progressive

- Men and women are equally diagnosed
- Tends to occur 20 slightly older population 40s to 50s
- Mobility difficulties are a significant component

MS types Secondary progressive

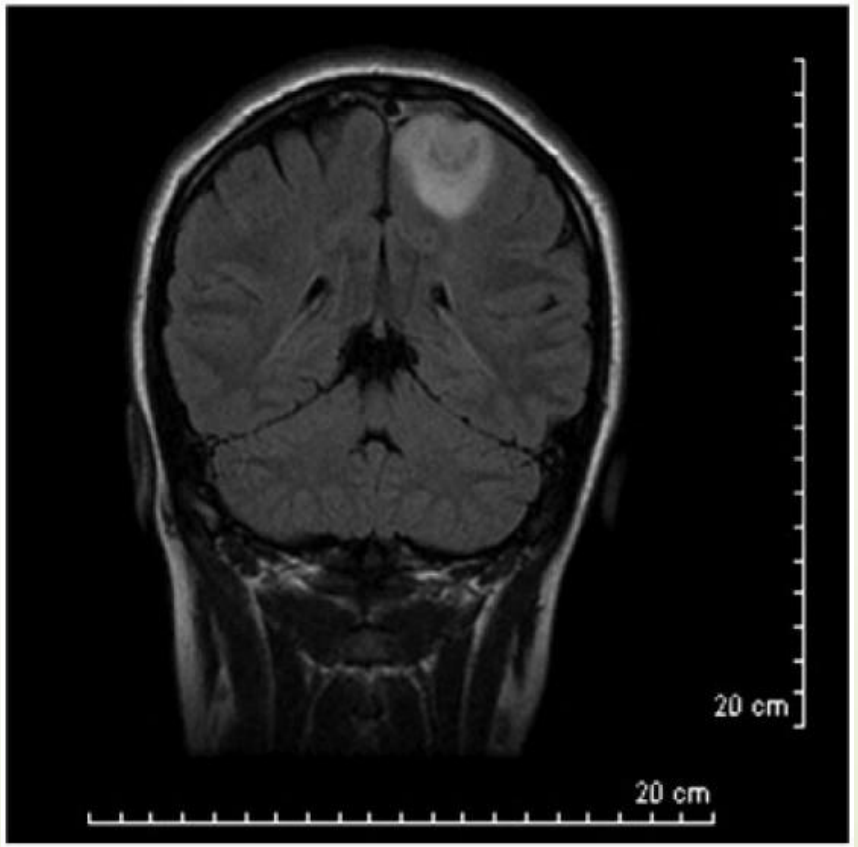
- Tends to occur in patients that have multiple sclerosis for 10+ years

MS types Tumfactive MS

- This is an exceedingly rare type
- Patients present with very large intracranial lesions
- Lesions will have a significant amount of mass effect often more than 2 cm
- Lesions are ring-enhancing it may be an open ring
- 39% the time these are misdiagnosed as a low-grade astrocytoma
- 11% time these are misdiagnosed as a high-grade lesion
- source
- Kaeser, M. A., Scali, F., Lanzisera, F. P., Bub, G. A., & Kettner, N. W. (2011). Tumefactive multiple sclerosis: an uncommon diagnostic challenge. Journal of Chiropractic Medicine, 10(1), 29-35.

MS types->Tumfactive MS

Kaeser, M. A., Scali, F., Lanzisera, F. P., Bub, G. A., & Kettner, N. W. (2011). Tumefactive multiple sclerosis: an uncommon diagnostic challenge. Journal of Chiropractic Medicine, 10(1), 29-35.



Neuromyelitis optica

- Clinically different disease and multiple sclerosis
- Patients tend to have a poor recovery with their optic neuritis
- Anti aquaporin 4 antibodies are helpful but not mandatory for the diagnosis
- Clinical features include optic neuritis, acute extensive transverse myelitis, and area postrema syndrome.

Multiple sclerosis symptoms from Steven W. Nissen, M.S., CRC

- Fatigue (most common)
- • Vision problems
- • Stiffness (spasticity)
- • Cognitive changes (memory, attention, processing)
- • Walking difficulties (weakness, imbalance)

Multiple sclerosis symptoms from Steven W. Nissen, M.S., CRC

- • Emotional changes (depression, mood swings)
- • Bladder/bowel dysfunction
- • Sexual problems
- • Sensory problems (tingling/numbness)
- • Heat sensitivity
- • Speech/swallowing difficulties
- • Pain
- • Tremor

Multiple sclerosis treatment options

- FDA-Approved Disease-Modifying Agents
- • Aubagio (teriflunomide), oral, 2012
- • Avonex (interferon beta-1a), intramuscular injection, 1996
- • Betaseron (interferon beta-1b), subcutaneous injection, 1993
- • Copaxone (glatiramer acetate), subcutaneous injection, 1996
- • Extavia (interferon beta-1b), subcutaneous injection, 2009
- • Gilenya (fingolimod), oral, 2010
- • Glatopa (glatiramer acetate), subcutaneous injection, 2015
- [generic equivalent of Copaxone 20mg]
- • Lemtrada (alemtuzumab), IV infusion, 2014
- • Novantrone (mitoxantrone), IV infusion, 2000
- • Plegridy (pegylated interferon beta-1a), subcutaneous injection,
- 2014
- • Rebif (interferon beta-1a), subcutaneous injection, 2002
- • Tecfidera (dimethyl fumarate), oral, 2013
- • Tysabri (natalizumab), IV infusion, 2006

MS/CIS treatment->beta interferon 1A NEJM 2000

- Study was completed from 1996-2000 patient's had two or more lesions as well as symptoms of clinically isolated syndrome
- All patient's received 1 g of Solu-Medrol daily for 3 days followed by an oral taper
- 190 patient's were placed on placebo
- 193 patient's received beta interferon 1A
- 50% of the placebo group developed multiple sclerosis
- 35% of the treated group developed multiple sclerosis
- It was a three-year study if patients develop multiple sclerosis they were converted from placebo to treatment

MS/CIS treatment->interferon beta-1b 2006

- Double placebo randomized controlled trial
- 176 patient's received placebo
- 229 patient's received interferon 1B 250 mg subcutaneously every other day
- Within 2 years 45% placebo patients had developed multiple sclerosis
- Patient's were followed for 24 months

MS/CIS treatment-> Copaxone Lancet 2009

- 80 side 16 countries-> 481 clinically isolated patient's with 2 or more lesions on mri
- Patients placed on copaxone or placebo for up to 36 months.
- Copaxone decreased risk obtaining by 45%
- Copaxone treated patients delayed unset of disease as compared to placebo
  - 336 days placebo
  - 722 days copaxone


Injection
syringe
to Jack Yellow Fox

MS Treatment Avonex injectable

- FDA approved in 1996for relapsing remitting multiple sclerosis as a disease modifying agent
- Interferon beta-1a taken once a week intramuscular
- Avonex® is a medication manufactured by a biotechnological process from one of the naturally-occurring interferons (a type of protein). It is made up of exactly the same amino acids (major components of proteins) as the interferon beta found in the human body.(MS Society)

MS Treatment Avonex injectable

- Over 455,000 patient exposures
- Decreases the risk of relapse by one third
- Annualized relapse rate-> 0.61 for Avonex 0.9 for placebo
- Good Avonex support system sponsored by the company

MS Treatment Avonex injectable

- Most common side effect flulike symptoms
- More significant side effects
  - Depression
  - Liver issues
  - Thyroid dysfunction
  - Bone marrow suppression
- Skin site reactions

- Rare but listed in the literature-> Heart failure and seizure

MS Treatment Betaseron injectable

- FDA approved 1993 for relapsing remitting multiple sclerosis as a disease modifying agent
- Decreases the risk of relapsed by one third
- Interferon beta-1b taken every other day subcutaneous
- Decreases the risk of relapse by one third
- New lesions on MRI> 3.7 for Betaserson 8.5 for placebo
- Good Betaseron support system sponsored by the company

MS Treatment Betaseron injectable

- Most common side effect flulike symptoms and injection site reactions
- More significant side effects
  - Depression
  - Liver issues
  - Thyroid dysfunction
  - Bone marrow suppression
- Rare but listed in the literature-> Heart failure and seizure

MS Treatment Extavia injectable

- Interferon 1B
- Some as Betaseron
- Same benefits and risk as Betaseron
- Betaseron® and Extavia® are brand names for interferon beta 1b, a medication manufactured by a biotechnological process from one of the naturally occurring interferons (a type of protein).(ms society web site)

MS treatment Rebif injectable

- Interferon beta-1a 3 times a week subcutaneous dosing
- FDA approved 2002
- Comes into strength 22 mg and 44 mg-> Better efficacy with 44
- Decreases risks of relapse by one third
- Over a two-year study 0.5new lesions on MRI with Betaseron as compared to 2.25 lesions wit placebo
- Comparison study between Avonex and Rebif 44 3 times a week-> At 64 weeks 56% of the Rebif patient's were relapse free as compared to 48% of the Avonex patient's
- Rebif® is a medication manufactured by a biotechnological process from one of the naturally-occurring interferons (a type of protein). It is made up of exactly the same amino acids (major components of proteins) as the interferon beta found in the human body.(MS Society)

MS treatment Rebif injectable

- Most common side effect flulike symptoms and injection site reactions
- More significant side effects
  - Depression
  - Liver issues
  - Thyroid dysfunction
  - Bone marrow suppression
- Rare but listed in the literature-> Heart failure and seizure

MS treatment Plegridy injectable

- Pegylated interferon beta-1a subcutaneous approved in 2014
- Pegylated interferon beta-1a is a “pegylated" form of interferon, meaning that polyethylene glycol is attached to the interferon molecules to allow them to maintain their biologic effects in the body for longer periods of time. Because the biologic effects in the body last longer, dosing can occur at less frequent intervals. (MS Society)
- This medication is manufactured by a biotechnological process from one of the naturally-occurring interferons (a type of protein). It is made up of exactly the same amino acids (major components of proteins) as the interferon beta found in the human body. (MS Society

MS Plegridy

- Injectable utilize twice / month subcutaneous injection
- MRI study revealed 3.6 new lesion with Plegridy as compared to 10.1 new MRI lesions for placebo patients
- Has a good patient support system

MS treatment Plegridy injectable

- Most common side effect flulike symptoms and injection site reactions
- More significant side effects
  - Depression
  - Liver issues
  - Thyroid dysfunction
  - Bone marrow suppression
- Rare but listed in the literature-> Heart failure and seizure

MS Treatment Copaxone injectable

- Approved in 1996 as a daily 20 mg subcutaneous injection
- approved in 2014 as 40 mg 3 times a week medication
- Glatiramer acetate
- Glatiramer acetate is a synthetic protein that simulates myelin basic protein, a component of the myelin that insulates nerve fibers in the brain and spinal cord. This drug seems to block myelin-damaging T-cells through a mechanism that is not completely understood.(MS society)
- Good patient support system

MS Treatment Copaxone injectable

- Most common side effects are redness of the injection site & lipoatrophy
- Side effects can include: shortness of breath, chest pain
- Rare side effects can include lymphadenopathy
- Pregnancy category B
- No monitoring labs required

MS treatment Glatopa injectable

- The first generic medication FDA approved for the treatment of MS 2015
- It is the generic glatiramer acetate 20 mg subcutaneous injection daily

MS Treatment Zinbryta Injectable

- Zinbryta™ is a laboratory-created monoclonal antibody. It is designed to inhibit certain inflammatory functions of T cells and increase important immune cells that help regulate the immune system. (MS Society)
- Zinbryta is approved by the U.S. Food and Drug Administration (FDA) to treat adult patients with relapsing forms of MS. It should be reserved for people who have had an inadequate response to two or more disease-modifying medications.(MS Society)
- Daclizumab generic name/chemical name
- Once a month subcutaneous injection

MS Treatment Zinbryta Injectable

- Three-year study
- 919 patient's on Zinbryta as compared to 922 patient's on Avonex
- 45% decreased risk of clinical relapse
- 54% decreased new lesions on MRI
- Zinbryta is very strong MS medication

MS Treatment Zinbryta Injectable

- Because of the risk of serious liver problems (including autoimmune-related liver problems) and other immune system problems, ZINBRYTA is only available through a restricted program called the ZINBRYTA Risk Evaluation and Mitigation Strategy (REMS) Program.(Zinbryta website)
- It is not FDA approved for children
- Liver labs required to be done each month in 6 months after medication is stopped
- Additional side effects including increased risk of infection including upper respiratory tract infections, depression, swelling and enlarged lymph nodes

MS treatment Aubagio

- Aubagio® (teriflunomide), a pyrimidine synthesis inhibitor, is an oral compound that inhibits the function of specific immune cells that have been implicated in MS. It is related to leflunomide, a drug used to treat rheumatoid arthritis. Aubagio can inhibit a key enzyme required by white blood cells (lymphocytes) – which in turn reduces the proliferation of T and B immune cells that are active in MS and also inhibits the production of immune messenger chemicals by T cells. (MS Society)
- FDA approved in 2012
- Once a day medication

MS treatment Aubagio

- Available in both 7 mg and 14 mg strength.
- 57% relapse free rate with 14 mg after 108 weeks as compared to 46% relapse free rate with placebo
- Topic Trail -> 72% relapse free rate after first event with 14 mg as compared to 62% relapse free after the first event with placebo

MS treatment Aubagio

- The most common side effects when taking AUBAGIO include: headache; diarrhea; nausea; hair thinning or loss; and abnormal liver test results(Aubagio)
- The more serious side effect potential is decreasing white blood cells will increased risk of infection
- Vaccinations need to be limited including 6 months after medication is been stopped
- **Pregnancy category X-> Effective contraceptive measures recommended for both male and female patients**

MS medications Gilenya

- Gilenya® is a new class of medication called a sphingosine 1-phosphate receptor modulator, which is thought to act by retaining certain white blood cells (lymphocytes) in the lymph nodes, thereby preventing those cells from crossing the blood-brain barrier into the central nervous system (CNS). Preventing the entry of these cells into the CNS reduces inflammatory damage to nerve cells.(MS Society)
- FDA approved 2010 once a day->at the same time each day

MS medications Gilenya

- In a one-year study compared Avonex-> 83% in the Gilenya patient's had no relapses where as 70% of the Avonex patient's had no relapses
- Under two-year study-> 70% of patients on June he had no relapses. 46% of the placebo-controlled patient's had no relapses

MS medications Gilenya

- At least a dozen cases of PML have been reported patient's transition positioning from Tysabri to Gilenya
- As of January 2016 at least 5 cases have been reported with monotherapy with Gilenya
- It is likely that further cases of PML with Gilenya will be reported

- Continuum on June 2016

MS medications Gilenya

- **Side effects can include bradycardia-> Hence first dose has to be monitored**
- Prior to starting patients have to be evaluated for macular edema
- Liver lab abnormalities can occur
- Risk of herpetic infection is elevated-> varicella vaccine recommended prior to starting medication

MS medications Tecfidera

- Dimethyl Fumarate
- FDA approved 2012 twice a day medication
- Tecfidera® is an oral therapy contained in capsules taken two times per day. Tecfidera, formerly known as BG-12, is dimethyl fumarate, a formulation that was developed specifically for use by people with multiple sclerosis. A chemically related compound, called Fumaderm (dimethyl fumarate and fumaric acid esters), has been used at higher doses for decades in Germany to treat acute flare-ups of psoriasis. Although its exact mechanism of action is not known, Tecfidera is thought to inhibit immune cells and molecules, and may have anti-oxidant properties that could be protective against damage to the brain and spinal cord.(MS Society)

MS medications Tecfidera

- Two-year study 29% of patients on Tecfidera had a relapse as compared to 41% on placebo
- A decreased number of new lesions were noted-> 85% decrease in the number new lesions
- 190,000 worldwide patient exposures

MS medications Tecfidera

- TECFIDERA may cause serious side effects including allergic reactions, PML, which is a rare brain infection that usually leads to death or severe disability, and decreases in your white blood cell count. Your doctor may check your white blood cell count before you take TECFIDERA and from time to time during treatment.
- The most common side effects of TECFIDERA include flushing and stomach problems. These can happen especially at the start of treatment and may decrease over time. Taking TECFIDERA with food may help reduce flushing. Call your doctor if these symptoms bother you or do not go away. Ask your doctor if taking aspirin before taking TECFIDERA may reduce flushing.

- Tecfidera web site

MS medications Tecfidera

- As of November 2015 for cases of PML have been reported more are expected to occur
- Continuum june 2016

MS treatment Tysabri

- Natalizumab
- IV formulation once a month approve 2006
- Tysabri® is a laboratory-produced monoclonal antibody. It is designed to hamper movement of potentially damaging immune cells from the bloodstream, across the “blood-brain barrier” into the brain and spinal cord.(MS Society)

- Tysabri is approved by the U.S. Food and Drug Administration (FDA) as a monotherapy (not to be used in combination with other disease-modifying therapies) to treat relapsing forms of MS(MS Society)

MS treatment Tysabri

- Two-year study 627 patient's on Tysabri as compared to 315 patient's on placebo
- 97% of Tysabri patient's had no new lesions on MRI as compared to 72% of the placebo patients
- Significantly helps patient's fatigue per clinical observation

MS treatment Tysabri & PML

- Your risk of getting PML is higher if you:
- have received TYSABRI for a long time, especially for longer than 2 years
- have received certain medicines that can weaken your immune system before you start receiving TYSABRI
- have been infected by the John Cunningham Virus (JCV). Before or while you receive TYSABRI, your doctor may do a blood test to check if you have been infected by JCV. JCV is a common virus that can cause PML in people who have weakened immune systems, such as people taking TYSABRI.(Tysabri web site)

MS treatment Tysabri

- Additional side effects increased risk of infection particularly herpetic
- Increased risk of liver abnormalities
- Increased risk for infection
- Urinary tract infections and headaches are common side effects

MS treatment Lemtrada

- FDA approved in 2014 IV therapy
- 12 mg daily for 5 days then one year later 12 mg daily for 3 days
- Lemtrada™ is a humanized monoclonal antibody directed at CD52 (a protein on the surface of immune cells).(MS Society)
- AnnualizedRelapse rate 0.26 Lemtrada as compared to 0.52 Rebif during a 2 year duration

- Lemtrada is approved by the FDA for the treatment of patients with relapsing forms of MS. Because of Lemtrada's safety profile, the FDA recommends that this medicationgenerally be reserved for people who have had an inadequate response to two or more MS therapies (MS Society)

MS treatment Lemtrada (info company web site)

- Pre- and concomitant medications1
- For infusion reactions
- Premedicate patients with high-dose corticosteroids (1000 mg methylprednisolone or equivalent) immediately prior to LEMTRADA infusion and for the first 3 days of each treatment course
- Consider pretreatment with antihistamines and/or antipyretics prior to LEMTRADA administration
- Infusion reactions may occur despite pretreatment
- For infections
- Administer anti-viral prophylaxis for herpetic viral infections starting on the first day of each treatment course and continue for a minimum of 2 months following treatment with LEMTRADA or until the CD4+ lymphocyte count is ≥200 cells per microliter, whichever occurs later

MS treatment Lemtrada (info company web site)

- Monitoring is required after the first treatment course, continuing until 48 months after the last course of LEMTRADA, or longer, if clinically indicated. Monitoring will include complete blood count with differential, serum creatinine levels, urinalysis with urine cell counts, and thyroid function tests.

- Patient's, pharmacies, and providers almost complete a risk evaluation irrigation strategy program prior to patient being allowed to be started on this.

MS treatment Lemtrada (info company web site)

- 3% of the patients develop to serious infection as compared to 1% of the Avenox patient
- Increased risk of transfusion reactions for 24 hours patients have to be monitored for at least 2 hours
- Increased risk of cancer including thyroid melanoma and lymphoproliferative
- Increased risk of autoimmune reaction
- Cases of fungal infection & Listeria meningitis of been reported

MS treatment Novantrone

Mitoxantrone

FDA approved in 2000

There were 2 clinical trial showing its efficacy and MS advanced cases

Not commonly used due to concerns for cardiac toxicity and leukemia

MS treatment Novantrone

- Novantrone belongs to the general group of medicines called antineoplastics. Prior to its approval for use in MS, it was used only to treat certain forms of cancer. It acts in MS by suppressing the activity of T cells, B cells, and macrophages that are thought to lead the attack on the myelin sheath. (MS Society)

MS treatment Novantrone

- The U.S. Food and Drug Administration (FDA) has approved Novantrone for reducing neurologic disability and/or the frequency of clinical relapses (attacks) in:
- Patients with secondary progressive MS (disease that has changed from relapsing-remitting to progressive at a variable rate)
- Progressive-relapsing MS (disease characterized by gradual increase in disability from onset with clear, acute relapses along the way);
- Worsening relapsing-remitting MS (disease characterized by clinical attacks without complete remission, resulting in a step-wise worsening of disability.
- Note: Novantrone has not been approved for the treatment of primary-progressive MS (characterized by progression from disease onset with no acute attacks or remissions).(MS Society)


Other

Multiple sclerosis treatment

- Vitamin D deficiency is associated with increased risk of MS as well as MS attacks
- Study referenced below-> 114 clinically isolated syndrome patient's workup I waited 52% of them had vitamin D deficiency.
- Vitamin D deficiency was determined to be 50 or less
- Some neurologists encourage patient's to be closer to 80

Dalla Costa, G., Messina, M. J., Farina, A., Moiola, L., Rodegher, M., Colombo, B., ... & Martinelli, V. (2016). Vitamin D Metabolic Pathway Alterations and Risk of Multiple Sclerosis in Patients with Clinically Isolated Syndromes (P1. 393). Neurology, 86(16 Supplement), P1-393.

methylprednisolone

- IV 1 g 3-5 days for the treatment of acute attack

Amprya

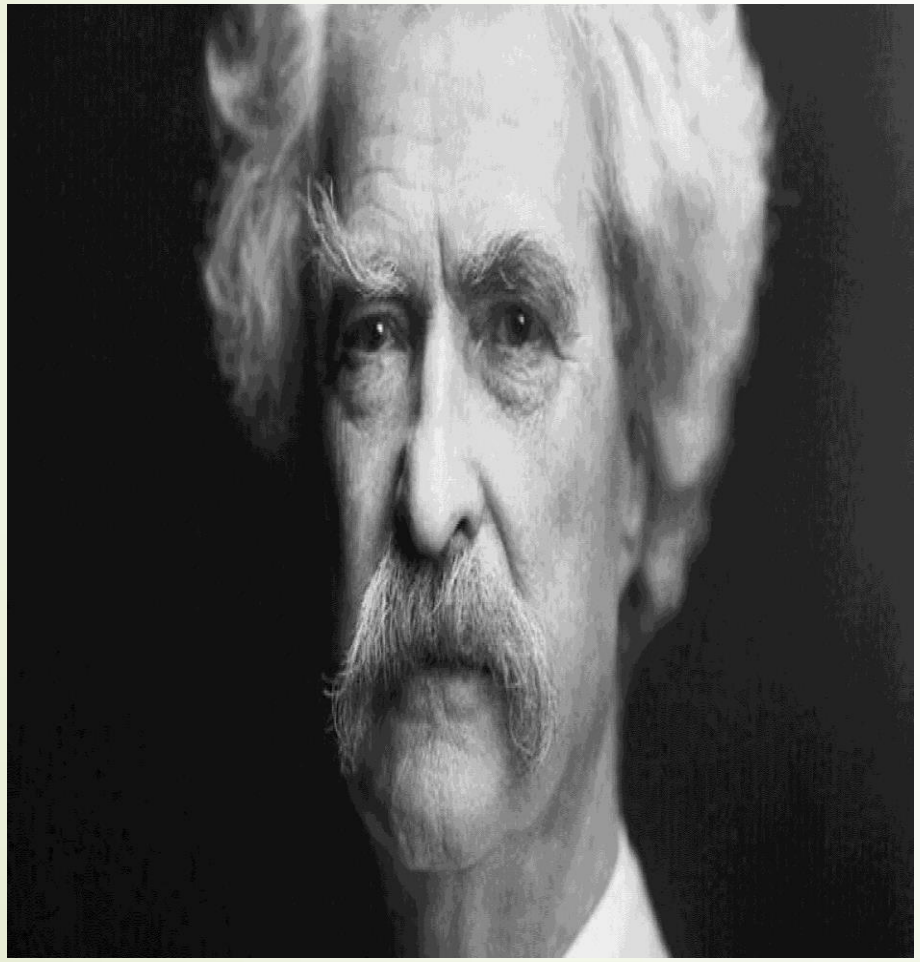
- Dalfampridine (Ampyra®) is an oral medication, in tablet form, which blocks tiny pores, or potassium channels, on the surface of nerve fibers. Blocking potassium channels may improve the conduction of nerve signals in along nerve fibers whose insulating myelin coating has been damaged by MS.(MS Society)

- Dalfampridine is approved by the U.S. Food and Drug Administration (FDA) to improve walking in patients with multiple sclerosis, as demonstrated by an increase in walking speed.(MS Society)
- This is not a disease modifying agent and is only for assisting with walking

MS treatment complications->source neurology journal July 2016

- 6662 patient's responded-> 6582 had health insurance however 1472 (22%)reported a negative insurance changed 12 months prior.
- Approximately 25% reported relying on free or discounted drug programs for the cost of medications
- Less than 1% fully paid for the MS medications themselves
- Up to 40% of MS patients are not compliant with medication due to cost concerns
- 3% initially have their medication denied by their insurance companies
- 2% report insurance companies denied the right to change medications

MS Life style advice



- Mark Twain Qoute
- “Do not put off until tomorrow what can be put off until the day after tomorrow just as well”

MS lifestyle advice

- Fatigue management
- Proper stress management
  - Financial, Emotional, Physical
- Exercise
- Proper nutrition
- Obesity avoidance
- Temperature control
- Medication compliance

MS lifestyle modifications

Adapting to new normal

- Handicap parking sticker's
- Adaptive equipment

Workplace modifications

Disability

Driving evaluations

Therapy evaluations speech, physical ,occupational

Neuro Rehabilitation and Balance Center on the Southview campus is an excellent resource->> 401-6109

Experience Ability:
Multiple Sclerosis (MS) Awareness
Steven W. Nissen, M.S., CRC

- http://www.targetcenter.dm.usda.gov/sites/default/files/MS%20Awareness%20Month%20slides_0.pdf

- Wonderful resource has information about medication , symptoms and employment considerations.


CONTROVERSIAL
ISSUES

Multiple Sclerosis and Domestic Violence

- If we don't ask to questions we do not know the answers
- Physical ,emotional ,& sexual abuse occurs to our patients and its our responsibility to help identify the problem.
- Do not ignore caregiver burnout
- Encourage the use of counseling
- Encourage the family to become familiar with the national MS Society website
- Encourage the patient and family to apply for all financial assistance they qualify for.

MS & Pregnancy

- Needs to be a patient centered issue
- Multi factorial process-> The needs of the patient, spouse, and future child need to be considered.
- No MS medication is 100% safe in pregnancy
- Copaxone is pregnancy category B
  - Some physicians will use throughout pregnancy
- MS& nursing is also controversial
  - Some school of thought the Copaxone in the interferons may be safe

My opinion

- I encouraged them to get pregnant off medication if they will want a pregnancy.
- I do not endorse medications while pregnant
- We discussed breast-feeding if they want to breast-feed I do not prescribe medication
- I encourage another adult to help out the home for the first few months->longer for multiple pregnancy

- Keep in mind that MS affects different people differently
- Keep in mind multiple sclerosis affects the whole family.

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- Experience Ability: Multiple Sclerosis (MS) Awareness by Steven W. Nissen, M.S., CRC

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