

## Multiple Sclerosis

### Some Basics Worth Understanding



## Multiple Sclerosis: Some Basics Worth Understanding

A. Paul Chous, M.A. O.D., FAAO  
Tacoma, WA

### Disclosure

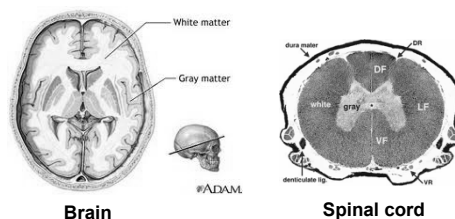
- I have been a consultant for, been on advisory boards or spoken on behalf of the following:  
AI Optics, Bausch & Lomb, EyeNuk, Genentech, Glaxo Smith Kline, Novo Nordisk, Prodigy Diabetes Care, Regeneron, Risk Medical Solutions, VSP, Zeavision, Zeiss

My affiliations with these companies have not affected the materials within this lecture



### What is MS?

- Autoimmune Disease of the CNS
- Demyelination of white matter

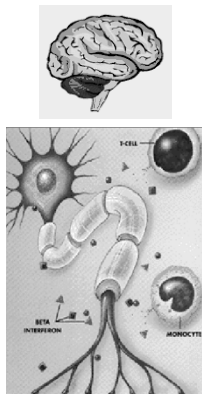


Brain

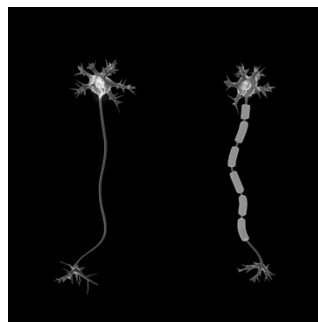
Spinal cord

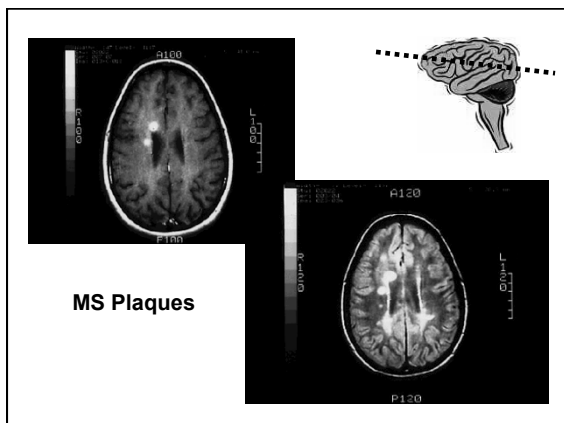
### What is MS?

- MS is an immune-mediated disease of the brain and spinal cord
  - ≈ 1 million affected in US
  - ≈ 12,000 new cases/yr
- Immune system attacks and destroys myelin and axons
- Characterized by demyelination and axonal loss
- Demyelinating plaques: well-demarcated areas characterized by loss of myelin



### Loss of 'saltatory conduction' along nodes of Ranvier





### Features of MS

- Demyelination results in
  - Paresthesia (numbness & weakness)
  - Loss of skeletal muscle coordination
  - Loss of autonomic function
- Multiple sites of CNS involvement
- Multiple attacks over time

### Most Relevant Signs and Symptoms of MS in the Primary Care Setting

Numbness	Fatigue	Pain
Diplopia	Vertigo	Depression
Bladder Dysfunction	Bowel Dysfunction	Sexual Dysfunction
Gait impairments	Cognitive Dysfunction	Paresis

### Epidemiology

- Prevalence that ranges between 2 and 291 per 100,000 depending on the country or specific population
  - Primarily a disease of Northern and Central Europeans and their descendants
  - Sunlight & Vitamin D intake appear to lower risk
  - Rare in East Asia and unknown in blacks in Africa
- Migration in children before the age of 15 years adopt the risks of the new locale

### MS and Human Herpesvirus (HHV)

- Subjects with HHV-6A antibodies doubly likely to have MS than those with the more common HHV-6B antibodies
  - 80% of humans have HHV-6 Ab by age 2 years
- 8700 patients and 7200 matched controls
- Epstein Barr virus Ab further increased risk in subjects with HHV-6A Ab
- Response to HHV modulated by Human Leukocyte Antigen (HLA) that links MS to other autoimmune diseases

Increased Serological Response Against Human Herpesvirus 6A Is Associated With Risk for Multiple Sclerosis. *Frontiers in Immunology*, 2019

### Infectious Mononucleosis Doubles the Risk of MS

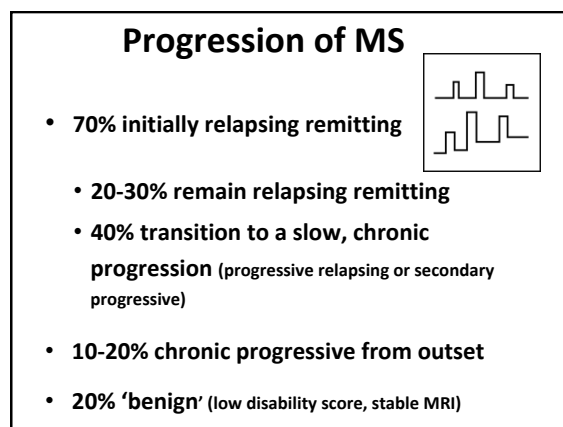
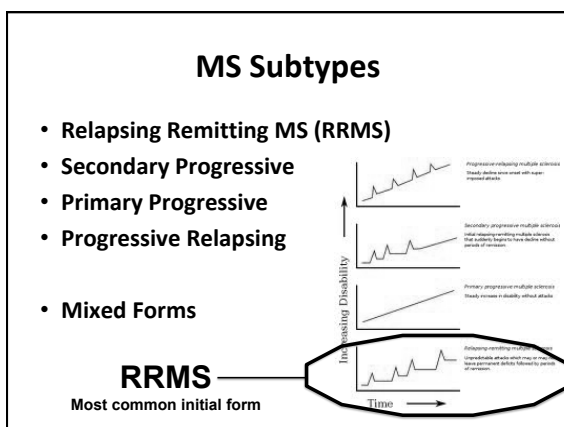
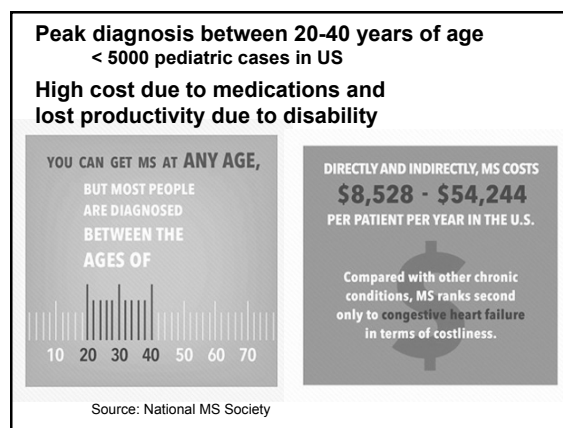
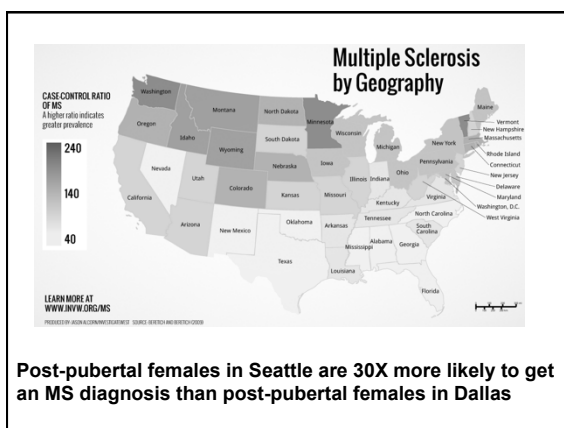
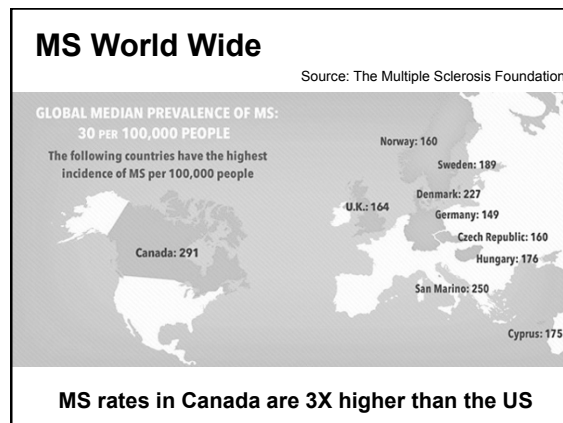
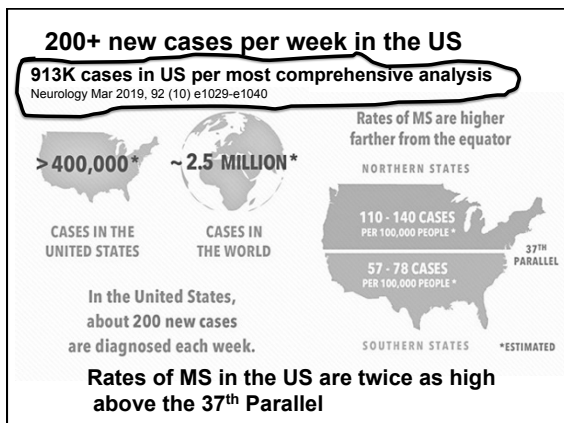
PLoS One 2010 Sep 1;5(9):e12496.

FOX 59

NEWS INDY NOW WEATHER TRAFFIC MORNING NEWS SPORTS JOBS

### Common 'kissing disease' among teens may trigger multiple sclerosis





### Genetics & Gender

- 7-20 times more common among those with an affected family member
- Identical twins = 40% concordance rate
- 10% higher risk if T1DM, autoimmune thyroid disease (Grave's, Hashimoto's), IBD
- Women 2:1

Am J Epidemiol (2005) 162 (8): 774-778.

### MS Risk Linked to Breast Feeding

- Mothers who breastfed  $\geq 15$  months were half as likely to develop MS compared to women who breastfed  $\leq 4$  months
- Observational study of pts with newly diagnosed MS/CIS (n = 397) and matched controls (n = 433)
- Adjusted OR for longer breastfeeding = 0.47  
– p = 0.003 for significance

Neurology. 2017 Aug 8;89(6):563-569.

### What is CIS?

- The initial demyelinating event is referred to as “Clinically Isolated Syndrome” (CIS)
- Common presentations include:
  - Optic neuritis
  - Transverse myelitis
  - Brainstem syndromes (INO, cranial neuropathy, nystagmus)

### Transverse Myelitis

myelitis = inflammation of the spinal cord

- Ascending numbness from the feet up through the torso or hands to the arms
- Balance problems
- Partial or complete motor paralysis
- Lhermitte's Sign
- Bladder & sexual dysfunction are common



### Diagnostic Work-Up for Patients With Suspected CIS and/or MS

#### MRI imaging studies

- Brain w/ contrast
- Cervical spine w/ contrast
- Thoracic spine w/ contrast
- Areas where symptoms manifest should guide imaging



#### Blood tests

- Rule out MS mimetics, other autoimmune diseases



#### Additional tests

- Evoked potential testing
  - Visual
  - Auditory
  - Somatosensory
- Helpful in detecting multifocal disease

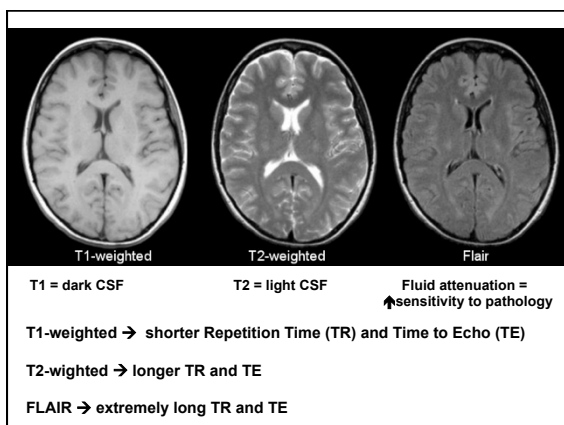


- CSF/lumbar puncture
  - Assess degree of immune cell infiltration of CNS

CSF: cerebrospinal fluid.  
Garcia Merino A, Blasco MR. *Int MS J.* 2007;14:58-63.

### Diagnosis of MS

- Requires multiple sites of CNS involvement over time
- MRI of brain and spinal cord
  - T2 weighted FLAIR (fluid attenuated inversion recovery)
  - T1 weighted with gadolinium contrast
- Number of MRI lesions is the single most important predictor of conversion to clinically definite MS (CDMS) and disability progression



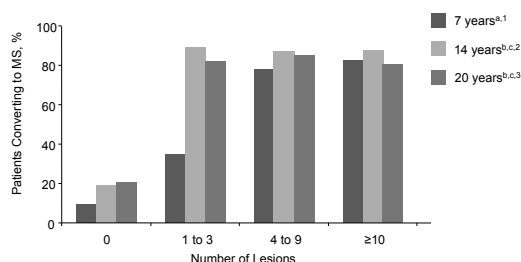
### T2-Weighted/FLAIR Brain MRI<sup>1-3</sup>



- Reveals hyperintense lesions
- Shows total number of lesions
- Indicative of disease burden
- Lesions may sometimes mimic brain tumors
- Available scanning protocols
  - Sagittal Fluid Attenuated Inversion Recovery (FLAIR)
  - Axial FLAIR

1. Image obtained from <http://www.melivingwell.org/new/understanding-your-mri>. Accessed March 31, 2010.  
 2. Filippi M, Mutt Söler. 2000;6:320-326. 3. Inglesse M. *Psychiatr Times*. 2007;3(7). <http://www.psychiatrictimes.com/display/article/10168/56481?pageNumber=2>. Accessed March 31, 2010.

### Baseline MRI Correlates With Risk of Conversion to MS



<sup>a</sup> McDonald criteria. <sup>b</sup> Poser criteria. <sup>c</sup> Same patient cohort.

1. Tintore M et al. *Neurology*. 2006;67:968-972. 2. Brex PA et al. *N Engl J Med*. 2002;346:158-164.  
 3. Fisniku LK et al. *Brain*. 2008;131:808-817.

### Disability from MS

- **Extended Disability Status Score (EDSS)**
  - Scoring for each of 8 functional systems
- **Pyramidal (ability to walk)**
- **Cerebellar (coordination)**
- **Brain stem (speech and swallowing)**
- **Sensory (touch and pain)**
- **Bowel and bladder functions**
- **Visual**
- **Mental**
- **Other (includes any other neurological findings due to MS)**

### Baseline MRI Correlates With Disability Progression at 5 years

# of Lesions on Baseline MRI	Patients With EDSS ≥ 3 at 5 years
0	5.8%
1-3	8.7%
4-9	11.1%
≥ 10	25.4%

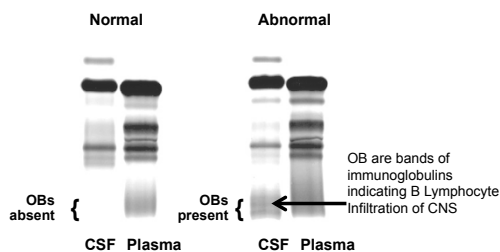
EDSS > 3 means moderate disability

EDSS: Expanded Disability Status Scale.  
 Tintore M et al. *Neurology*. 2006;67:968-972.

### Diagnosis of MS

- **Lab tests to R/O mimetics**
  - Serum B12, ESR, Lyme titer, ANA, RF, anticardiolipin, TSH, NMO-IgG
- **Lumbar puncture with CSF analysis**
  - Oligoclonal banding: B-lymphocyte infiltration of CNS
  - Elevated IgG Index (antibodies typical of autoimmune disease)

### Oligoclonal Bands (OBs) in CSF<sup>1,2</sup>



- 95% of patients with MS have CSF OBs
- IgG index is rarely elevated in CSF OB-negative patients

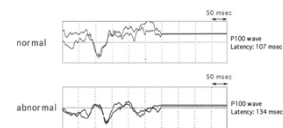
1. Link H, Huang YM. *J Neuroimmunol.* 2006;180:17-28. 2. Image adapted from: [http://library.med.utah.edu/kw/mml/ms\\_oligoclonal.html](http://library.med.utah.edu/kw/mml/ms_oligoclonal.html). Accessed February 25, 2010.

### Other Tests

#### • Evoked Potentials

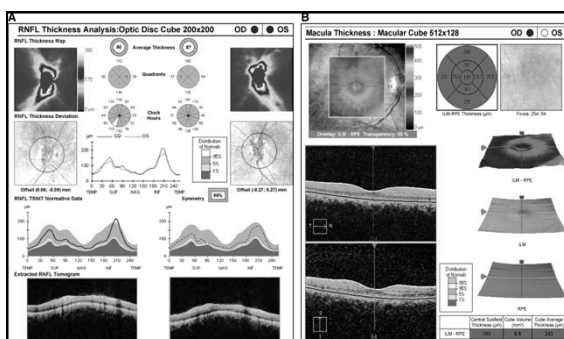
- Visual
- Auditory
- Somatosensory

#### Visual Evoked Potentials



- OCT: meta-analysis shows RNFL thinning and reduced low contrast acuity in pts with MS (with & w/o previous optic neuritis)

*Arch Neurol.* 2009 Nov;66(11):1366-72.

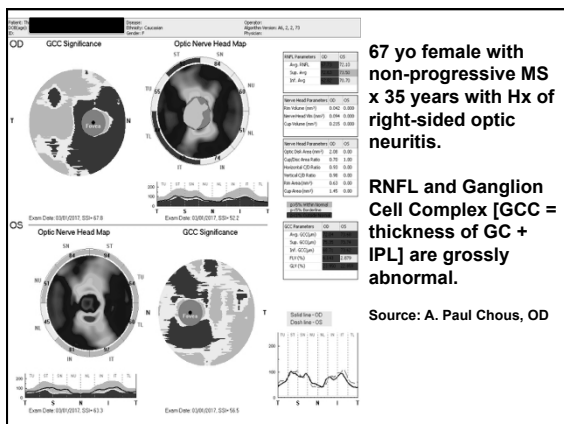
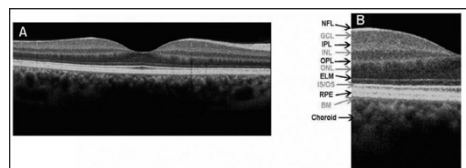


37 yo woman with MS diagnosed x 8 years and no Hx of Optic Neuritis

*Brain* January 20, 2011

### GC/IPL Thinning

- Recent evidence suggests thinning of the ganglion cell and inner plexiform layers is more sensitive for MS progression than RNFL thinning *Neurology.* 2013 Jan 1;80(1):47-54



RNFL and Ganglion Cell Complex [GCC = thickness of GC + IPL] are grossly abnormal.

Source: A. Paul Chous, OD

### Building Your Practice with Vision

- Any patient with MS will benefit from annual OCT examination of the retinal nerve fiber layer (RNFL) and GCL/IPL to track disease progression
- OCT reports to treating Neurologists and PCPs will grow your practice

## MS Progression

### EARLY

- Inflammation
- Demyelination
- Plaques



RELAPSES

### LATE

- Increasing tissue destruction
- Axonal loss
- Atrophy



DISABILITY

## Ambulation & Mortality

- 90% of pts ambulatory at 10 years
- 75% ambulatory at 15 years
- Mean decrease in life expectancy: 5-10 years

## Ocular Complications

- Optic Neuritis
  - 40-55% of MS pts will experience
  - Initial event in 20% of pts
  - Sudden loss of vision in one or both eyes
  - Pain on eye movement
  - Color desaturation
  - Visual field defects
  - Recovery of acuity over days to weeks
  - DDx: neuromyelitis optica (Devic's Disease) – NMO IgG antibodies (targets cellular aquaporin receptors)



## 33 yo female

- "I see double when I look up at road signs"
- BCVA 20/20 OD/OS
- PERRLA without APD
- Vision dims in the shower
- Eyes are straight on cover test
- EOMs are abnormal

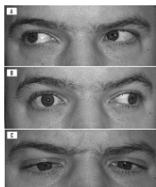


What Is This??

**Bilateral INO**

## Ocular Complications

- Internuclear Ophthalmoplegia (INO)
  - Brainstem demyelination (MLF)
  - Loss of adduction with intact convergence
    - + Horizontal Nystagmus of abducting eye
  - Diplopia on lateral gaze

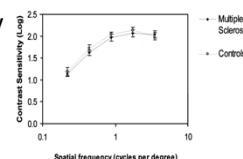


Right INO

*Bull Soc Belge Ophtalmol. 2009;65-8.*

## Other Eye Findings

- Nystagmus with oscillopsia
- Cranial nerve palsies (typically CN VI)
- RNFL Thinning and perimetric defects
  - Reduced contrast sensitivity
- Phosphenes
- Uhthoff's Sign
- Ocular Inflammation
  - Pars planitis
  - Retinal periphlebitis
  - Granulomatous uveitis

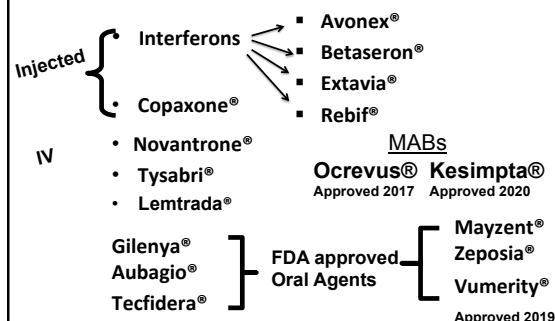


*Curr Opin Ophthalmol. 2005 Oct;16(5):315-20*  
*Ocul Immunol Inflamm. 2004 Jun;12(2):137-42*

## MS Treatment Goals

- Prevent relapses
- Decrease severity and shorten relapses
- Decrease disability
- Slow or prevent conversion from Relapsing Remitting (RRMS) to Secondary Progressive (SPMS)

## Disease-Modifying Therapy (DMT)



## Treatment of MS – Hx 1<sup>st</sup> Line

- Disease Modifying Drugs (DMDs)
  - Interferon *B* (1a and 1b)
    - *B* 1a IM (Avonex<sup>TM</sup>)
    - *B* 1a SC (Rebif<sup>TM</sup>)
    - *B* 1b IM (Betaseron<sup>TM</sup>, Extavia<sup>TM</sup>)
  - Glatiramer acetate (Copaxone<sup>TM</sup>)
- These 3 primary DMDs demonstrate fairly equivalent reduction in event relapse rates and EDSS progression (roughly 35% reduction)

BMJ. 2000 Aug 12; 321(7258): 424

TH = T helper cells

Reduce antigen presentation  
Reduce MMP expression  
Inhibit T cell proliferation

TH1 → TH2 response  
Activation of Treg cells

## Key Principles for Early Treatment of CIS With Disease-Modifying Therapies

- Patients who present with CIS are at high risk of developing clinically definite MS
- This risk is increased if their baseline MRI suggests the presence of multi-focal disease
- Treatment with DMDs at the initial episode of demyelination may:
  - Postpone progression of CIS to clinically definite MS
  - Reduce risk of disability progression

Goodin DS, Bates D. *Mult Scler*. 2009;15:1175-1182.

## Adverse Events with 1<sup>st</sup> Line DMDs

- Depression (IFβ)
- Injection site reactions (Both)
- Flu-like symptoms (fever, chills, nausea) (IFβ)
- Elevated liver function tests (IFβ)
- Chest Pain & Shortness of breath (glatiramer)
- 50% of pts D/C initial DMD due to AEs
- Management: pt education; prophylax anti-depressants with Interferons; rotate injection sites & warm meds; dose reduction



lipoatrophy

## Second Line Agents – IV infusion

- Natalizumab (Tysabri<sup>TM</sup>): humanized monoclonal antibody against α4-integrin CAM
  - Prevents T cell egress thru BBB
  - IV infusion Q28 days
  - Small risk of progressive multifocal leukoencephalopathy (PML) – 7311 total cases as of May 2017 (opportunistic typically fatal viral infection); increased risk on immunosuppressants and patients with + JC Virus antibodies
- Mitoxantrone (Novantrone<sup>TM</sup>): anti-cancer drug (topoisomerase inhibitor) used in 2<sup>nd</sup> progressive MS
  - Cumulative cardiac toxicity
  - 1 in 133 pts develop leukemia

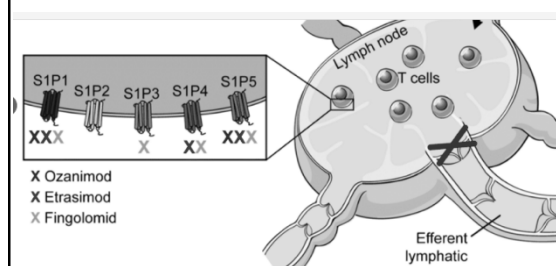


## New Oral Agents for MS

- **Goal:** equivalent or superior efficacy to injectable agents & convenience
- **First Oral: Fingolimod (Gilenya™)** – S1P inhibitor
  - Prevents egress of T cells from lymph nodes
  - Diminishes auto-aggressive lymphocytic infiltration of CNS
  - Superior reduction of relapses when compared head-to-head with Interferon  $\beta$ -1a
  - Increased risk of infection, HTN and bradycardia
  - 0.5-1.5% incidence of CME

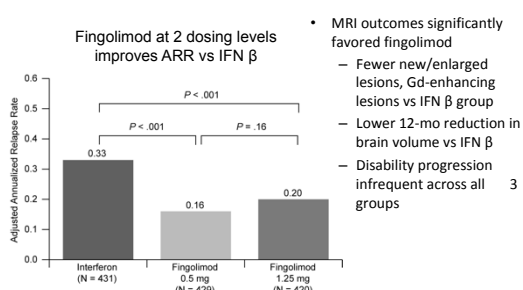
Cohen JA et al. *New Engl J Med.* 2010;362:402-415. Kappos L et al. *N Engl J Med.* 2010;362:387-401.

## S1P Facilitates T-cell Egress from Lymph Nodes



April 2019 *Current Gastroenterology Reports* 21(5)

## Fingolimod Improves ARR, MRI Outcomes vs IFN $\beta$



Cohen JA et al. *New Engl J Med.* 2010;362:402-415.

## More on Sphingosine-1-phosphate Inhibitors

- Fingolimod is only MS drug approved for children and adolescents (2018)
- Generic approval granted by FDA 12/5/2019
  - Full price Gilenya costs  $\approx$  \$8100/month
- Mayzent™ (simponimod) is a synthetic derivative of fingolimod approved 3/19 for CIS, RRMS, secondary progressive MS
- Zeposia™ (ozanimod) & Ponvory™ (ponesimod) now approved for RRMS/active SPMS (improved cognitive processing speed)

Benedict RJH et al. *Neurology* 2021; 96(3):e376-e386

## Other Oral Therapies:

- Aubagio™ (teriflunomide) – inhibits T cell mitosis – least effective oral agent
- Tecfidera™ (dimethylfumarate) – inhibits CAMs and inflammation; activates Nrf2 pathway  $\uparrow$  antioxidant defense
  - 4% have GI adverse events
- Vumerity™ (diroxamel fumarate) bioequivalent with fewer GI AEs

Relative Efficacy of oral agents assessed by ARR and % without relapse:

**S1P inhibitors = Tecfidera/Vumerity > Aubagio**

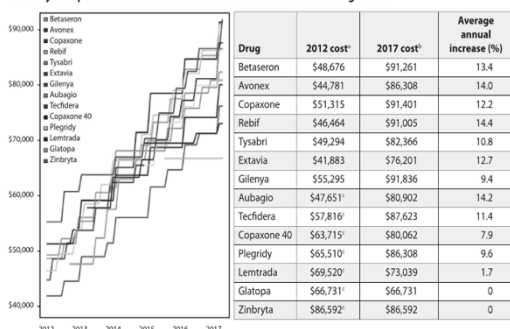
## Monoclonal AB: Newer 2<sup>nd</sup> or 3<sup>rd</sup> line Tx Ocrevus: 1<sup>st</sup> drug for PPMS

- Lemtrada® & Ocrevus®
- Annual IV infusion x 2 years (or Q6mos)
- Kesimpta® is monthly SC injection (convenient)
- Human monoclonal antibody to CD52 protein on surface of T and B lymphocytes
- 50+% reduction in ARR compared with interferon  $\beta$ 1a
- 30% develop autoimmune thyroiditis with Lemtrada and 3X higher rate of neoplasm with Ocrevus

*Mult Scler.* 2015 Jan; 21(1): 22–34  
*N Engl J Med.* 2017 Jan 19;376(3):209-220.

## MS Drugs are Expensive and Costs Have Risen

Stairway to expensive: Relentless climb of the annual costs of DMT drugs for MS



## Alternative/Complementary Strategies

### • Dietary

- **Swank Diet:** low fat (< 20 g/d) showed 84% reduction in MS mortality over 34 years
- **Best Bet Diet:** low saturated fat, correction of leaky gut, elimination of food allergens (gluten, eggs, added sugars) using ELISA
- **Wahls Diet:** modified Paleo diet sans eggs & nightshades with 9+ F/V/day (berries, dark greens)
- All three diets recommend elimination of eggs, dairy and highly processed foods
  - Recent RCT of RRMS subjects suffering chronic fatigue showed physical improvement with both Swank & Wahls diets; cognitive improvement with Wahls only

### – Activate Nrf2

The WAVES randomized parallel-arm clinical trial. Multiple Sclerosis Journal - Experimental, Translational and Clinical. July 2021.

## Dietary Activators of Nrf2

- Nrf2 is the master nuclear regulatory factor of antioxidant defense
- Upregulated by:
  - polyphenols - green tea, curcumin, resveratrol
  - Sulforaphane – broccoli, cabbage, kale
  - Allicin – garlic
  - Lycopene – tomatoes
- Protandim™ – patented dietary supplement with 'phytochemical Nrf2 activators'

## Alternative Meds

- **Low Dose Naltrexone (LDN)** – opioid antagonist
  - Very popular amongst MS bloggers
  - Lots of anecdotal evidence of benefit
  - Limited scientific evidence for improved QoL

Ann Neurol. 2010 Aug;68(2):145-50

### • Estrogen & Testosterone Therapies

- Reduced MRI lesions and relapses during pregnancy (estriol effect) and lower AI Dz in men
- UCLA pilot and Phase 2 studies show dramatic improvement in RRMS MRI lesions and 50% additional drop in ARR with supplemental estriol in women when added to Copaxone

J Immunol. 2003 Dec 1;171(11):6267-74.

Arch Neurol. 2007 May;64(5):683-8.

Lancet Neurol. 2016 Jan;15(1):35-46.

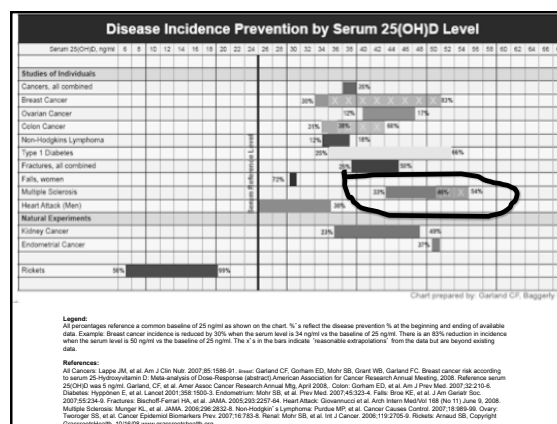
## Impact of Vitamin D on MS

- Should you add vitamin D to your MS treatment regimen?
  - Vitamin D deficiency is a risk factor for MS; multivitamin is recommended (1,000-2,000 IU/day vitamin D3)
  - One cohort study showed significant reduction in ARR with increased serum vit D in patients on Tysabri™ (n = 170, p = 0.02)

Mult Scler Relat Disord. 2016 Nov;10:169-173.

54% risk reduction  
@ 54 ng/ml 25(OH)-vitamin D

Higher serum 25-OH vitamin D levels are associated with up to a 54% decrease in MS Dx



### Vitamin D3 in Optic Neuritis Pts

- 30 subjects with ON were given weekly doses of 50,000 IU D3 or placebo
- 68% less conversion to CDMS in the Tx group ( $p=0.007$ ) after 12 months

**Vitamin D may help prevent progression from optic neuritis to clinically definite MS**

Acta Neurol Belg. 2013 Sep;113(3):257-63

### Coimbra Protocol



- Cicero Coimbra, MD, PhD
  - Sao Paolo, Brazil
  - Protocol used in 4000+ patients with CDMS
- 1,000 IU vitamin D3 per Kg body weight/day
  - Drive parathyroid hormone to low end of normal range and adjust
  - Co-supplementation with vitamin B2 (riboflavin), low calcium diet and 2.5 L water/day
- Claims 95% of patients go into symptomatic & radiologic remission

### HALT-MS Trial

- A single round of hi-dose immunosuppressive therapy combined with autologous infusion of patients' own stem cells → no relapses, MRI lesions or worsening disability in 69% of patients after 5 years
- n = 24 with RRMS

JAMA Neurology DOI: 10.1001/jamaneurol.2014.3780 (2014).

### Cannabis



- Cannabis – small studies show reduced muscle spasticity that affects 80% of MS patients per surveys (13% are severe)

CMAJ. 2012 Jul 10;184(10):1143-50.  
J Neurol Neurosurg Psychiatry. 2012 Nov;83(11):1125-32

- Recent evidence suggests cannabis use may accelerate cognitive dysfunction associated with reduction in brain volume

Neuroimage Clin. 2015 Apr 9;8:140-7.

### Sleep Apnea

- Multiple studies show that OSAS is at least doubly common in MS patients
- Sleep apnea may contribute to fatigue commonly experienced by MS patients
- Inquire about OSAS symptoms (daytime sleepiness, snoring, etc.)
- Refer to sleep medicine

J Clin Sleep Med. 2014 Feb 15;10(2):155-62

### Re-Myelination Therapies?

- Bexarotene (skin cancer agent) → remyelination in rat models of MS
  - Induces hypothyroidism/elevated TGs in humans and minimal affect on brain MRI in a small human trial
- Metformin ↑A muciniphila, Tregs and signalling molecules that → remyelination in a mouse model of MS
  - Human trials underway
  - Excellent safety profile

Front. Immunol., 10 August 2021  
Lancet Neurol 2021 Sep;20(9):709-720.

Pharmacol Rep. 2020 Jun;72(3):641-658.

### **Good Optometric Tests to Help Dx and Monitor Progression**

- **Contrast sensitivity**
  - Vistech, Pelli-Robson, M&S Technologies
- **Color vision**
  - Rabin Cone Contrast Test (Innova Systems)
  - ColorDx (Konan)
- **sdOCT: GCC thickness & RNFL**
- **VEP (Konan, Diopsys)**
- **Good Case History: Uhtoff's, L'Hermitte's**

### **Conclusions**

- **Ocular findings are common in MS**
- **Optometrists should be aware of the pharmacologic and non-pharmacologic management of MS**
- **Encouraging patients to continue with DMD/DMT may help reduce disability**

DMD = disease-modifying drug  
DMT = disease-modifying therapy

**SYNONYMOUS**

**THANK YOU!**

**PAUL CHOUS  
DR\_CHOUS@DIABETICEYES.COM**