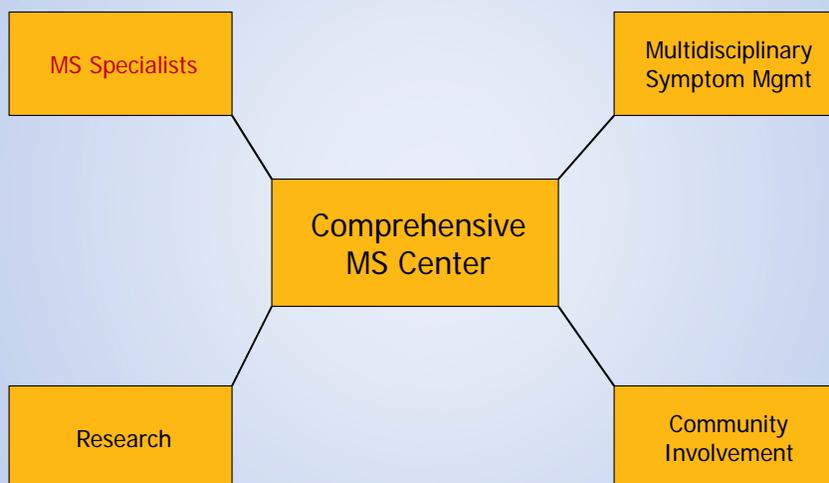


Finding the Right Care / Using Your Appointment to the Fullest

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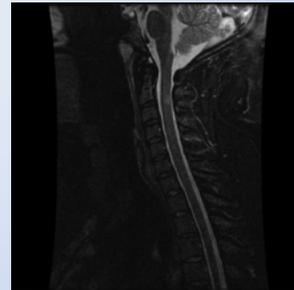
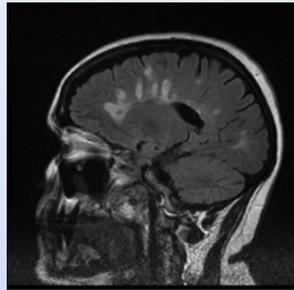
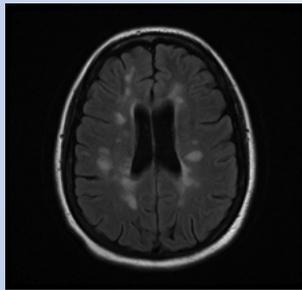
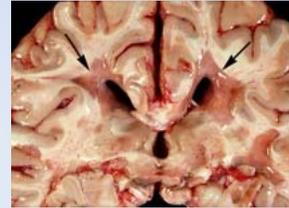
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Comprehensive Care of MS



Multiple Sclerosis

- Likely, a chronic, inflammatory condition of the CNS likely induced by an environmental trigger in a genetically susceptible patient
- “Neurological lesions disseminated in time and space” without an alternative explanation for symptoms



Multiple Sclerosis

- Possible environmental triggers
 - Infection
 - EBV infection (perhaps late exposure)
 - 99.9% of MS patients have been exposed to EBV
 - EBV DNA has been isolated from meningeal lymphoid follicles
 - Absence of infection
 - Inverse correlation between gut parasites and risk of MS
 - Clean hygiene hypothesis
 - Adaptive immune system develops, is not hard-coded in genome
 - Vitamin D deficiency
 - Explains geographic distribution of MS
 - Higher risk further from the equator, migrational studies
 - Inverse correlation between vitamin D level and level of MS activity
 - Vitamin D interacts with DNA and is involved with regulation of multiple genes, including genes known to be risk factors for MS

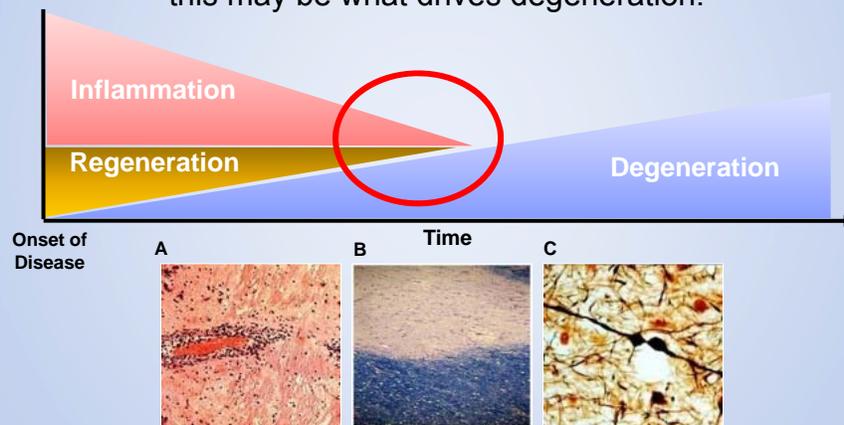
Multiple Sclerosis

- Genetic predisposition
 - Risks
 - One parent with MS - 3-4%; two parents with MS - 10%
 - One monozygotic twin with MS, other twin's risk is 30%
 - Common in Caucasians; uncommon in Africans, Asians
 - Genes
 - IMSSC has identified over 50 other genes, most with role in the immune system
- Prevalence (Old numbers!)
 - 400,000 in US; 2.5 million worldwide
 - Female:male is 3:1
 - Average age at diagnosis is ~30 years, but wide Bell-shaped curve
 - I've seen between 3yo and 69yo
- Incidence seems to be increasing
 - Better diagnostics vs. more cases?

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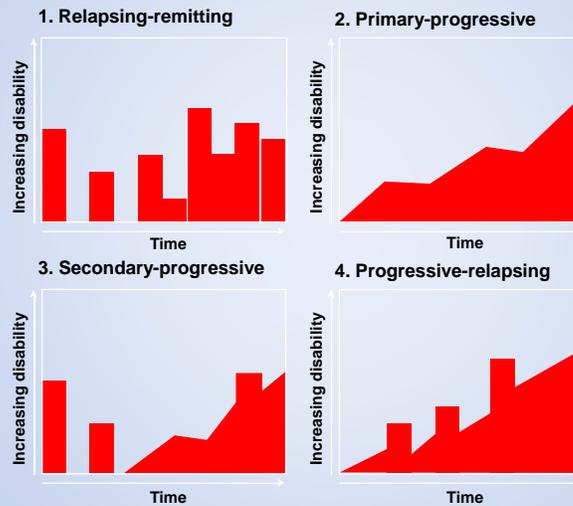
Immunopathogenesis of RRMS

Early inflammation lead to demyelination and axonal loss; this may be what drives degeneration.



Compston A, et al. *Lancet*. 2008;372:1502-1517 Kuhlmann T, et al. *Brain*. 2002;125:2202-2212; Paolillo A, et al. *J Neurol*. 2004;251:432-439.

Subtypes of MS



Lublin FD, Reingold SC. Neurology. 1996;46:907-911.

Relapsing Remitting MS

- RRMS
 - 85% of patients with MS start with a relapsing remitting course
 - Exacerbations / Flares / Relapses
 - Rapid onset of new symptoms
 - Association with gadolinium enhancement on MRI
 - May improve resolve over weeks to months (remission)
 - » Steroids (iv) speed up the improvement and may delay future events
 - » Many result in residual disability
 - Pseudo-exacerbation
 - Previous symptoms can reoccur / worsen in setting of infection, heat, stress
 - Inflammation plays a big role, but there is evidence of degeneration / atrophy in RRMS
 - We think treatment delays progression into SPMS

Progressive MS

- Degeneration plays more of a role in progressive MS
- Secondary Progressive Multiple Sclerosis (SPMS)
 - Follows relapsing-remitting MS (RRMS)
 - Is about 30% of MS patients
 - Transition from episodic flares to slow, gradual worsening of symptoms independent of flares
 - Often occurs 10-20 years after beginning of MS (highly variable)
- Primary Progressive Multiple Sclerosis (PPMS)
 - ~10% of multiple sclerosis patients
 - Gradual worsening of symptoms without preceding flares
 - But have fluctuations in symptoms
 - Rare cases of PPMS will have occasional relapse (PRMS)
 - 85% predominance of spinal cord symptoms (myelopathy)
 - Slow worsening of gait is the most common presentation
 - Sex ratio 1:1
 - Later onset of symptoms (~45yo)

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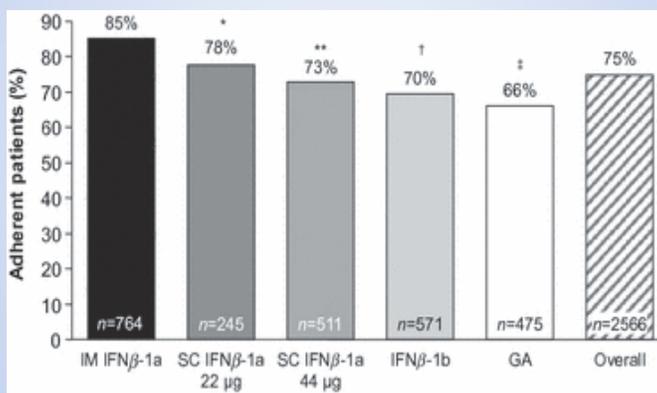
Disease Modifying Therapies

- Goal
 - Reduce relapses and new MRI lesions; delay disability
- Approved injectable medications for relapsing MS
 - Interferons: Avonex, Betaseron, Rebif
 - Copaxone (glatiramer acetate)
- Approved infusions for relapsing MS
 - Novantrone (mitoxantrone)
 - Tysabri (natalizumab)
- Approved oral medications for relapsing MS
 - Gilenya (fingolimod)
 - Aubagio (teriflunomide)
 - Tecfidera (dimethylfumarate or BG-12)

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Disease Modifying Therapies

- Compliance is key!



Devonshire Eur J Neuro 2010.

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Treatment of Progressive MS

- All of our agents work on the inflammatory component of the disease; however, progressive MS may be more degenerative.
 - Thus, we urge early treatment!
- None of the currently approved medications have been proven to alter the course of progressive MS
 - Failed trials in PPMS
 - Rituxan – possible response if <50yo with relapses or enhancing lesions
 - Copaxone
 - Novantrone
 - Trials suggesting effects in disease transitioning to SPMS
 - Betaseron (European trial)
 - Mitoxantrone
 - Failed trials in SPMS
 - Betaseron (North American trial)
 - Dirucotide (MBP 8298)
 - Ongoing trials offer hope of breakthrough ...
 - Tysabri
 - Gilenya
 - Ocrelizumab

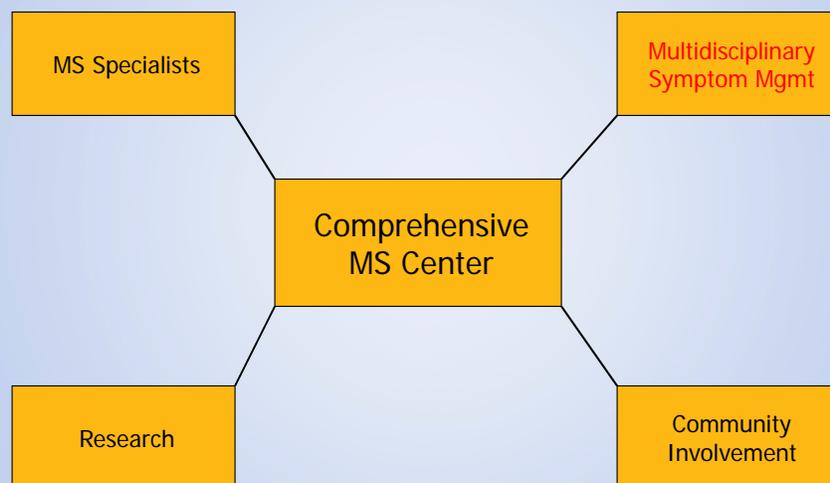
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Treatment of Progressive MS

- There is even more hope ...
 - In NY database of MS patients, up to 25% of patients with PPMS do not require a cane at 20 years.
- And, there are significant benefits attainable with appropriate multidisciplinary symptom management in a comprehensive MS center!

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Comprehensive Care of MS



Mindfulness ... A Good Sequel?

- MS quality of life, depression, and fatigue improve after mindfulness training - A randomized trial
 - 150 patients, 76 randomized to a mindfulness program; 74 not
 - Mindfulness group showed significant improvement in quality of life, depression, and fatigue

Grossman Neurology 2010.

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Physical Activity

- De-conditioning is a big problem in the MS population!
 - Increased risk of osteoporosis, depression, fatigue, and heart disease
- Contrary to popular opinion, physical activity is beneficial in MS!
 - Meta-analysis of 22 studies of exercise in MS
 - Exercise training associated with improved ambulation
 - Endurance training (mild to moderate)
 - Conflicting results on improvement of fatigue
 - Improvement in HRQOL and depression
 - Some suggest possible disease modifying effect
 - A trial of resistance training
 - 15% improvement in strength; 21% improvement in functional status
 - Improvements in mood, fatigue, HRQOL
 - Biopsy -- increase in size of muscle fiber
- Exercise physiologist / physical therapy
 - Customizing the routine depending on disability
- Yoga?

Abnormal Mobility

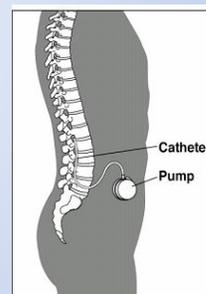
- Goal - safely maximize independence
 - “Nothing robs independence faster than a broken hip”
- Earlier interventions can help prevent larger future problems
 - Joint pain / changes
- Potential issues limiting ambulation
 - Leg weakness
 - Muscle weakness
 - Strengthening with physical therapy
 - Exercise / prevent deconditioning
 - Foot drop
 - Bracing with ankle-foot orthosis (AFO)
 - Peroneal stimulator



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Abnormal Mobility, cont'd

- Potential issues limiting ambulation
 - Spasticity
 - Velocity dependent resistance to muscle stretch
 - Double edged sword
 - Stiffness can compensate for weakness
 - Stiffness can inhibit movement
 - Exacerbating factors
 - Stress, infection, pain, temperature changes
 - Treatment
 - Stretching / Range of motion exercises
 - Baclofen, tizanidine (Zanaflex), clonazepam (Klonopin)
 - Intrathecal baclofen
 - Focal Botox
 - Combination of the above



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Abnormal Mobility, cont'd

- Potential issues limiting ambulation
 - Poor balance due to sensory loss, incoordination
 - Gait retraining (physical therapy)
 - Equitest
 - Balance Master
 - Assistive device
 - Cane. (I like Strong Arm)
 - Lofstrand (Canadian crutches)
 - Rollator
 - Walker
- Common sense
 - Handrails for stairs
 - Remove throw-rugs
 - Bathroom safety
 - Grab bars, shower seats
 - Night lights



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Abnormal Mobility, cont'd

- Patients with more limited ambulation
 - Manual wheelchair
 - Can be just for distance
 - Requires UE strength (or assistance)
 - Scooter
 - Requires good core strength
 - Power wheelchair
 - One size does not fit all
 - Appropriateness of seating is very important
- Augmenting ability to transfer
 - Grab bars
 - Transfer boards
 - Hoyer lift



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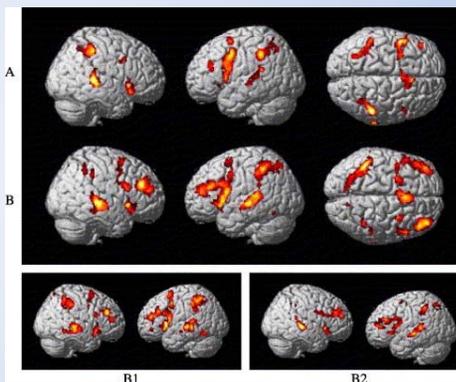
Fampridine (Ampyra)

- Oral medication for symptomatic management in MS
 - Long-acting form of 4-aminopyridine (4-AP)
 - Potassium channel blocker
 - May speed up slowed nerve conduction along denuded axons
 - Phase III trials measured 25 foot walk
 - Responder – 3 of 4 walks on treatment faster than 5 walks off treatment
 - 35-43% of patients were responders (Recognized early)
 - Increased walking speed by >20%
 - Low risk of seizure
 - SE: insomnia, dizziness
- Empiric experience with 4-AP
 - Improvement in fatigue, heat sensitivity, walking, nystagmus
- Posters at ECTRIMS
 - Possible benefit with cognition
 - Continued benefit in 2 year open-label extension

Fatigue

- Most common (and often most disabling) symptom of MS

- Physical lassitude that hits “like a Mack truck” and feels like “carrying weights”
 - Perhaps in part a sensory phenomenon
- Compounded by increased energy expenditure of spasticity, effort to compensate for motor disability
- Functional MRI suggests that more areas of brain are activated in an MS brain than in non-MS brain to perform the same task



Fatigue, cont'd

- Potential confounders, especially if “sleepiness”
 - Obstructive sleep apnea
 - Physical deconditioning
 - Drug side effects
 - Frequent nocturia
 - Depression
- Treatment
 - Exercise / reduce de-conditioning
 - Energy conservation – pacing, planning activities
 - Maintain appropriate sleep
 - Cognitive behavioral therapy
 - Mild exercise to prevent physical de-conditioning
 - Stimulants
 - Amantadine
 - Provigil / Nuvigil
 - Ritalin / Adderall



Neurogenic Bladder

- Bladder dysfunction occurs in up to 80% of MS patients
 - Can be the presenting symptom
- 2 basic problems
 - Failure to store – spastic, overactive bladder wall (detrusor)
 - “Gotta go, gotta go, gotta go right now”
 - Urinary frequency, urgency, and incontinence
 - Can also have bladder spasms
 - Appropriate bladder emptying (no residual)
 - Treatment
 - Timed voids
 - Pelvic floor therapy
 - Avoid bladder irritants (caffeine, alcohol)
 - Anticholinergics - Detrol, Ditropan, etc.
 - » Side effects: dry mouth, ?decreased cognition
 - Bladder BOTOX



Neurogenic Bladder, cont'd

- 2 basic problems, cont'd
 - Failure to empty – detrusor sphincter dyssynergia, atonic bladder wall, or spastic sphincter
 - Urinary hesitancy and retention
 - » Frequent bladder infections
 - Overflow incontinence
 - Residual urine after voiding
 - Treatment
 - Double voids
 - Pelvic-floor therapy
 - Flomax?
 - Clean intermittent catheterization
- Need to rule out gynecologic, prostate issues
 - Not everything in an MS patient is due to MS
- Indwelling catheters
 - Try to avoid
 - Prefer suprapubic over urethral (Foley) catheter



Neurogenic bowel

- Neurogenic bowel often refers to constipation
 - Fecal incontinence is often due to overflow with constipation
- The most common cause of neurogenic bowel is fluid restriction to reduce symptoms of neurogenic bladder.
 - Recommended fluid intake is 2000mL/day
- Other factors
 - Poor diet; lack of fiber
 - Lack of mobility
 - Abdominal wall weakness
 - Pelvic floor spasticity
 - Medication side effects
- Treatment
 - Dietary modifications
 - Bowel training
 - Stool softeners
 - Mild laxatives
 - Limit suppositories, enemas

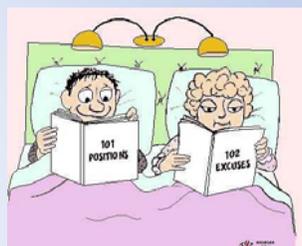


Pain

- Common causes of primary MS pain
 - Parathesias, including Lhermitte's symptom
 - Most common type of pain in MS
 - Ephatic transmission between denuded axons
 - Often, responds to anticonvulsants
 - Often, lack of response to typical analgesics (i.e., narcotics)
 - Trigeminal neuralgia
 - Spasticity is painful!
- Secondary MS pain
 - Osteoarthritis / joint pain can be attributed to abnormalities of gait
 - Musculoskeletal pain, skin breakdown, compression fractures
- Psychiatric / emotional component to pain, especially chronic
 - Duloxetine (Cymbalta) is approved for depression and neuropathic pain
- Role for PT / OT, acupuncture, massage, exercise (yoga, aqua)

Sexual dysfunction

- Sexual dysfunction is very common in MS
 - Issue with 40-80% of women, 50-90% of men with MS
 - Does this lead to added stress on the relationship?
- Primary sexual dysfunction
 - Issues with libido (desire)
 - Communication
 - Women
 - Decreased vaginal lubrication
 - Lubricants, fore-play
 - Abnormal vaginal tone
 - Anti-spasmodics
 - Altered pelvic sensation
 - Anti-convulsants, sex aides, "Bag of frozen peas"
 - Weak or unobtainable climax
 - Men
 - Erectile dysfunction
 - Viagra, Levitra, Cialis
 - Caverject
 - Altered pelvic sensation
 - Reduced capacity to achieve orgasm



Sexual dysfunction, cont'd

- Secondary sexual dysfunction: MS-related symptoms affect the ability to have a pleasurable sexual response

- Weakness
- Spasticity / Coital spasms
- Tremors
- Fatigue
- Bladder / bowel dysfunction
- Depression



- Tertiary sexual dysfunction: Psychosocial barriers to a pleasurable sexual response

- Loss of self-esteem, change in self-image
- Alterations in perceived roles (Care-taker vs. sexual partner)
- Reconciling sexual activity with disability
- Perceived norms about sexual practices
- Relationship
 - Issues with communication
 - Comfort level discussing sexuality
 - Socioeconomic stressors
 - Perception of "not the same person" / less "sexy"



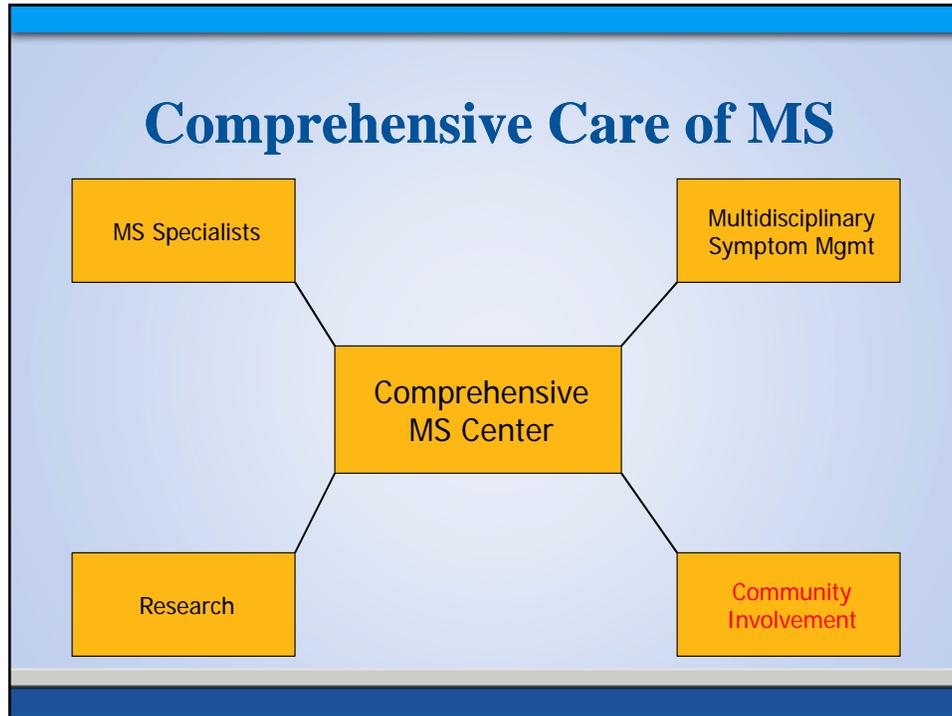
Neuropsychiatric Issues

- Depression in MS

- Situational stressors AND neurotransmitter deficiencies
- More common in MS than in other neurological diseases
- Requires multi-disciplinary care
 - Psychologist
 - Psychiatrist
 - Activating antidepressants (Effexor, Prozac, Wellbutrin)

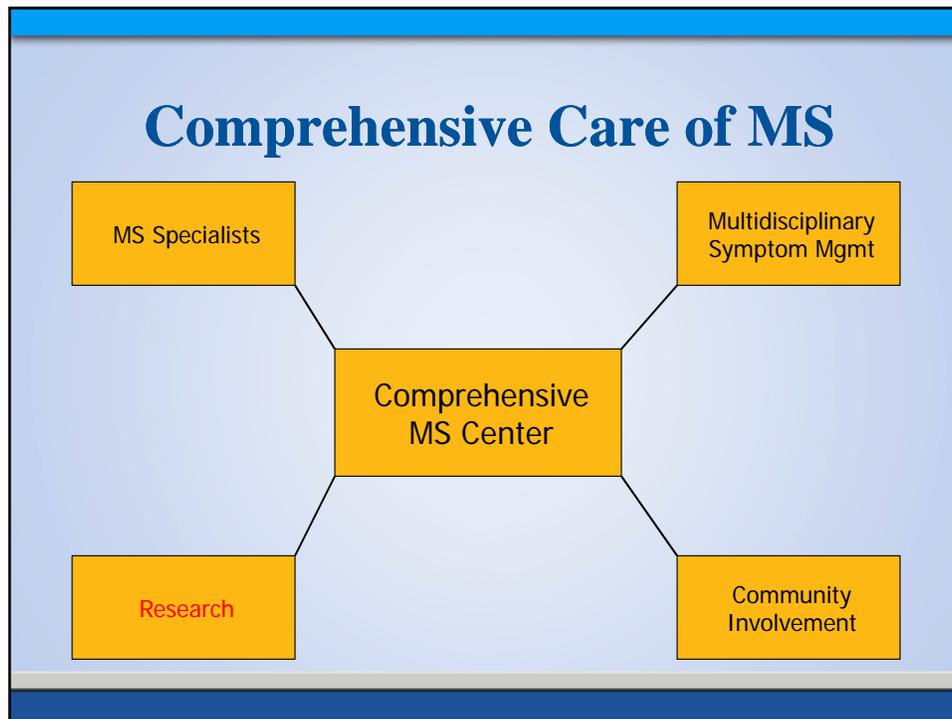
- Memory issues

- Prevalence is well over 50%
- Difficulty with processing speed, multi-tasking, rapid word retrieval, problem solving, and maintaining attention
- Data is limited for cognitive rehabilitation
 - Could smartphones, tablets help patients compensate?
- No data to support use of Alzheimer's medications like Aricept, Namenda
- Fatigue, depression, medications can worsen



Community Resources

- Patients with MS have needs in many domains (including social, family, home care)
 - There are many resources that can help
 - National Multiple Sclerosis Society (NMSS)
 - Multiple Sclerosis Foundation (MSF)
 - Multiple Sclerosis Association of America (MSAA)
 - Government resources
 - Centers for Independent Living, Vocational Rehab
 - Local MS centers
 - Local support groups
 - Patient (and spouse) support groups
 - Wellness programs
 - Patient education
- A case manager / social worker can assist patients navigate the maze of services and the process to obtain them



Research

- Risk factors
 - Environmental – Vitamin D
 - Genes – over 52 genes identified
- Disease Modifying Therapies
 - Coming soon for relapsing MS?
 - Alemtuzumab (Campath)
 - In development for relapsing MS
 - More selective S1P agonists (similar to Gilenya)
 - Daclizumab, Ocrelizumab, anti-LINGO
 - Biomarkers
- Rehabilitation

Conclusions

- Our therapeutic armamentarium for relapsing MS is expanding rapidly
- Symptomatic management is also an important component of MS care
- Non-pharmacologic interventions are important in symptomatic management
- Don't forget mindfulness and exercise
- Strive to be a person who happens to have MS and not an MS patient!