Management of Multiple Sclerosis for the Primary Care Provider

Ruth Ann Marrie, MD, PhD
Professor
University of Manitoba
March 2, 2018

Disclosures

- Relationships with commercial interests:

  None

Copyright

- This copy is provided exclusively for research purposes and private study. Any use of the copy for a purpose other than research or private study may require the authorization of the copyright owner of the work in question. Responsibility regarding questions of copyright that may arise in the use of this copy is assumed by the recipient.

Objectives

- At the conclusion of this educational activity you will be able to:

1. Describe common signs & symptoms of MS
2. State the diagnostic tests used for MS
3. Describe the role of the family physician in managing MS

Multiple Sclerosis

- Disorder of central nervous system (brain, optic nerves, spinal cord)
- Inflammatory demyelination
- Axonal degeneration
- Causes plethora of neurologic s/sx

Epidemiology

- Most common, non-traumatic cause of disability in young adults
- Affects an estimated 93,000 Canadians
- Female > Male: ratio incr. from 2:1 to 3:1
- Caucasians most often affected (but not always)
- Onset typically 20-40 years but may occur in childhood (5%) or after age 60 (0.5%)

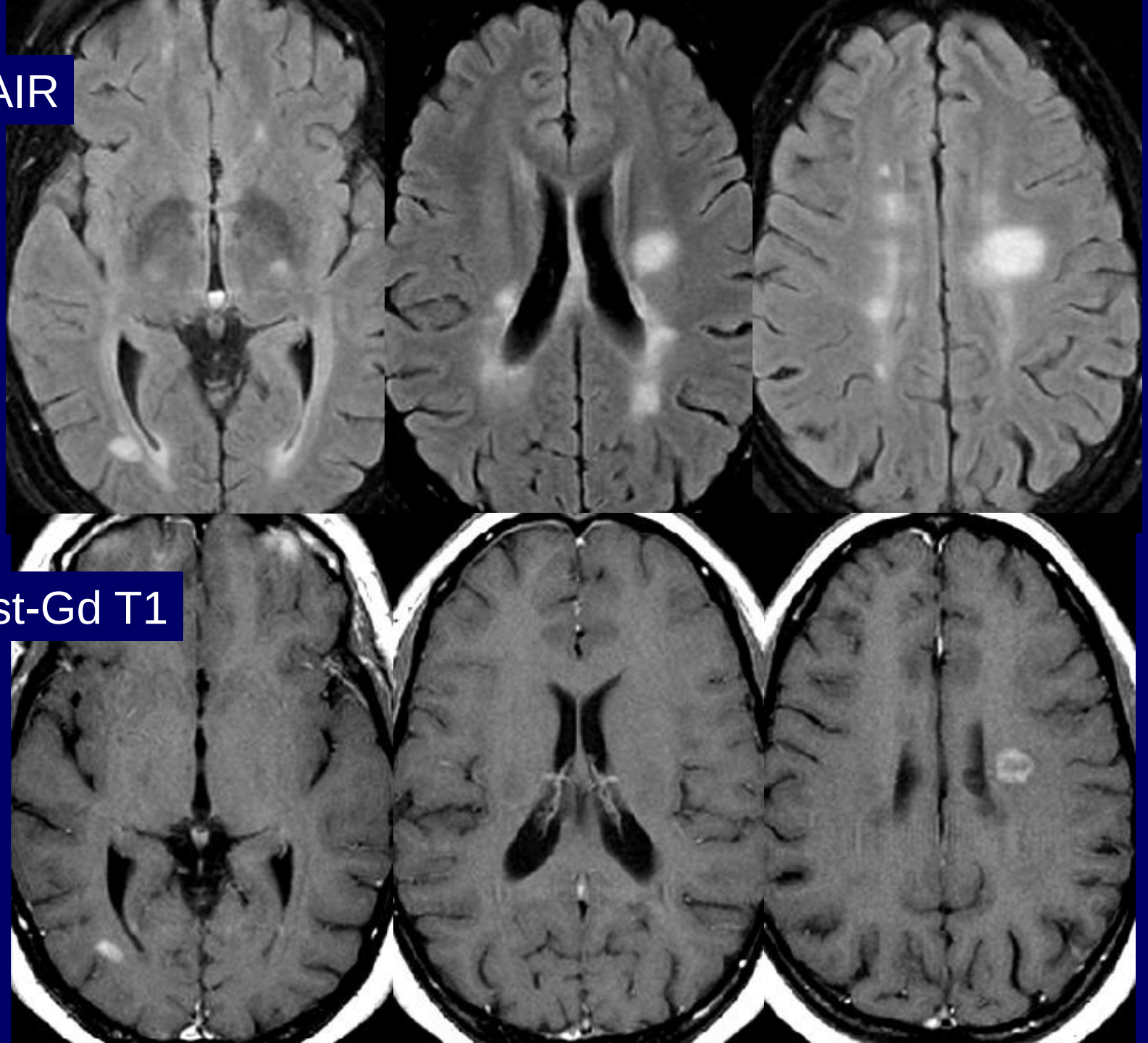
Typical Clinical Presentations

- Clinically isolated syndrome (CIS)

- Term for individuals with probable MS based on:
  - typical focal CNS demyelinating event with objective signs
  - an MRI with features strongly suggestive of MS, and
  - no better cause for the findings

Case

- 24 year old right-handed woman
- Previously healthy, no prior neuro. symptoms
- Visual blurring right eye x 1 week
- Reduced color vision
- Pain with eye movement
- On exam: RAPD; VA 20/50; impaired color vision


FLAIR
Post-Gd T1

Most Common CIS in MS

- Optic neuritis
  - Acute unilateral visual loss progressing over max of 2 weeks, orbital pain, afferent pupillary defect, retrobulbar or mild disc swelling
- Brainstem
  - Internuclear ophthalmoplegia, 6th nerve palsy, multifocal signs (e.g. facial sensory loss, vertigo, hearing loss, ataxia)
- Spinal Cord (transverse myelitis)
  - Evolution of symptoms over hours to days
  - Sensory and/or motor symptoms

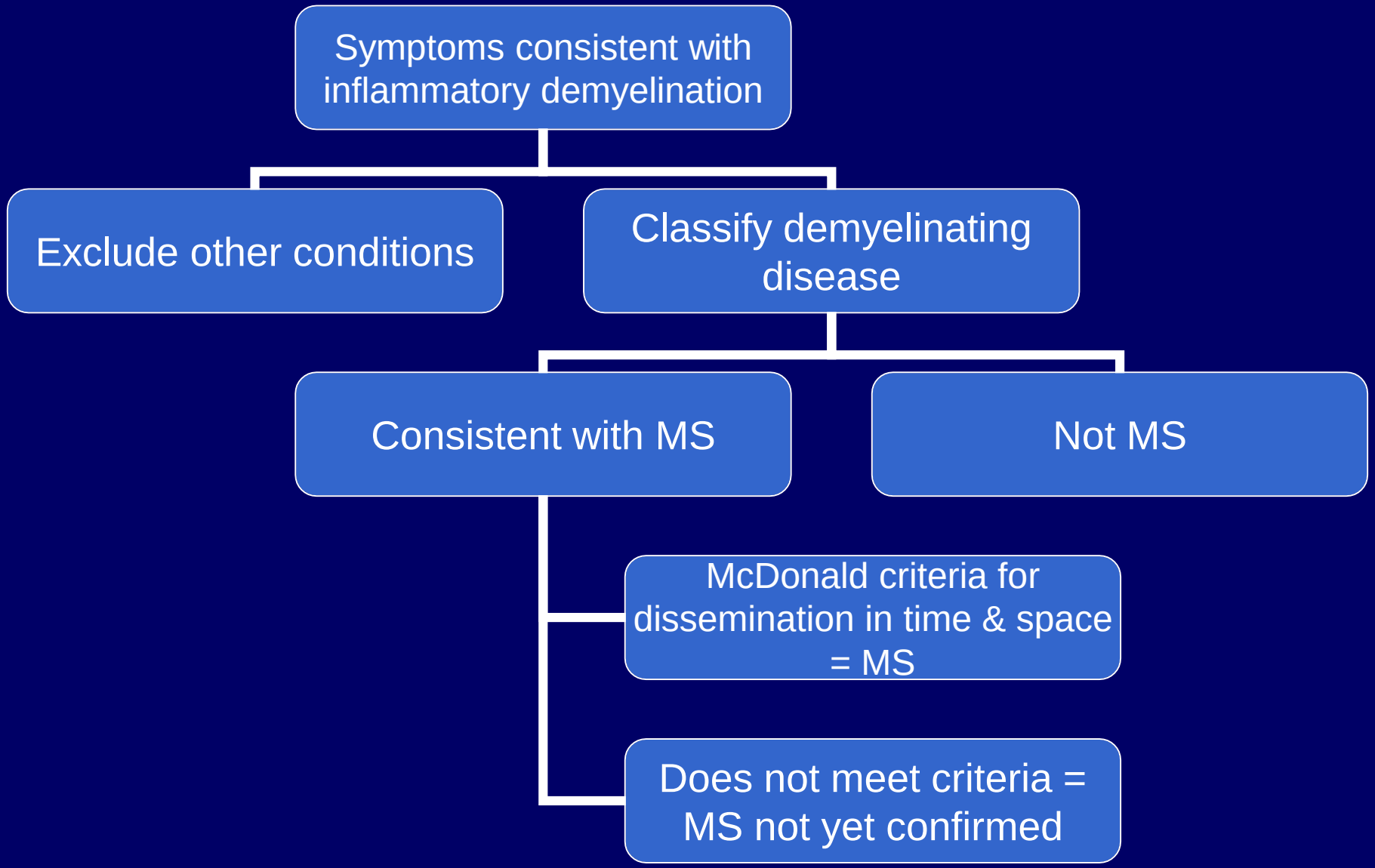
Risk of MS with CIS

- What is her risk of developing MS if we do not consider MRI results (older criteria)?
  - Reported risk varies widely 30-88%
- What can we use to risk stratify?
  - If normal **brain MRI** → 0-22% (low risk)
  - If abnormal **brain MRI** → 56-88% (high risk)
  - With new criteria Gd+/- lesions allow diagnosis now
- CSF
  - May be used to confirm a diagnosis of MS if the MRI alone is insufficient
  - May be helpful in excluding other etiologies

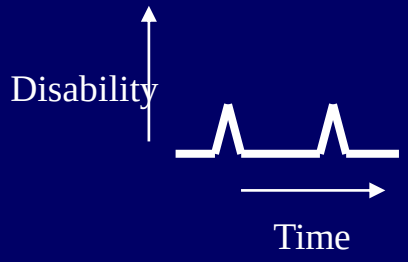
Making the Diagnosis of MS

- Multifocal CNS process (dissemination in space)
  - Clinical features, MRI, evoked potentials
- Evolution over time (dissemination in time)
  - New lesions by history, clinical features, MRI, evoked potentials
- Inflammatory
  - MRI, CSF
- No other cause
  - Clinical features, MRI, CSF, Blood Studies

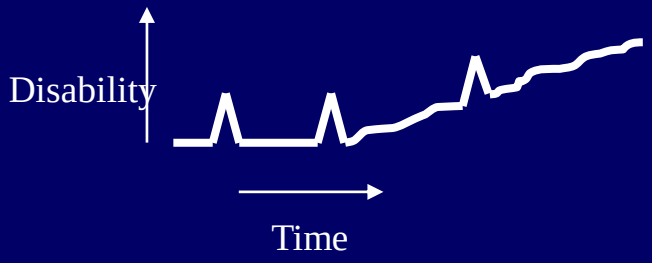
Diagnostic Algorithm



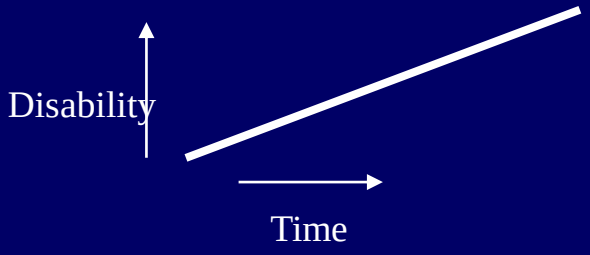
After diagnosis, classify course of MS



Relapsing Remitting



Secondary Progressive
(following Relapsing Remitting)



Primary Progressive

What you should do if your patient has a CIS….

- History and physical examination including detailed neurologic exam
- Labs: TSH, B12, folate, ANA, RF, ESR or CRP, syphilis screen, Lyme titer (if potential exposure history), HIV (in appropriate setting)
- Referral for MRI brain ± cervico-thoracic spine
- Referral to Neurology

Referrals Process I

- Referral to the MS clinic, not a specific physician
- Fax 204-787-3808
- Standardized referral form
  - Sent to family physicians & neurologists in Fall 2008
  - http://www.wrha.mb.ca/prog/medicine/mscare.php
  - Ensures all necessary information provided at the time of referral
  - Incomplete referrals not triaged until necessary data received

Date of Birth: Day Month Year	Main Phone #	Alternative Phone #	Treaty #
Sex: ☐ F ☐ M	Canadian Military #		
Family Physician (If not referring physician) – Please print name, telephone, address and fax number			

Reason for Referral

Major Concern/Symptoms

New Patient

- ☐ Newly diagnosed/At Risk for MS
- ☐ Confirmation of Diagnosis
- ☐ Moved to MB/NW Ontario
- ☐ Other (specify)

Referral for Follow-up

Name MS Physician _____

- ☐ Disease Modifying Treatments
- ☐ Symptom Management (Specify)
- ☐ Query Progression of Disease
  - ☐ Worsening in motor abilities
  - ☐ Worsening symptoms interfering with ADL
  - ☐ Worsening of cognitive function

☐ Consideration for involvement in clinical trials

Required Reports and Diagnostics

*Note: Referrals will not be processed without the following information and diagnostics.

- ☐ *Recent Medical History and Findings
- ☐ *MRI Brain

  Location:
  - ☐ HSC ☐ St.Boniface
  - ☐ Brandon ☐ Boundary Trails
  - ☐ Not done ☐ Other _____
- ☐ MRI Spine

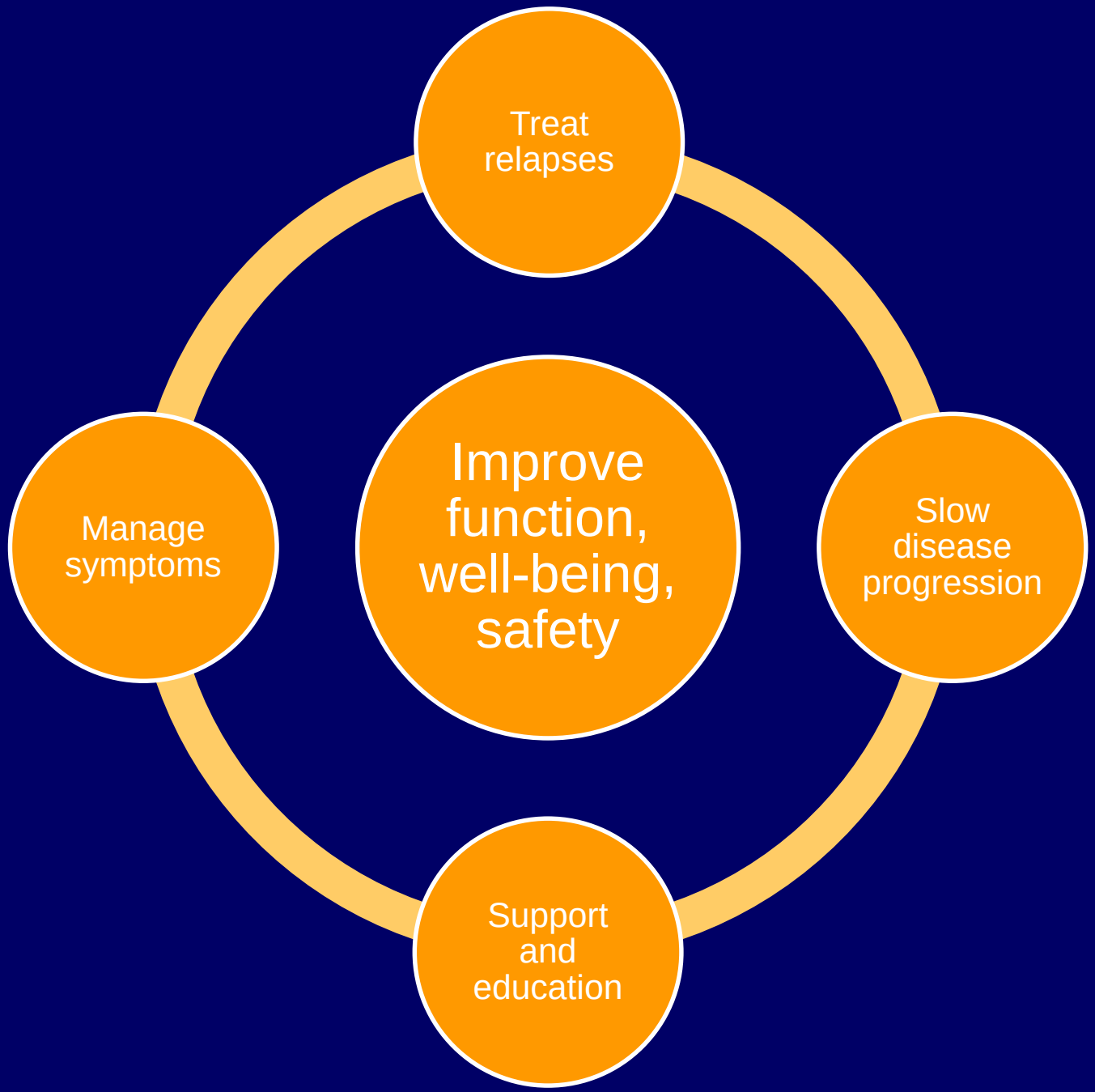
  Location:
  - ☐ HSC ☐ St.Boniface
  - ☐ Brandon ☐ Boundary Trails
  - ☐ Not done ☐ Other _____
- ☐ Evoked Potentials
- ☐ Lumbar Puncture
- ☐ Neurology assessment
- ☐ Ophthalmology assessment

Additional Comments:

Referral Priority

- Highest for:
  - Newly diagnosed
  - CIS/ at risk of MS
  - Patients with known MS & active symptoms
- Lowest for:
  - Patients with known MS & reassessment requested without any specific concerns

Treatment


Treat relapses
Slow disease progression
Support and education
Manage symptoms
Improve function, well-being, safety

Case II

- 28 y.o. female with RRMS
- 3 day history of difficulty walking, numbness both legs, impaired balance
- On examination her strength is 3/5 in the RLE, 4/5 in the LLE, she has a T10 sensory level, hyperreflexia
- Able to walk & care for her children
- Cannot do her job at the factory

Definition of Relapses/ Attacks

- New neurologic symptoms or signs characteristic of MS
- Developing over days- weeks
- Lasting at least 24 hours
- Not associated with fever, intercurrent illness
- Full or partial recovery over weeks- months

Treatment of MS Relapses

- Exclude precipitating factors
  - e.g. infection, esp. urinary tract infection even if no urinary symptoms
  - Presence of infection → pseudorelapses
- If clear that it is a relapse, evaluate functional impact
  - Treat attacks with functional impairment → hastens recovery; does not change long-term outcome
- Treatment options:
  - corticosteroids
  - plasma exchange (in severe cases not responding to steroids)

Using Corticosteroids

- Optimal dose corticosteroids, route, duration?
  - Route
    - Intravenous (e.g. methylprednisolone) best studied
    - Oral produces equivalent effects
  - Doses: range from 500-1000mg/d (lower doses are ineffective)
  - Duration: Usually 3–5 day course (1 day not beneficial)
  - taper not needed to obtain benefits

- Short courses usually well tolerated:
  mood changes may occur, avascular necrosis

- Long term use side effects: hypertension, diabetes, osteoporosis, cataracts, ulcers, weight gain

If your patient presents to you with a relapse…

- If comfortable assessing, then do so
  - Exclude infection, esp. UTI
  - If infection, treat and reassess
  - If no infection and functional impairment, treat
  - If no functional impairment, observe

- Notify neurologist of relapse: will determine
  - If urgent assessment needed
  - If follow-up assessment for symptom mgmt/ rehab needed
  - If institution/ change of DMT needed

Disease-Modifying Therapies

- Decrease relapse rate
- Decrease relapse severity
- Delay accumulation of disability (short-term)
- Partially effective
  - Benefit greater early in disease course
  - Benefit small in SPMS (only if ongoing relapses/MRI activity)
- Continued search for more effective therapies

Disease-modifying therapies

- First line therapies

Injectables

Betaseron (IFN-beta-1b) s.c.

Avonex (IFN-beta-1a) IM

Rebif (IFN-beta-1a) s.c.

Copaxone (glatiramer acetate) s.c.

Plegridy (pegylated IFN-beta) s.c.

Oral agents

Tecfidera (dimethyl fumarate)

Aubagio (teriflunomide)

- Second line therapies

Intravenous

Tysabri (natalizumab)

Lemtrada (alemtuzumab)

*Ocrevus (ocrelizumab)**

Injectable

Zinbryta (daclizumab)

Oral agent

Gilenya (fingolimod)

If your patient is taking a DMT…

- Talk to your patient about importance of adherence
  - If concerns identified, notify treating neurologist
- Be aware of potential interactions of DMT with therapies you prescribe
  - Presently a substantial concern with fingolimod, dimethyl fumarate, teriflunomide*
  - Fingolimod:
    - No other anti-neoplastic, immunosuppressive or immunomodulating therapies
    - Do not use HR-lowering drugs or those that prolong the QTc interval
    - Use CYP3A inhibitors with caution (e.g. ketoconazole, itraconazole, fluconazole, clarithromycin, erythromycin, indinavir, nelfinavir, ritonavir, saquinavir)

If your patient is taking a DMT…

- Dimethyl fumarate:
  - Should not be used simultaneously with other fumaric acid derivatives
  - Use with caution in patients receiving chronic treatment with medications assoc. with potential nephrotroxic risk (e.g. aminoglycosides, diuretics, NSAIDs, lithium)
  - Avoid live attenuated vaccines
- Teriflunomide
  - Warfarin (↑INR), Diuretics, *Drugs metabolized by:* CYP2C8 (e.g. repaglinide, pioglitazone, rosiglitazone, nateglinide ↑ conc)
  - OCPs (↑ conc)
  - Some Abx (cefaclor, penicillin G, cipro, rifampin, AZT ↑ conc)
  - BCRP/OATP (statins, methotrexate, mitoxantrone, tootecan, daunorubicin, doxorubicin)
  - CYP1A2 (duloxetine, theophylline, tizanidine ↓ conc)

If your patient is taking a DMT…

- We will do safety monitoring unless we explicitly state otherwise
- You will be copied on labs, imaging reports
- We tend not to investigate for known adverse effects (such as mild leukopenia) but will ask you to follow-up for unexpected findings we do not think are DMT-related
- If uncertain whether you should be addressing a lab abnormality please ask

Common Symptoms of MS: Usually Noted by Health Care Providers

- Vision – loss of vision, diplopia, oscillopsia
- Motor – weakness, spasticity, ataxia, tremor
- Sensation – sensory loss, positive sensory phenomena
- Vestibular – vertigo, imbalance
- Gait impairment – weakness, spasticity, ataxia, imbalance, sensory loss, fatigue

Common Symptoms of MS:
Underappreciated by Health Care Providers

- Cognition – concentration, memory, executive, slowed thinking
- Mood - depression, anxiety, emotional lability
- Bladder – urgency, frequency, hesitancy, retention, incontinence
- Bowel – constipation, urgency, incontinence
- Sexual – decreased libido, erectile dysfunction
- Fatigue
- Pain

Symptom Management in MS

- Actively seek symptoms → Some are “invisible”
- Keep things simple
  - Look for contributing factors to eliminate (e.g. sleep disturbance due to poor sleep hygiene)
  - Lifestyle modification (e.g., diet, energy mgmt, work accommodations)
- Prioritize
  - Monotherapy → Start low & go slow
  - Use one medicine to address >1 symptom
- Rehabilitation
- Specialty consultation when needed
- Goal: Improve function, quality of life

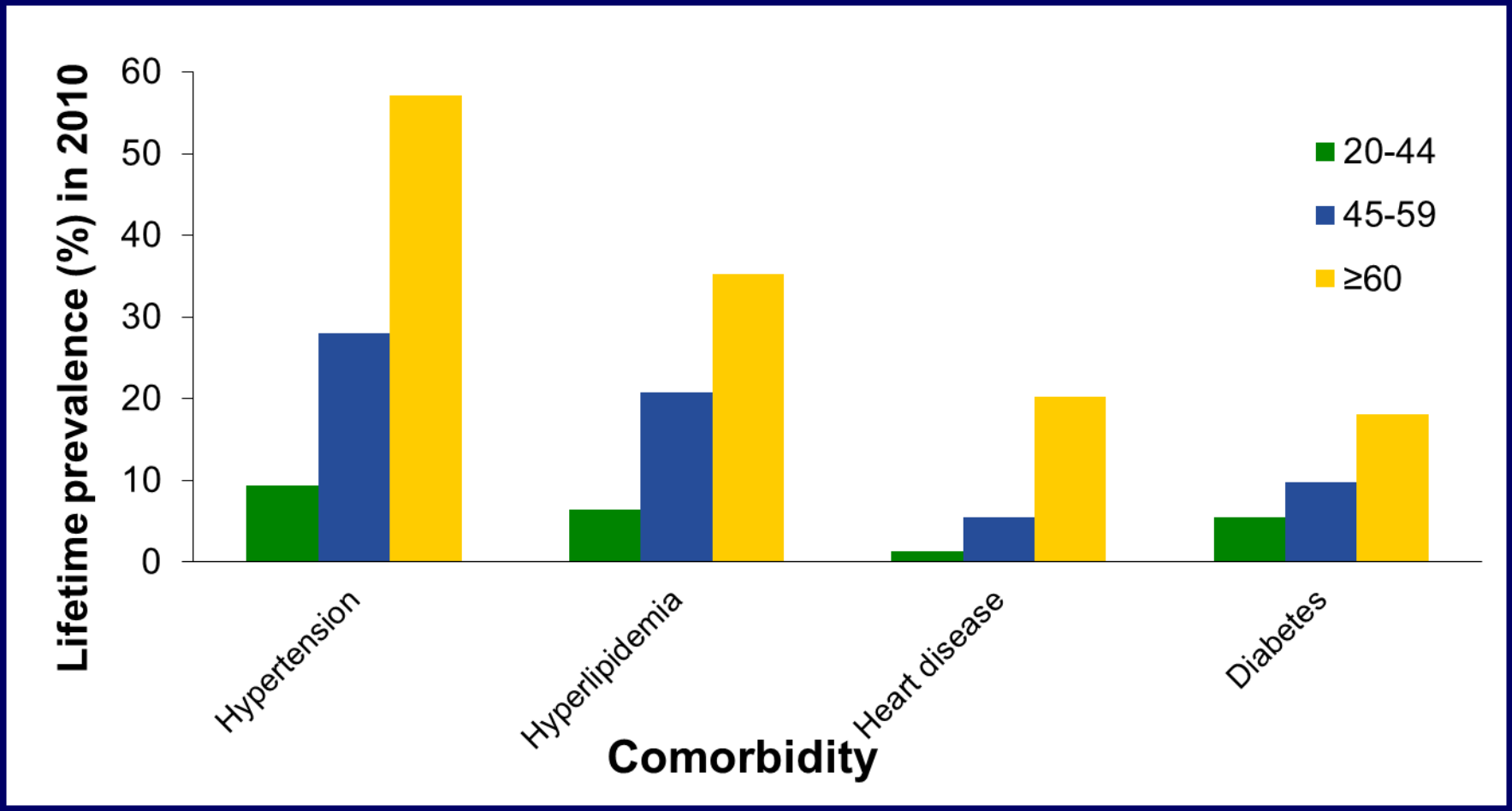
General Care

- Diagnosing and managing comorbidity

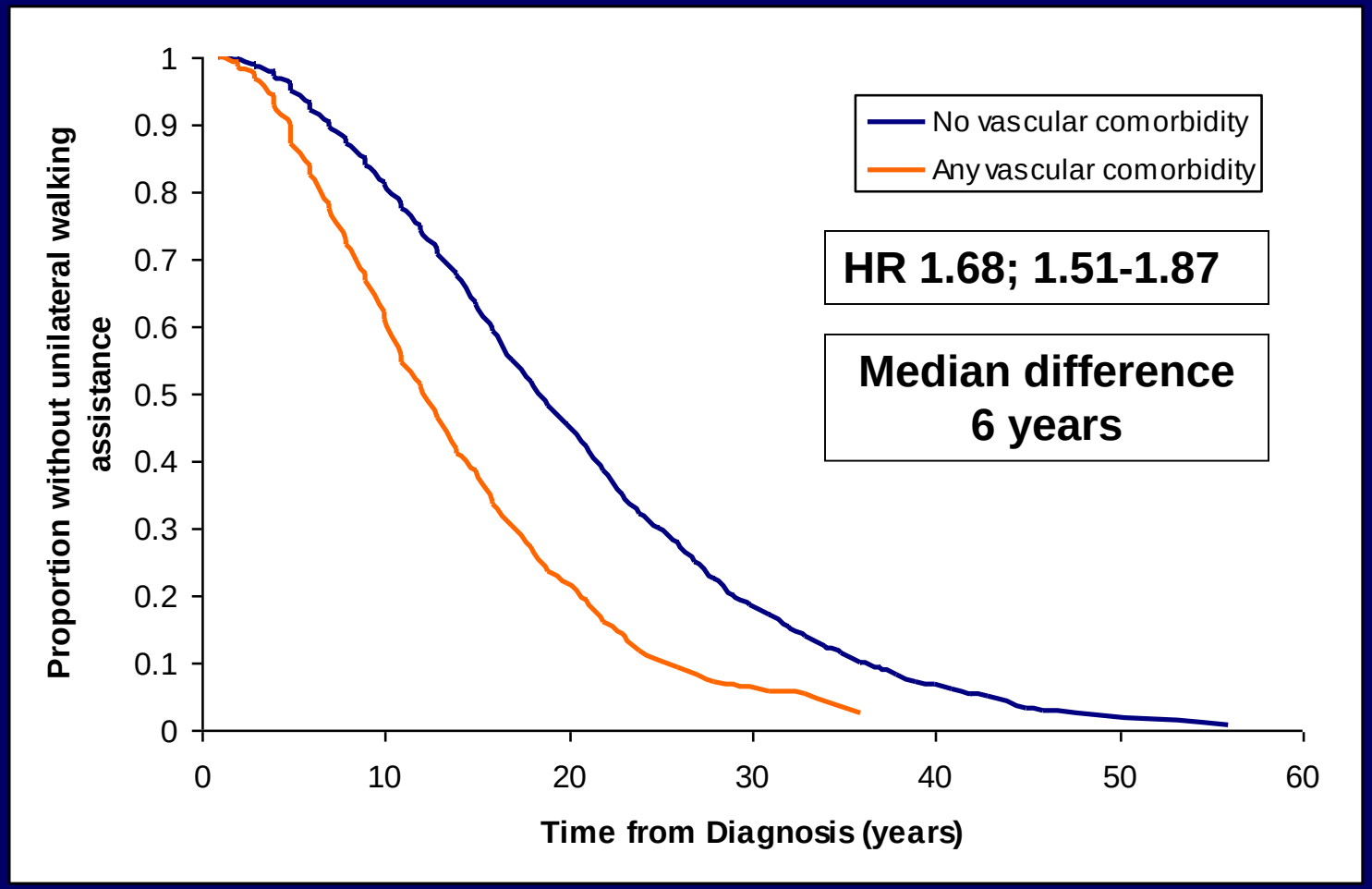
- Health promotion & prevention
  - Health behaviours, flu shots
  - General recommendations re cancer screening: mammograms, pap smears (refer to Women's Hospital if office not equipped for disabled patients)
  - Osteoporosis

- Pay attention to the caregiver: ?respite

Vascular comorbidity increases with age



Vascular Comorbidity at Diagnosis & Progression to Using a Cane



Neurology 2010;74:1041–1047

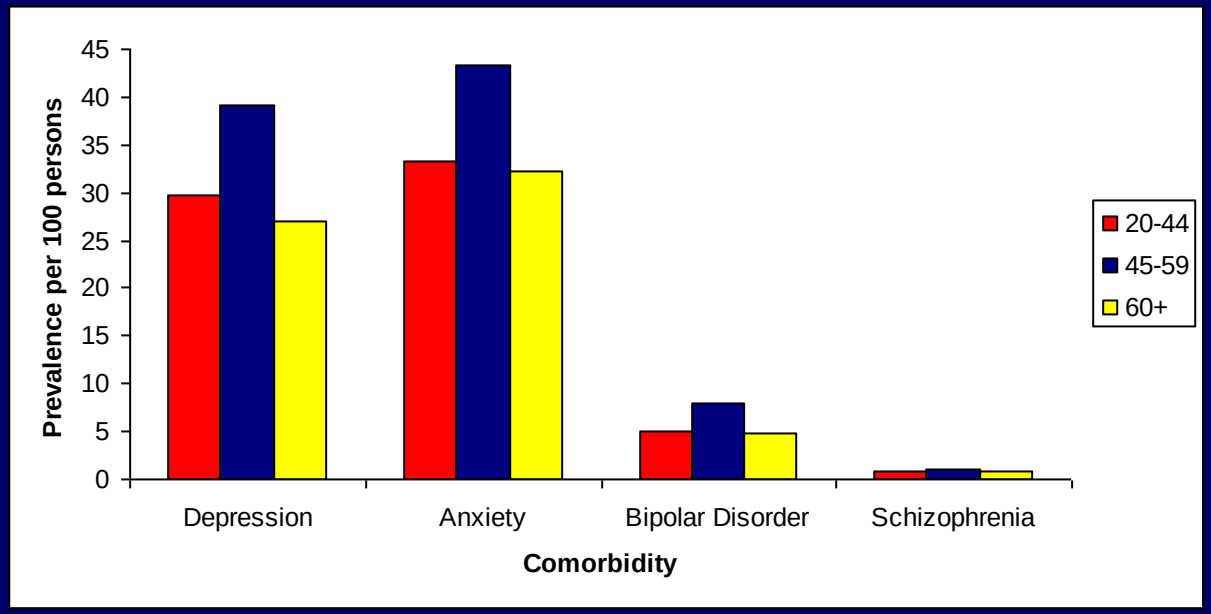
Vascular Comorbidity & Disease Progression II

- Hyperlipidemia assoc. with
  - higher relapse rate
  - Increased development of lesions on MRI

- Vascular comorbidities assoc. with
  - Increased rates of hospitalization
  - Increased mortality

Psychiatric Comorbidity

- Psychiatric comorbidity is common
- Associated with pain, fatigue, lower quality of life, reduced adherence to therapy, ↑ disability progression
- Monitor mood and treat as appropriate
- If followed in MS Clinic, social work can assist with counselling & CBT



What health behaviours you can encourage…

- Quit smoking!
  - Smokers with CIS 1.8X more likely to be diagnosed with MS than non-smokers with CIS
  - Smoking accelerates disability progression (3X more likely to develop progressive disease) & associated with more brain atrophy

- Healthy diet and weight
  - Obesity associated with chronic inflammation, lower vitamin D levels

What health behaviors you can encourage….

- Regular exercise

- Aerobic
  - Reduces fatigue
  - Provides cardiovascular conditioning
  - Assists with stress management
  - Improves quality of life
  - May enhance cognition*

- Strength training
  - Two times per week

Summary

- Diagnosis
  - History, examination, labs, imaging, neurology referral
- Relapse management
  - Exclude infection, consider steroids, update neurologists
- Preventive care & general health care
  - Comorbidity management particularly important

Resources

- For your patients:
  https://mssociety.ca/support-services

- For you
  - http://www.mscare.org/
    - Clinical practice guidelines, publications, podcasts
  - https://www.nationalmssociety.org/For-Professionals/Clinical-Care/Resources-for-You-and-Your-Practice
    - Links to MS clinical management, a diagnosis and management app for smartphone, articles on symptom management

References

- Thompson AJ et al. Diagnosis of multiple sclerosis: Recommended 2017 Revisions of the “McDonald” Criteria. Lancet Neurology *2017; Dec 21 Epub ahead of print.*
- Marrie RA. Comorbidity in multiple sclerosis: Implications for patient care. Nature Reviews Neurology 2017;13(6):1093-1100. doi:10.1038/nrneurol.2017.33
- Miller D, Weinshenker B, Filippi M, Banwell B, Cohen J, Freedman M, et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. Mult Scler. 2008 November 1, 2008;14(9):1157-74
- Lublin FD et al. Defining the clinical course of multiple sclerosis. The 2013 revisions. Neurology 2014;83:1-9
- Le Page E, Veillard D, Laplaud DA, Hamonic S, Wardi R, Lebrun C, et al. Oral versus intravenous high-dose methylprednisolone for treatment of relapses in patients with multiple sclerosis (COPOUSEP): a randomised, controlled, double-blind, non-inferiority trial. The Lancet. 2015;386(9997):974-81

Questions?