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Multiple Sclerosis Treatment

OU Health | College of Medicine
The UNIVERSITY of OKLAHOMA

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Conflict of interest

Sanofi: speaker engagement, not relevant to this talk

Learning Objectives

Upon completion of this session, participants will improve their competence and performance by being able to:

- Identify common clinical presentations of multiple sclerosis (MS), sensory disturbances, and brainstem syndromes in adults age 20–50 years.
- Describe 4 most common disease modifying treatments for MS (Glatiramer Acetate, Fumarates, monoclonal antibodies, anti–CD20 B–cell depletion monoclonal antibodies) and recognize key monitoring requirements and adverse effects.
- identify the essential components of comprehensive MS care requiring multidisciplinary collaboration and the roles of various specialists in optimizing patient outcomes.

Pre knowledge survey

A 55-year-old female with known diagnosis for MS presents for follow up with you. She has worsening difficulty of walking, frequent falls and worsening spasticity for 2weeks. She also has worsening urinary frequency and urgency without dysuria. She is taking baclofen 10 mg TID and recently ran out of dimethyl fumarate.

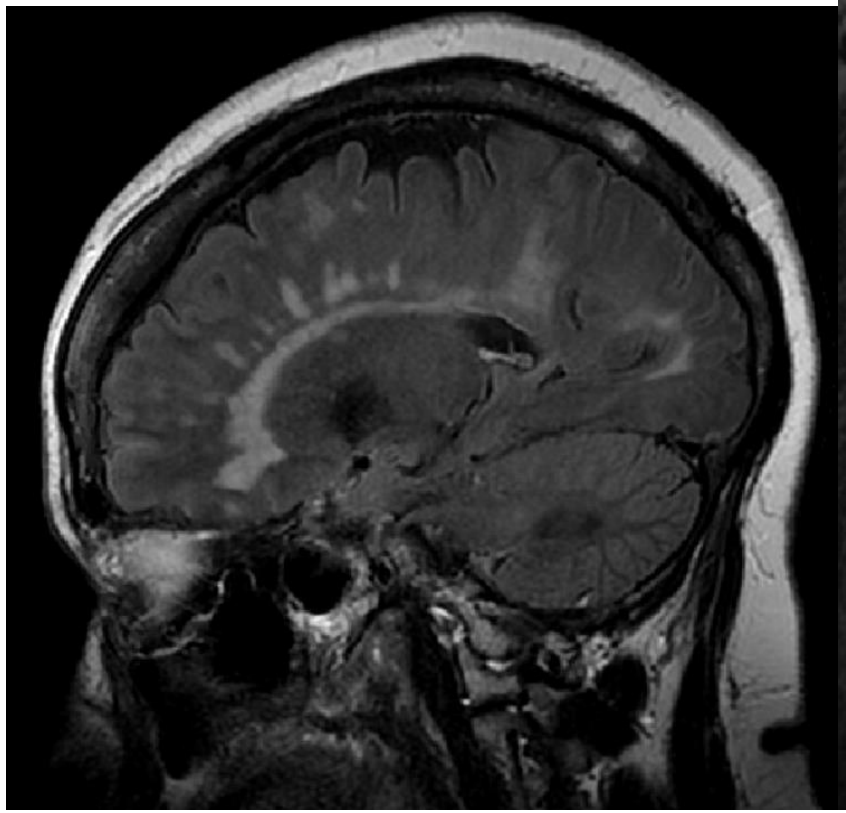
What is most appropriate next step?

A. Advise patient to call Neurologist
B. Check UA
C. Increase the dose of baclofen and restart dimethyl fumarate
D. Obtain MRI of brain and spinal cord
E. Prescribe Medrol dose pack

Patient

- A 56 year-old female with known diagnosis of hypertension presents to primary care's office
- 02/2018: numbness and tingling in both hands
- 03/2018: EMG and NCS study showed bilateral carpal tunnel syndrome
- 09/2018: Saw orthopedic, no improvement with splint and steroid injection in carpal tunnel, also reports some gait imbalance.
- 01/2019: MRI of Cervical spine
- 02/2019: referred to Neurologist

- 1999: Transient double vision in setting of stress and lack of sleep
- 2007: Tingling in all finger tips, constant without progression
- 2016: Stiffness in both hands, Rt leg heaviness on walking for a long time causing gait imbalance and urinary urgency
- MRI of Brain and thoracic spine.



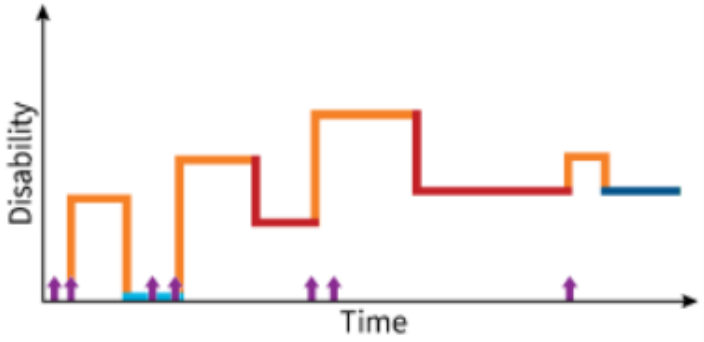
Why is it important for you to learn about MS

- MS is an Immune mediated chronic disease of central nervous system which causes **multiple attacks on CNS separated by time and space.**
- It is a common cause of non traumatic disability.
- Prevalence of MS in US as of 2010 is the highest ever reported, with 727,344 reported cases. (1)
- Non neurology provider (usually primary care provider) is often the first care provider that MS patients presents to.
- Early diagnosis is important as early initiation of treatment may prevent disability (2).
- Mean age of presentation 40s, more common in females

1)Mitchell T. Wallin et al, Neurology, March05,2019
2)Joao J Cerqueira et al, Journal of Neurology, Neurosurgery & Psychiatry, Volume 89, issue 8

Phenotypes of MS

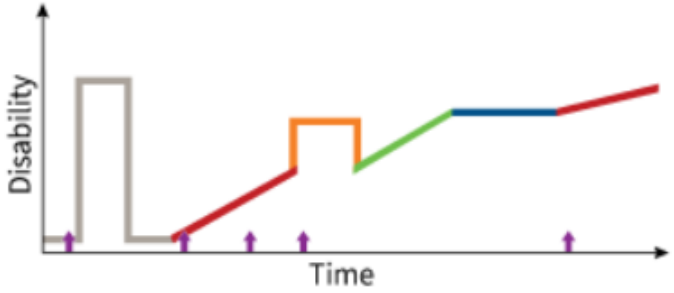
RRMS



- Relapse
- Active without worsening
- Worsening (incomplete recovery from relapse)
- Stable without activity
- New MRI activity

Source: Lublin et al., 2014.

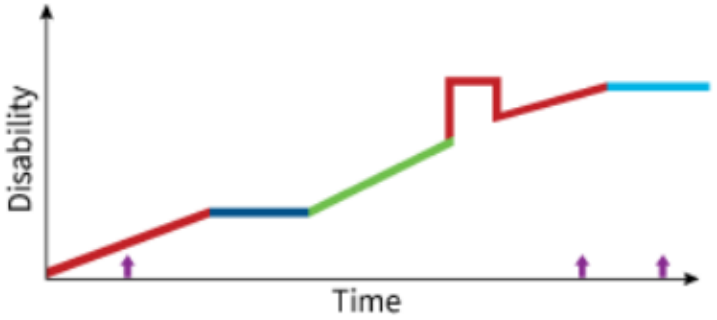
SPMS



- RRMS
- Active (relapse or new MRI activity) with progression
- Active (relapse or MRI activity) without progression
- Not active with progression
- Not active without progression (stable)
- New MRI activity

Source: Lublin et al., 2014.

PPMS



- Active (relapse or new MRI activity) with progression
- Not active without progression (stable)
- Not active with progression
- Active without progression
- New MRI activity

Source: Lublin et al., 2014.

Symptoms

Relapse	New Symptom that last for >24 hours constant in absence of fever.	Treat with high dose steroid.
Pseudo relapse/Pseudo exacerbation	Worsening of old symptoms in setting of fever, stress, dehydration or heat.	Does not need steroid. Treat underlying cause.

1) Cerebral hemisphere :

- Weakness or numbness on one side or the other
- Memory loss and confusion– Rare presentation of a relapse
- Difficulty finding words, difficulty multitasking and processing

2) Optic Nerve :

- Vision loss with pain on moving eye and with altered color vision
- Good recovery of vision with or without steroids

Symptoms

3) Spinal cord :

- Lhermitte's sign: shock like sensation from neck to all 4 extremity on neck flexion
- Numbness: all 4 extremity (cervical cord), lower extremity (thoracic cord), travelling up starting from feet
- Weakness: one side or the other, foot drop, weakness of hands
- Gait imbalance
- Bowel and Bladder changes: Urinary urgency (most common), frequency, constipation and bowel urgency. Recurrent Urinary Tract Infections.
- Sexual dysfunction
- Spasticity

Symptoms

4) Cerebellum or brainstem :

- Ataxia, double vision or vertigo

5) Other symptoms :

- Pain syndrome : Trigeminal neuralgia, paroxysmal tonic spasms and dysesthetic limb pain
- Anxiety, depression, insomnia (secondary)
- Fatigue :
  - Fluctuates with heat, exercise or as day proceeds.
  - Relived by a period of rest, often a nap.
  - Different from depression associated lack of energy, with other depression features.
  - Often herald the diagnosis of MS by years.

Work up

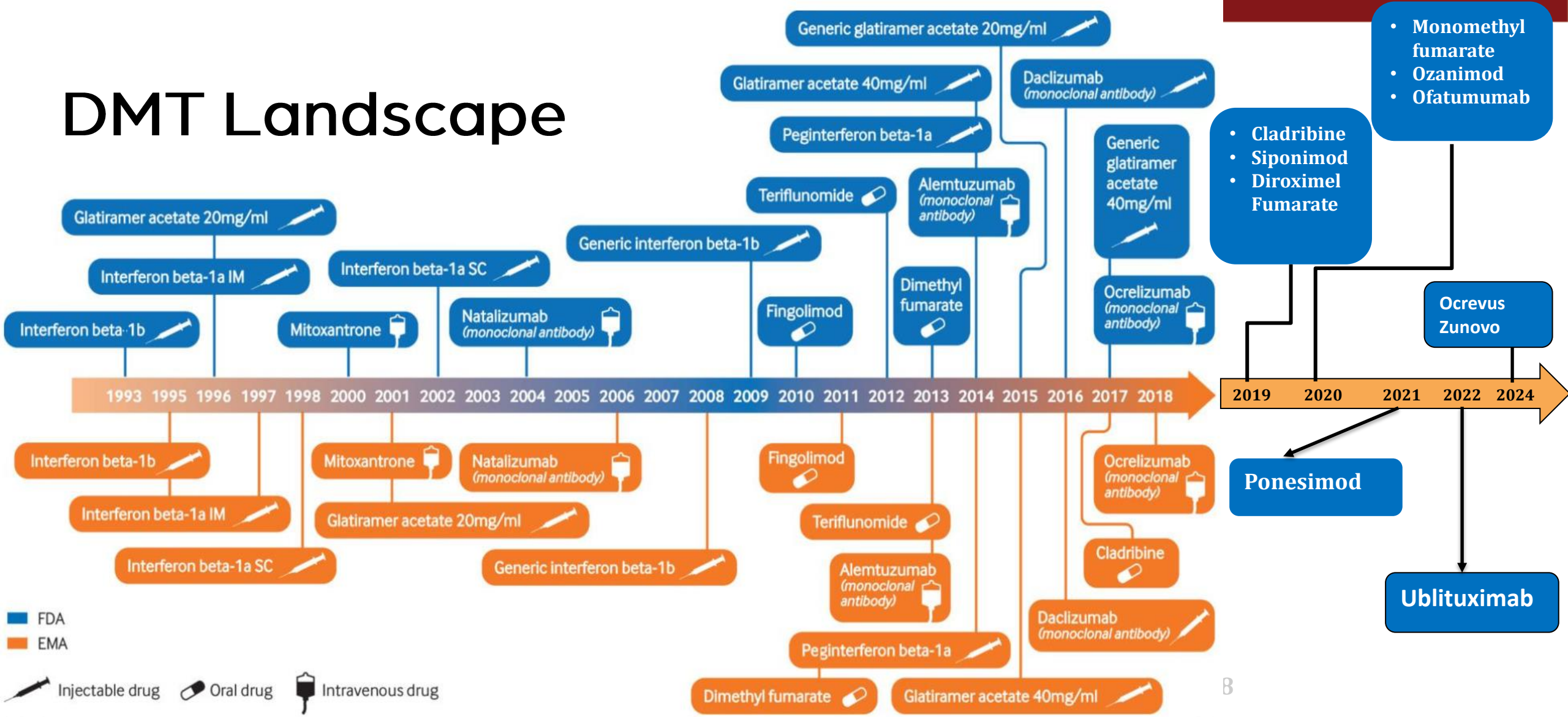
- History and examination
- MRI of brain, cervical and thoracic spine with and without contrast
- MRI orbit with and without contrast if vision issues
- Blood work
- Spinal fluid testing

Treatment approach for MS patient

- Individualized to each patient
- Patient centered with active engagement of patient in decision making ie shared decision making.
- Target Neuroinflammation with Disease Modifying Therapies (DMT)
- Target Neurodegeneration
- Target and treat symptoms
- Address lifestyle modification, management of other medical comorbidities and risk factors for example vitamin D deficiency, stress and smoking.

DMTS

DMT Landscape



Floriana De Angelis et al. BMJ 2018

Injectable	Oral	IV infusion
Interferon beta 1a and 1b (Avonex, Rebif, Betaseron, Plegridy and Extevia)	Teriflunomide (Aubagio)	Natalizumab (Tysabri) Natalizumab (Tyruko)
Glatiramer acetate (Copaxone, Glatiramer Acetate, Glatopa)	Fumarates: Dimethyl fumarate (Tecfidera) Diroximel fumarate (Vumerity) Monomethyl fumarate (Bafiertam)	Ocrelizumab (Ocrevus) Ublituximab (Briumvi)
Ofatumumab (Kesimpta)	Sphingosin-1 Phosphate (S1P) modulators: Fingolimod (Gilenya) Fingolimod (Tascenso) Siponimod (Mayzent) Ozanimod (Zeposia) Ponesimod (Ponvory)	Alemtuzumab (Lemtrada)
Ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo)	Cladribine (Mavenclad)	Mitoxantrone (Novantrone)

Glatiramer acetate

- **Formulations:** Copaxone, Gatiramer Acetate (generic) and Glatopa (generic)
- **Dose :** 20 mg SC daily or 40 mg SC three times a week

- **Mechanism of action: T cell immunomodulation**

- **Side effects: Local injection site reaction**, transient post injection systemic reaction (chest pain, flushing, dyspnea, palpitation and anxiety), lipoatrophy at injection site

- **Monitoring**: none

- **Indication**: CIS (Clinically isolated syndrome/early MS), RRMS (relapsing remitting MS), Active SPMS (secondary progressive MS)

Fumarates

- Dimethyl Fumarate (Tecfidera) 240 mg BID
- Diroximel Fumarate (Vumerity) 462 mg BID
- Monomethyl Fumarate (Bafiertam) 190 mg BID

- **Side effects: Gastrointestinal symptoms** (better if taken with food), flushing, **lymphocytopenia**, elevation in LFTs, rash, hypersensitivity, rarely PML (Progressive Multifocal Leukoencephalopathy, a rare and fatal brain infection caused by JC virus)

- **Monitoring:** CBC, LFT

- **Indication:** CIS, RRMS, Active SPMS

Monoclonal antibody

- Natalizumab (Tysabri)
- B cell therapy:

1) Ocrelizumab (Ocrevus), Every 6 month infusion
2) Ofatumumab (Kesimpta) Every month SC injection
3) Ublituximab (Briumvi) Every 24 weeks infusion
4) Ocrelizumab Zunovo Every 6 month SC infusion

Monoclonal antibody: Natalizumab

- **Dose:** 300 mg IV Q4 weeks
- **Mechanism of action:** Monoclonal antibody to Alpha-4 integrin receptor. Decreases activated T cell migration through blood brain barrier
- **Side effects**: Headache, fatigue, arthralgia, UTI, respiratory tract infection, hypersensitivity, elevated LFTs, **high risk of PML. Rebound MS after stopping infusion.**
- **Monitoring**: LFT and JCV antibody with index every 3-6 M. MRI brain 6-12 months.
- **Indication:** CIS, RRMS, Active SPMS

Monoclonal Antibody: B cell therapy

- **Mechanism of action**: Monoclonal antibody to CD-20 present on B cells, leading to rapid depletion of B cells

- **Side effects**: **Infusion reactions**, respiratory tract infection, herpes infection, risk of malignancy (**breast cancer**), PML (low), reactivation of hepatitis B. Fetal risk. Rarely colitis and elevation in liver enzyme.

- **Monitoring**: Quantiferon, hepatitis B and C, HIV, VZV IgG before starting. Lymphocyte subset, CBC, immunoglobulin and yearly mammogram

- **Indication**: CIS, RRMS, Active SPMS, **Primary Progressive MS (PPMS, only for Ocrevus)**

1. Symptomatic therapies
2. Lifestyle modifications
3. Management of other Medical Comorbidities

Symptomatic treatment

1) Walking and balance: Dalfampridine (Ampyra), Physical therapy
2) Spasticity: Stretching exercises, baclofen, tizanidine, Flexeril, valium and medical marijuana (1)
3) Pain: Gabapentin, Lyrica, amitriptyline, duloxetine, carbamazepine (for trigeminal neuralgia and Lhermitte's phenomenon) and medical marijuana(1)
4) Bowel and bladder dysfunction: Stool softeners, Urology evaluation, Ditropan, Flomax, bladder training
5) Depression: SSRIs and other antidepressants, counselling
6) Fatigue: Exercise, high protein diet, good quality sleep, energy conservation technique, amantadine, Provigil and nuvigil
7) Cognitive: Neuropsychology, OT evaluation
8) Social and financial support: cost of medications, handicap equipment, MRIs

1) BarbaraS. Koppel et al. Neurology April 29, 2014

Lifestyle modification

- Healthy Diet
- Avoid smoking
- Take vitamin D supplementation
- Hydration
- Exercise: improves fatigue
- Sleep: often contributes to fatigue
- Cooling west, cooling cap, cooling neck collars; helps with pseudo exacerbation due to heat
- Energy conservation techniques: taking frequent breaks

Management of Comorbidities

- Coexisting medical comorbidities significantly delays the diagnosis of multiple sclerosis(1)
- Physical and mental comorbidities are associated with increased morbidity at the time of diagnosis (2).
- Vascular comorbidities are associated with rapid progression of disease(3).
- Depression, diabetes and ischemic heart disease shown to increase mortality rate in MS patients(4).

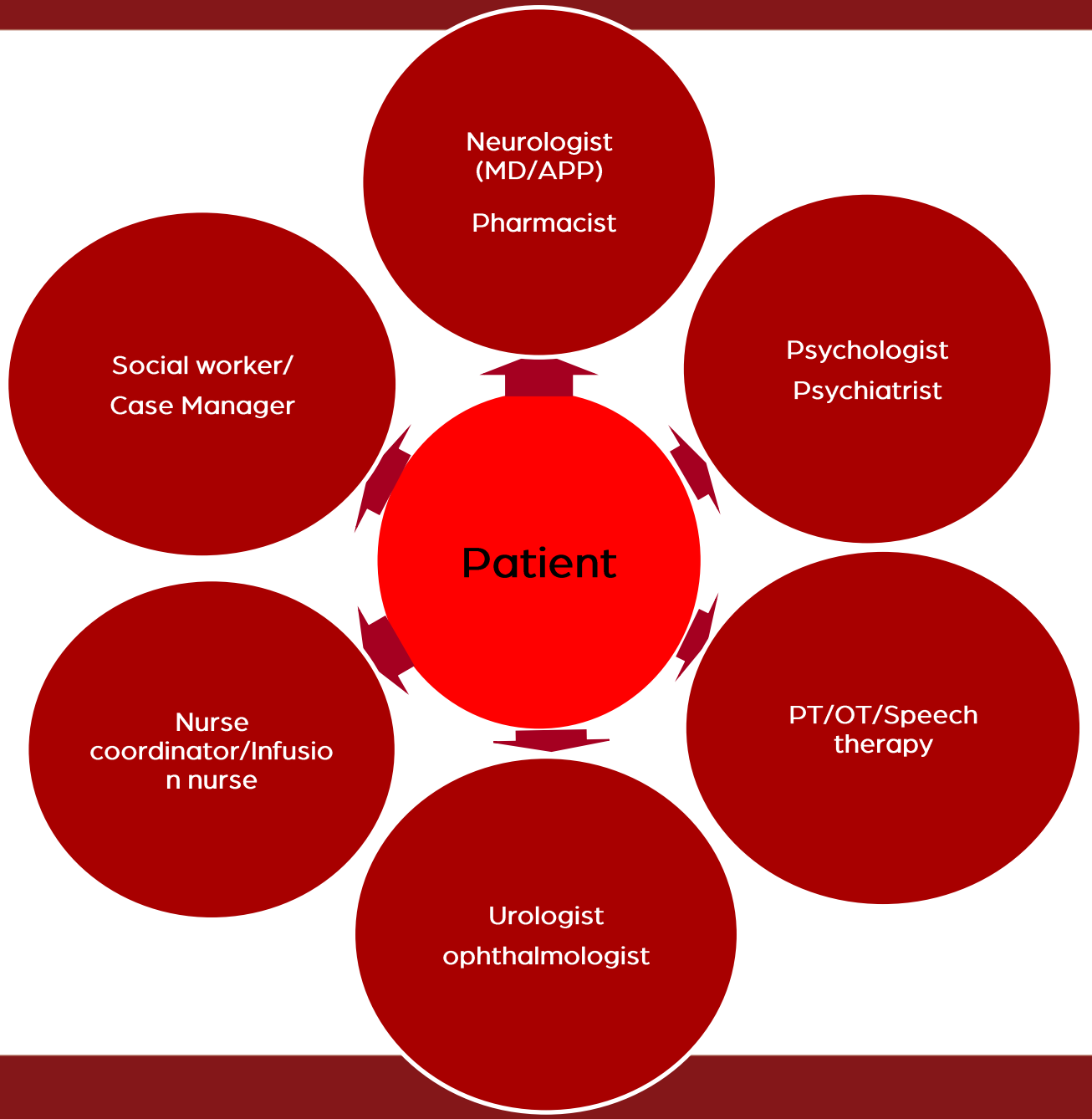
1) Anja Thormann et al, Neurology Oct17,2017. 2) R. A.Marrie et al Neurology Jan 13, 2009
3) R.A. Marrie et al. Neurology March 30, 2010. 4) R.A. Marrie et al. Neurology July 21,2015

Multidisciplinary approach to treatment

Approach to treatment beyond medication

- Physical therapy
- Occupational therapy
- Speech therapy
- Case manager and Social worker
- Lifestyle modifications like Yoga, mindfulness, meditation, healthy diet
- Cognitive behavioral therapy and counseling

Our model of MS treatment: Multidisciplinary model



Neurology IPE (Interprofessional Education) clinic

- OU health Neurology clinic houses one and only IPE clinic in OU Health Physician's clinic.
- We bring students from various schools across OUHSC campus including MD, nursing, social worker and pharmacy school.
- Students evaluates the patient as a team.
- This setting has helped our patients and learner.

Student evaluation (n=16)	
I prefer IPE over individual education	4.44
IPE is valuable part of my education	4.81
Because of IPE clinic I am more likely to engage in interdisciplinary practice after graduation	4.75
I believe that IPE clinic improve healthcare outcome for patients.	4.88

Patient evaluation (n=7)	
I understood the benefit of having interdisciplinary care team.	5.00
I believe that interdisciplinary team can improve my healthcare outcome.	4.86
I would chose an appointment that involves IPE team in future.	4.86

Back to our patient

- She was diagnosed with MS
- Started on disease modifying therapy: teriflunomide
- Started on symptomatic therapy: baclofen
- 2 years after being on teriflunomide she had cellulitis of leg leading to septic shock so immunosuppressive therapy was discontinued.
- Started on glatimer acitate
- Clinically stable.

Post knowledge survey

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Take home message

1) High index of suspicion in young female with personal or family history of autoimmune disease, presenting with multiple neurological symptoms at different times.
2) History and examination is utmost important for diagnosis of MS.
3) Early diagnosis and treatment is important to prevent disability.
4) Keep in mind, symptoms fluctuate with weather, stress, fever and infection. Check urine if MS symptoms are worse.
5) Disease modifying therapies increases risk of infection.
6) Educate patients about lifestyle modifications and management of other comorbidities.
7) MS treatment should be individualized and patient centered. Multidisciplinary team approach is the best way to treat MS patients.
8) Do not hesitate to get opinion from your Neurology colleagues

QUESTIONS?