



Virginia Mason™

Hot Topics in Neurology

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Hot Topics in Neurology

Migraine

- New Acute Treatments
- New Preventative Treatment options
- Review of migraine action plans

Multiple Sclerosis

- Updates in differential diagnosis, workup and referral recommendations
- New therapies for Relapsing and Progressive MS
- MS Relapse, what is it, and how to treat

Fibromyalgia

- Updates in diagnosis and differential
- Associated neurologic conditions
- Referrals, workup and management

Migraine Updates

Migraine Headache

Prevalence

- about 15% of the population has migraines (Women > Men)
- 2nd most common headache type

Impact

- Headache - 4th or 5th most common reason for ED visits (~3% of all)¹
- 7th leading cause of disability globally, leading neurological cause²

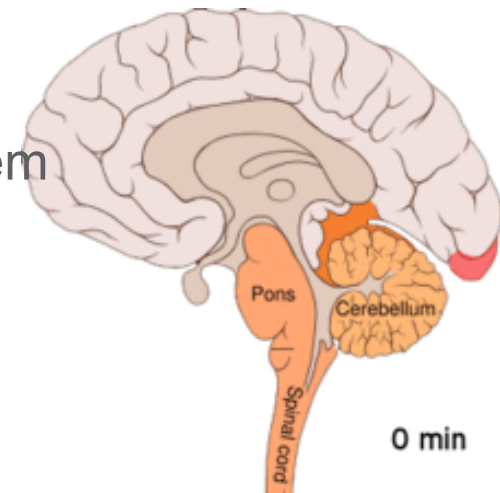


1) Birch et al. Headache 2018; 2) 2015 Global Burden of Disease Study

Migraine Headache - Prevention

When to consider preventative treatment? (MORE OFTEN)

- Significantly interfere with a patient's quality of life
- Frequent headaches (>4 attacks / month or >8 days per month)
- Failure of acute medications
- Presence of certain migraine conditions:
 - hemiplegic migraine; basilar migraine (now called migraine with brainstem aura); frequent, prolonged, or uncomfortable aura symptoms; or migrainous infarction



Migraine Prevention - Medication Treatments

Tricyclics: Amitriptyline, Nortriptyline, Desipramine

Beta-Blockers: Propranolol*, Timolol*, Metoprolol, Atenolol

Anti-Epileptics: Topiramate*, Divalproex*, Gabapentin, CBZ

SNRIs: Duloxetine, Venlafaxine

CGRPs: Erenumab (Aimovig)*, Fremanezumab (Ajovy)*,
Glacanezumab (Emgality)*, Eptinezumab (Veypti)*
Rimegepant (Nurtec)*, Atogepant (Qulipta)*

ACE / ARBs / alpha-Agonists / CCBs / Botox for chronic migraine*

CGRP Inhibitors - New Treatments for Migraine

CGRP Inhibitors – now 6 FDA approved for migraine prevention and 2 for acute migraine treatment

Treatment for both Episodic and Chronic Migraine

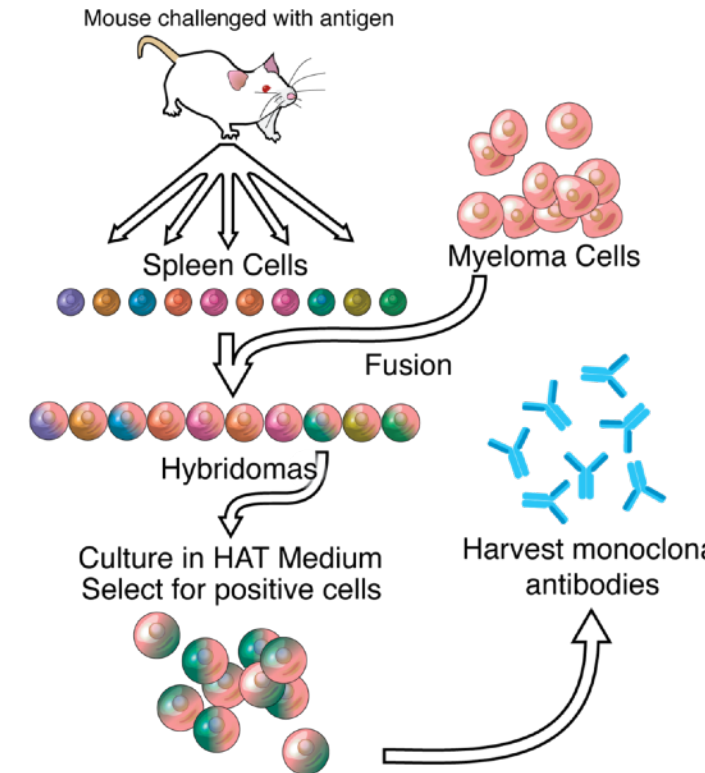
Why Use Monoclonal CGRP Inhibitors?

Pros:

- Infrequent dosing due to long half-life
- Highly selective targeting
- Low side effect profile
- No drug-drug interactions

Cons:

- Injectable, not orally bioavailable
- Expensive
- Long term effects / risks not well established

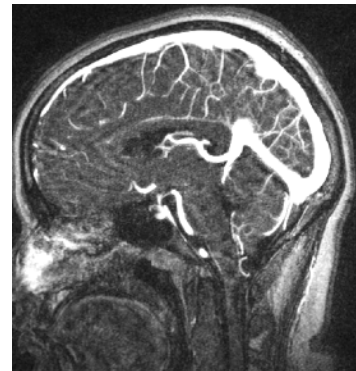


How do they work?

CGRP Inhibitors - New Treatments for Migraine

CGRP is a widely distributed vasodilatory neuropeptide that is involved in migraine pathophysiology and pain processing

- Giving IV CGRP causes a Migraine in many migraineurs
- Elevated CGRP serum levels in chronic and acute migraine
- Serum CGRP rise during migraine attacks (jugular vein collection)
- Triptan treatment lowers CGRP serum levels in parallel with symptoms



CGRP Monoclonal Ab Inhibitors – Migraine Prevention

Now 4 different FDA approved forms (since 5/2018)

CGRP Inhibitor

Erenumab (Aimovig)

Fremanezumab (Ajovy)

Giacanezumab (Emgality)

Eptinezumab (Veypti)

Dosing:

70mg or 140mg q1 month SC

225mg SC q1 month or 675mg q3 month

240mg loading, then 120mg SC Q1 month

100mg to 300mg q3 months IV (approved 2/2020)



All with 2 large phase 3 trials each

Both studied in chronic (>15 days) and episodic (< 15 days / month)

What is the evidence?

CGRP Inhibitors - New Treatments for Migraine

	Chronic Migraine	Episodic Migraine
	Reduced >50%	Reduced >50%
Erenumab (Aimovig) SC	41% ¹	50% ²
Fremanezumab (Ajovy) SC	41% ³	48% ⁴
Galcanezumab (Emgality) SC	28% ⁵	62% ⁶
Eptinezumab (Veypti) IV	57-61% ⁷	50-56% ⁷
Atogepant (Qulipta) (PO small molecule)		56-61% ⁸
Rimegepant (Nurtec) (PO small molecule)		49% ⁹
Botox	44 – 51% ¹⁰	
Placebo (from above trials)	15 – 39 %	27 – 41%

¹STRIVE Study; ²Tepper et al. Lancet Neurol, 2017; ³Dodick et al. JAMA 2018; ⁴Silberstein et al. NEJM, 2017; ⁵Evolve 1+2 trials; ⁶REGAIN Trial; ⁷PROMIS-1+2, ⁸ADVANCE, ⁹Croop et al. Lancet Neuro 2021, ¹⁰PREEMPT 1+2 Trials

Atogepant (Qulipta) - New Oral CGRP inhibitor for episodic migraine approved in 2021

- Phase 3 trial vs. placebo for episodic migraine prevention (NEJM 2021)¹
- Study:
 - 910 pts, episodic migraine (<15 days/month), Placebo vs. dose Atogepant (10, 30, 60mg) x 12 weeks. ITT analysis.
- Results:
 - 56-61% vs. 29% patients with 50% reduction in headache days with Atogepant vs. placebo ($p < 0.0001$ in all dose groups vs. placebo)
- Side effects vs. placebo:
 - **constipation** (6.9-7.7% vs 0.5%), **nausea** (4.4-6.1% vs 1.8%), and **upper respiratory tract infection** (3.9-5.7% vs 4.5%). No hepatic safety issues. (*more constipation / nausea than injectable CGRP's*)

¹ Alini et al. ADVANCE Trial - NEJM 8/2021

²Goadsby et al. Lancet Neurology, 9/2020

CGRP Inhibitors - New Treatments for Migraine

Who to try CGRP Inhibitors?

Cost / Coverage?

Limitations of Clinical Trials?

- Medication overuse headache
- Multiple concurrent preventatives
- Botulinum toxin
- Cardiovascular risk factors

Long term risks uncertain

Migraine Action Plan – Acute Therapies

Under prescribed / Utilized

Combination therapies

New options

Migraine – New Acute Therapies

- **Lasmiditan (Reyvow)**
 - Approved 10/2019
 - selective serotonin agonist – lacks vasoconstrictor activity
 - **17%** difference compared with placebo – headache free at 2 hours
 - **Frequent side effects** – dizziness, somnolence (no driving 8 hours); high cost ~\$96/pill
- **Ubrogepant (Ubrelvy)**
 - Approved 12/2019
 - Oral tablet CGRP antagonist small molecule
 - 9.4% difference compared with placebo – headache free at 2 hours
 - Low side effects – nausea, somnolence, dry mouth; high cost ~\$102 / pill; **drug-drug interactions**
- **Rimegepant (Nurtec)**
 - Approved 2/2020, **also approved as preventative** in 2021 (QOD)
 - **Oral dissolvable** CGRP antagonist small molecule
 - 7.6% difference compared with placebo – headache free at 2 hours
 - Low side effects; high cost ~\$127 / pill;

Migraine management

- Diagnose correctly and quickly
- Utilize Acute Treatments - action plan
 - Triptans are first line rx for most people who fail OTC combination therapies,
 - Can combine with NSAID with better response (e.g. Sumatriptan + Naproxen)
- Preventative treatments
 - Rx more frequently (>4 headaches per month is reasonable to consider)
 - Treat more than one condition if possible (e.g. anxiety, insomnia, depression)
 - FDA approval does not necessarily mean better efficacy
 - BBlockers, TCA's, SNRIs, Anti-epileptics, CGRPs...

Multiple Sclerosis Updates

Multiple Sclerosis Updates

- ~ 1 in 400 people will get MS in their lifetimes in the USA
 - **Updated** prevalence rates since 2019 (prior was ~1 in 1,000)
 - Higher prevalence in the Northern latitudes (~1 in 600 in WA)
- ~85% have **relapsing** forms of MS at the onset of the disease
- ~15% will have **progressive** forms of MS at onset
- Immune Mediated CNS Demyelinating Disease

Prevalence Autoimmune Disorders in USA

Lupus	1 in 1,000
Polymyalgia Rheumatica	1 in 500
Inflammatory Bowel Disease (Crohn's and UC)	1 in 400
Multiple Sclerosis	1 in 400 (update 2019) 1 in 1,000 prior
Rheumatoid Arthritis	1 in 300
Type 1 Diabetes	1 in 300

MS Diagnosis – 2017 Updated Criteria

December 2017

Position Paper

Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria



Alan J Thompson, Brenda L Banwell, Frederik Barkhof, William M Carroll, Timothy Coetzee, Giancarlo Comi, Jorge Correale, Franz Fazekas, Massimo Filippi, Mark S Freedman, Kazuo Fujihara, Steven L Galetta, Hans Peter Hartung, Ludwig Kappos, Fred D Lublin, Ruth Ann Marrie, Aaron E Miller, David H Miller, Xavier Montalban, Ellen M Mowry, Per Soelberg Sorensen, Mar Tintoré, Anthony L Traboulsee, Maria Trojano, Bernard M J Uitdehaag, Sandra Vukusic, Emmanuelle Wau bant, Brian G Weinshenker, Stephen C Reingold, Jeffrey A Cohen

The 2010 McDonald criteria for the diagnosis of multiple sclerosis are widely used in research and clinical practice. Scientific advances in the past 7 years suggest that they might no longer provide the most up-to-date guidance for clinicians and researchers. The International Panel on Diagnosis of Multiple Sclerosis reviewed the 2010 McDonald

Lancet Neurol 2017
Published Online
December 21, 2017

MS Diagnosis – 2017 Updated Criteria

Lesions: ≥ 2 characteristic lesions ($>3\text{mm}$) in ≥ 2 different characteristic locations

Symptoms: objective clinical evidence of at least 1 lesion (relapse associated with lesion)

Changes over Time: +CSF Oligoclonal bands **or**
>1 attack over time **or**
new characteristic MS lesions over time
(including enhancing and non-enhancing)

***No other reasonable diagnosis**

MS Diagnosis – wary of misdiagnosis

Caution on Overdiagnosis – “My radiologist said it could be MS”

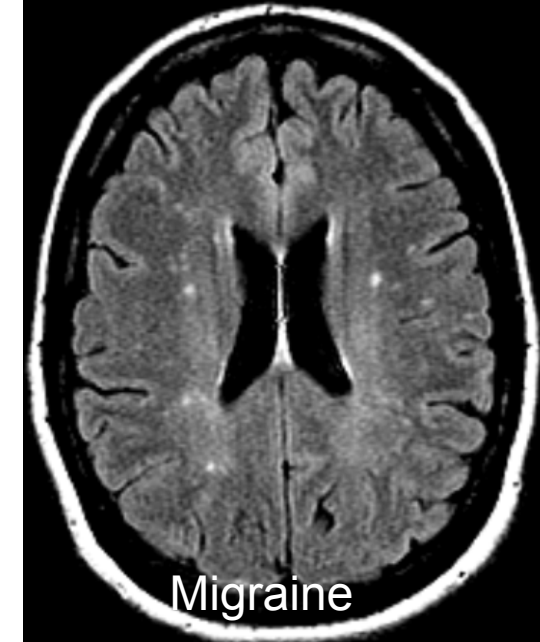
18% Misdiagnosed with MS

Previously diagnosed MS patients did not fit criteria for MS when seen for **second opinion at MS specialty centers** (UCLA or Cedars-Sinai)

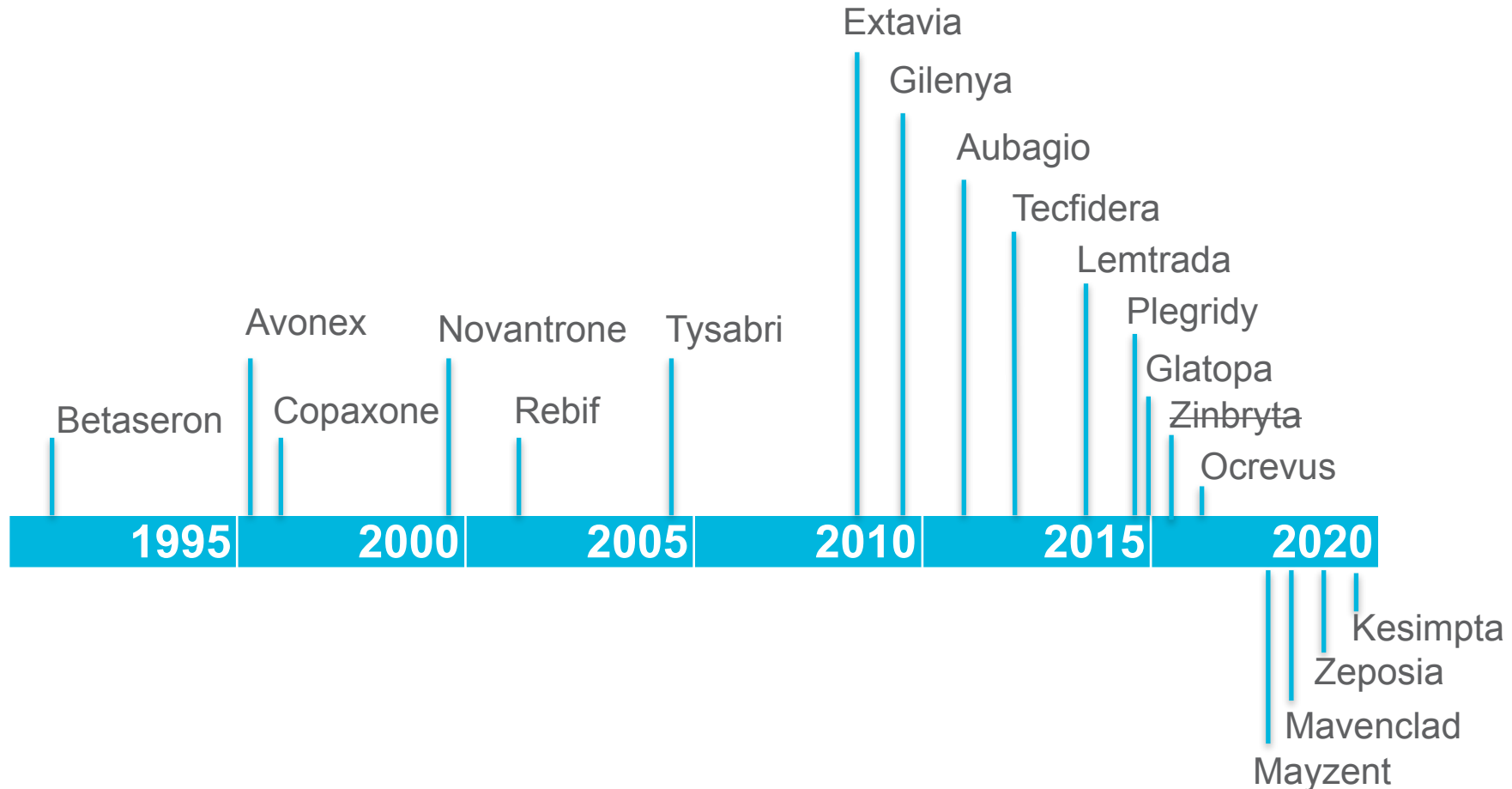
Other Diagnosis:

1. Migraine headache (most common)
2. Radiologically Isolated Syndrome (RIS)
3. Cervical spinal stenosis
4. Peripheral Neuropathy
5. Optic Neuropathy

Kaisey et al.ECTRIMS 2018 MS Conference



How do we treat to prevent MS relapses?



~20 currently FDA Approved Drugs for relapse prevention
medications specifically used for MS – Disease Modifying Therapies

MS Misdiagnosis

4 Academic Medical Centers

Prospectively identified patients by 24 MS neurologists during 13 months of the study

110 patients misdiagnosed with MS on referral to specialist

Definite Misdiagnosis (46%)

Probable Misdiagnosis (54%)

Solomon et al. Neurology 2016

Other Diagnosis	No. (%)
Migraine +/- other diagnosis	24 (22)
Fibromyalgia	16 (15)
Non-specific neurologic symptoms and abnormal MRI	13 (12)
Conversion or psychogenic disorder	12 (11)
Clinically Isolated Syndrome (CIS)	3 (3)
Neurodegenerative cerebellar syndrome	2 (2)
Cerebrovascular disease	2 (2)
Parkinsonism and non-specific MRI findings	2 (2)
Cervical Spondylosis with myelopathy	2 (2)

MS "Disease Modifying Therapies"

- **What MS DMTs DO**

- Prevention of relapses, new MRI lesions and slowing progression, not improvement of disability
- Can cause many side effects, risks

- **What MS DMTs do NOT do**

- Unlike Rheumatoid DMARD's, MS DMTs do NOT treat symptoms of MS
- Not indicated for "inactive" progression
- Do no harm, consider discontinuation when risks/burdens outweigh likely benefits

MS Disease Modifying Therapy – Updates

New DMT Versions

Fingolimod (Gilenya) – approved in 2010

- **Siponimod (Mayzent)** – approved in 2019 – no cardiac monitoring required, studied in Secondary Progressive MS
- **Ozanimod (Zeposia)** – approved in 2020 – no first dose cardiac monitoring or eye testing required, partial MAO-inhibitor
- Generic approved 12/2019 – but not yet available, legal battle halted this


Dimethyl Fumarate (Tecfidera) – approved in 2013

- **Dimethyl Fumarate** - Generic Available 9/2020
- **Droximel Fumarate (Vumerity)** – approved 10/2019, lower GI sx's in clinical trial
- **Monomethyl Fumarate (Bafiertam)** – approved 9/2020

Ocrelizumab (Ocrevus) – approved 2017 (*same mechanism as Rituximab - available since 1997*)

- **Ofatumumab (Kesimpta)** – Subcutaneous monthly injections, fully humanized CD20 monoclonal antibody – approved for relapsing forms of MS only (Ocrevus also for PPMS)
- **Ublituximab** - under FDA review

How do we treat MS?

		Treatment	FDA Approval	Efficacy	Safety
Glatiramers		COPAXONE (Glatiramer Acetate) GLATOPA (generic) Glatiramer Acetate (generic)	1997, 2015, 2017	Modest	Very Safe
Interferons		BETASERON, EXTAVIA (Interferon Beta-1b)	1993, 2009	Modest	Safe
		AVONEX (Interferon Beta-1a)	1996	Modest	Safe
		REBIF (Interferon Beta-1a)	2002	Modest	Safe
		PLEGRIDY (Peginterferon Beta-1a)	2014	Modest	Safe
Orals		AUBAGIO (Teriflunomide)	2012	Modest	Some Risks
	Fumarates		TECFIDERA (Dimethyl Fumarate) + Generic VUMERITY (Diroximel Fumarate) BAFIERTAM (Monomethyl Fumarate)	2013, 2019, 2020	More
S1P modulators		GILENYA (Fingolimod)	2010, 2019, 2020, 2021	More	Higher Risks
		MAYZENT (Siponimod)			
		ZEPOSIA (Ozanimod) PONVORY (Ponesimod)			
Monoclonals		MAVENCLAD (Cladribine)	2019	More	Higher Risks
		TYSABRI (Natalizumab)	2004 / 2006	Highest	Higher Risks
		OCREVUS (Ocrelizumab) KESIMPTA (Ofatumumab) - SC	2017, 2020	Highest	Higher Risks
		LEMTRADA (Alemtuzumab)	2014	Highest	Highest Risks

DMT Risks / Side effects for Primary Care:

Interferons (Avonex, Betaseron, Rebif, Plegridy)

- Rare risk for thrombotic microangiopathy – renal failure
- Rare risk for hypothyroidism
- Unclear if any association with depression, but possible

Fumarates (Tecfidera, Vumerity, Dimethyl Fumarate)

- Proteinuria (6%) without significant renal disease

S1P Modulators (Gilenya, Mayzent, Zeposia, Ponvory)

- Skin cancers – basal cell and melanoma
- Isolated lymphopenia – normal, mechanism of action
- Lowered vaccine responses - lowered IgG formation

CD20 Antibodies (Ocrevus, Kesimpta, Rituximab)

- Immunoglobulin deficiency – higher risks for infections
- Case reports of Psoriaform rashes
- No post-marketing signal of increased cancer risks (Ocrevus trial – breast cancer)
- Lowered vaccine responses - lowered IgG formation

Tysabri (natalizumab)

- Elevated lymphocytes, eosinophils, erythroblasts, myeloblasts - common

MS Relapse Management

- **Acute Relapse** - corticosteroids, plex
 - When to treat an acute relapse?
 - True inflammatory relapse vs. pseudo-relapse
 - Risks of steroids
 - Infection, Fracture, Falls, Delirium, Avascular Necrosis
 - Benefits of steroids
 - Mostly benefit time to recovery, may provide minimal if any long-term benefit
 - Faster but not better recovery expected
 - Oral vs. IV Steroids
 - Equivalency in studies for both effectiveness and tolerability with 1000mg IV Methylprednisolone to 1250mg PO Prednisone x 3-5 days without taper typically
 - PLEX
 - Possibly more likely effective for severe or refractory relapse – myelitis, optic neuritis, more effective for NMOSD relapse
 - Must be used early in relapse < 2 weeks, to have benefits

[News](#) > [Medscape Medical News](#)

Relapsing, Progressive MS Classifications Should Be 'Abandoned'

[Sue Hughes](#)

June 11, 2020

"We have to abandon the distinction between relapsing and progressive MS being different populations. The disease appears to be more of a continuum of disability progression, which is sometimes also accompanied by relapses." - lead author Ludwig Kappos, MD, University of Basel, Switzerland

Take Away Points about MS

- Multiple sclerosis is a chronic, relapsing and progressive, autoimmune disease of the central nervous system
- Updates in diagnostic criteria makes diagnosis faster
- Many diseases that can mimic MS symptoms and lesions
- MS affects ~1 in 400 people in the US (**new updates*)
- Rapidly evolving understanding of the disease
- Expanding treatment options, working toward improvement

Fibromyalgia / Chronic Widespread Pain

Fibromyalgia

What is it?

How common?

How is it diagnosed?

Who diagnosis, manages and follows this condition?

Fibromyalgia – what is it

A pain processing disorder without a known structural injury

Central neurologic amplification of pain perception

- Allodynia - a heightened sensitivity to stimuli that are not normally painful
- Hyperalgesia - an increased response to painful stimuli

Neuroimaging studies

- FM is associated with aberrant processing of painful stimuli in the central nervous system

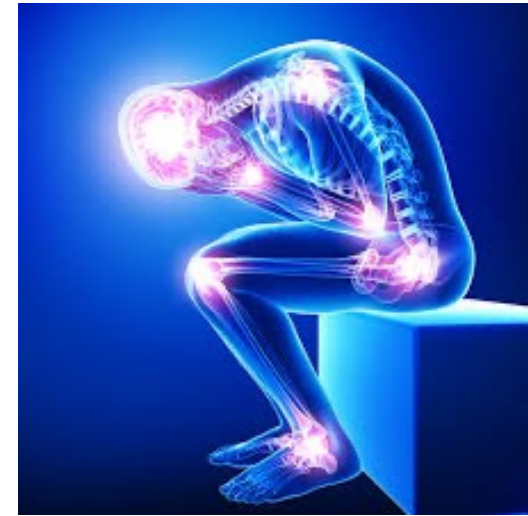
What it is NOT

- Unknown, Autoimmune, Inflammatory, Muscle/Tissue disorder, a “grab bag diagnosis”

Arnold et al. Improving the Recognition and Diagnosis of Fibromyalgia. *Mayo Clinic Proceedings*. 2011

Nebel and Gracely. Neuroimaging of fibromyalgia. *Rheum Dis Clin North Am*. 2009

Gracely et al. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum*. 2002



Fibromyalgia

What is it?

- Considered a central neurologic pain syndrome, a functional disorder of the nervous system

How common?

- Between 2 – 8% lifetime prevalence; Women > Men 3:1; Age 30 – 50yrs

How is it diagnosed?

- Often delayed (>2 years since symptoms onset and 3.7 average different physicians before diagnosis)
- American College of Rheumatology 2010 Criteria (updated from 2002)
- American Pain Society 2019 Criteria

Who diagnosis, manages and follows this condition?

- Primary Care, PMR, Rheumatology, Pain specialists, Neurology

Fibromyalgia diagnostic criteria (ACR 2010)

Chronic Widespread Pain in ≥ 7 areas (or ≥ 3 areas) over last 1 weeks

- no longer need "tender points"
- 19 locations of possible pain
 - Shoulder (L/R), Upper arm (L/R), Lower arm (L/R), Hip (L/R), Upper leg (L/R), Lower leg (L/R), Jaw (L/R), Chest, Abdomen, Upper back, Lower back, Neck)

Multiple Systemic Symptoms ≥ 5 score (or ≥ 9 score)

- Fatigue (0-3 points, 0= none, 1 = mild, 2= moderate, 3 = severe)
- Waking Unrefreshed (0-3)
- Cognitive Symptoms (0-3)
- PLUS: Somatic Symptoms (0 – 3, none, few, moderate, or a great deal of the following):
 - muscle pain, IBS, headaches, abdominal pain, numbness/tingling, dizziness, insomnia, depression, constipation, nausea, nervousness, blurred vision, fever, diarrhea, wheezing, dry mouth, itching, Raynaud's, heartburn, vomiting, loss of appetite, shortness of breath, frequent urination, painful urination, bladder spasms...

3 months duration

No other better explanation

Fibromyalgia – case examples

- 37yo woman with 6 months of aching pain in bilateral shoulders (2), abdomen (1), hips (2), and legs (2), severe fatiguability, cognitive fogging and insomnia.
 - No other characteristic diagnosis, normal physical exam otherwise, history of IBS-d, testing for inflammatory arthritis negative
 - +7 areas of chronic pain, +6 Systemic Symptoms (+3 severe fatigue, +3 cognitive symptoms)
 - Classic Fibromyalgia diagnosis

Fibromyalgia – case examples

- 37yo woman with 6 months of moderate fluctuating aching pain in bilateral hips (2), and legs (2). Moderate fatigue (2), moderate cognitive fogging (2), moderately un-refreshing sleep (2) and many other symptoms (3), headaches, numbness/tingling, dizziness, depression, constipation, nausea, nervousness, blurred vision, fever, diarrhea, dry mouth, itching, Raynaud's, heartburn... “pan-positive ROS”.
 - No other characteristic diagnosis, normal physical exam without structural etiology of leg and hip pain, extensive workup with normal L spine MRI, labs, EMG, xrays and consult with Rheumatology and PMR
 - +4 areas of chronic pain, +9 Systemic Symptoms
 - Fibromyalgia diagnosis (ACR 2010 criteria, although not with new APS 2019 criteria)
 - but only lower extremity chronic pain!

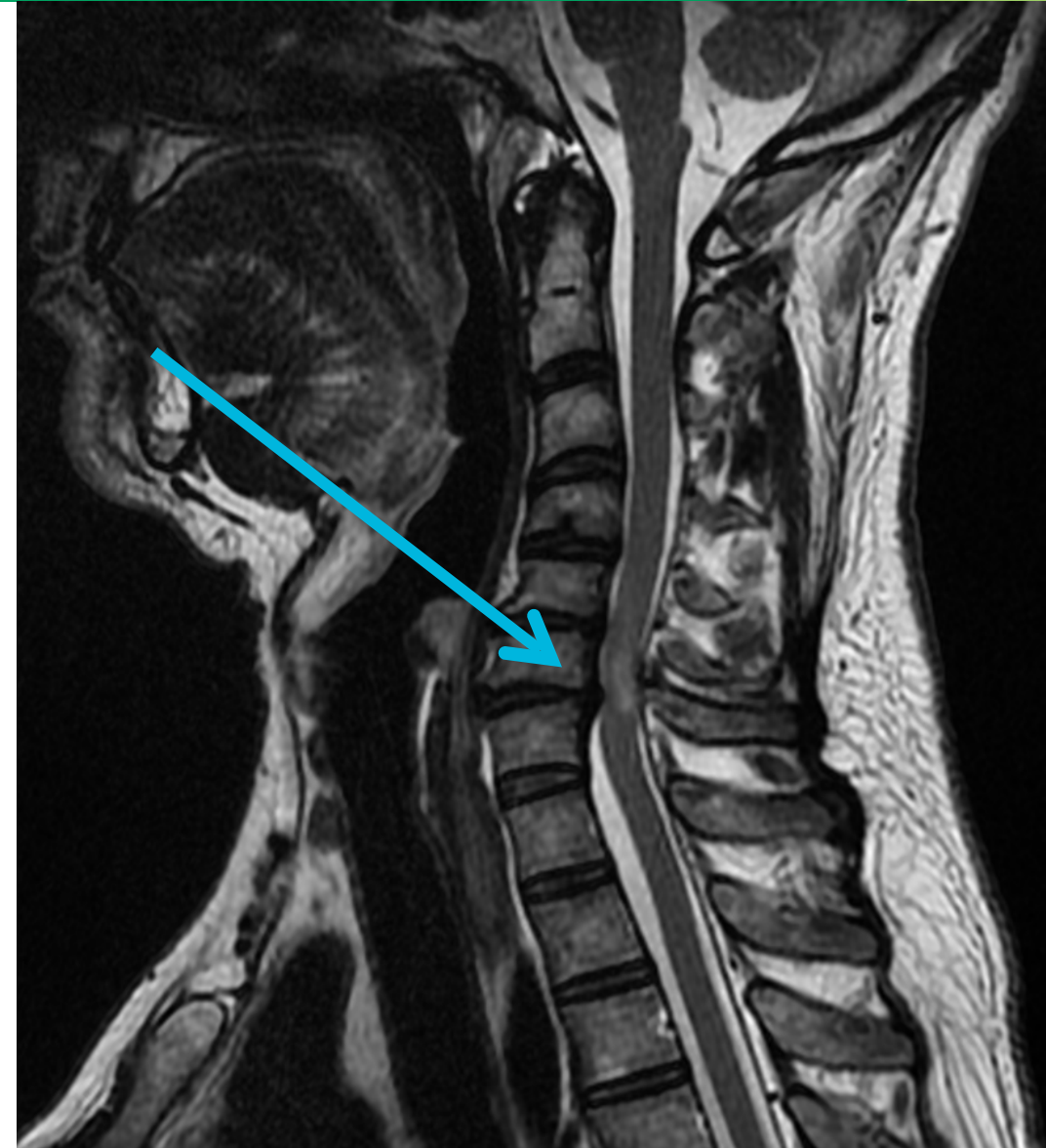
Fibromyalgia – case examples

- 37yo woman with 6 months of progressive pain in neck, arms, chest, abdomen, legs, tingling/aching pain, with stiffness, muscle spasms, urinary urgency/frequency, constipation, tingling/numbness, mild imbalance, insomnia.
 - Exam notable for mild diffuse hyperreflexia, mild low normal distal vibration sense, mild difficulty with tandem walking
 - Possible Fibromyalgia diagnosis

NOT Fibromyalgia – case examples

37yo woman with 6 months of progressive pain in neck, arms, chest, abdomen, legs, tingling/aching pain, with stiffness, muscle spasms, urinary urgency/frequency, constipation, tingling/numbness, mild imbalance, insomnia.

- Possible Fibromyalgia diagnosis
- MRI C-spine done for prominent neck pain and mild distal sensory loss found **severe cervical stenosis and myelopathy**
- **NOT Fibromyalgia**
- **Neuropathic pain from chronic myelopathy**

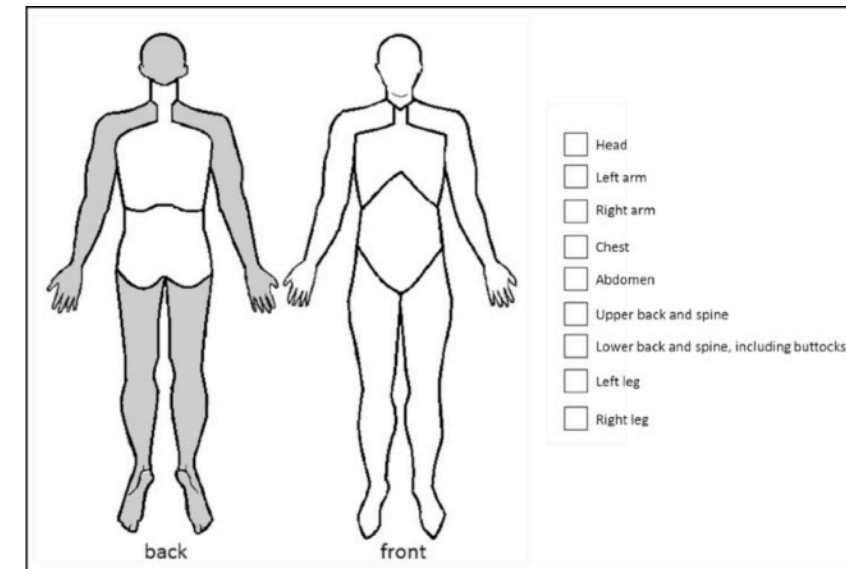


Fibromyalgia diagnosis— updated simplified criteria

Diagnostic Criteria (American Pain Society 2019)

- **Multisite pain**, ≥ 6 pain sites from 9 total (figure)
 - Head, Arm (L/R), Chest, Abdomen, Upper Back, Lower Back, Leg (L/R)
- **Sleep Problems** - moderate to severe
- OR
- **Fatigue** – moderate to severe (physical or mental)
- **>3 months in duration** (both symptoms)
- No other better explanation

- Common associated features:
 - Tenderness
 - Dyscognition (forgetfulness, disorganized thinking)
 - Stiffness
 - Environmental sensitivity (photo/phonophobia, smell sensitivity)



Fibromyalgia Workup Questions

- Have you had pain in your muscles or joints that has lasted 3 months or more?
 - chronic myofascial pain
- Do you have pain all over?
 - widespread pain
- Do you become fatigued during the day so that you have to stop normal activities?
 - moderate/severe fatigue
- Do you wake up in the morning and feel more tired than when you went to bed?
 - non-restoring sleep

Diagnostic Dilemma

”No one can tell me what is wrong with me”

“I have been to multiple doctors who give me different answers”

Improved satisfaction: Diagnosis of FM has no negative effect on clinical outcomes, and those newly diagnosed with FM report improved satisfaction with health and fewer long-term symptoms¹

Reduced costs: Utilization of medical resources and the associated costs decline after a diagnosis of FM²

**Don't “Turn off your brain” once diagnosis made – maintain differential diagnostic vigilance*

¹**White et al.** Does the label “fibromyalgia” alter health status, function, and health service utilization? *Arthritis Rheum.* 2002

²**Annemans et al.** Health economic consequences related to the diagnosis of fibromyalgia syndrome. *Arthritis Rheum.* 2008

Fibromyalgia associated conditions

Risk factors / Associated Conditions:

- Family history (8x higher risks)
- Female sex (7x higher diagnostic rate)
- Mood disorders
 - Anxiety 35-62% of FM patients
 - Major Depressive Disorder 58-86%
 - Bipolar Disorder 11%
- Other comorbid pain disorders
 - Irritable bowel syndrome (IBS), migraine, interstitial cystitis, chronic prostatitis, temporomandibular disorder (TMJ), chronic pelvic pain, and vulvodynia
- Prior physical or psychologic trauma
- Peripheral Neuropathy / Small fiber neuropathy

Fibromyalgia Summary

- Fibromyalgia is common
- Under diagnosed / Delayed diagnosis
- Diagnosis shouldn't take 3+ doctors and >2 years
- Current understanding - primarily neurologic – central pain sensitization condition
- Many associated conditions
- Association with small fiber neuropathy / central neuropathic pain syndromes

Hot Topics in Neurology

Migraine

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- New Preventative Treatment options
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Multiple Sclerosis

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Fibromyalgia

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Questions?