Therapies for Managing MS Symptoms

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Disclosures

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Objectives

• Discuss management of the following MS symptoms:
  – Fatigue
  – Pain/Spasticity
  – Urinary and bowel issues
  – Sexual dysfunction
  – Tremor
  – Impaired Gait
Symptomatic Management in Multiple Sclerosis

• Although the development of immunomodulatory therapies has altered the natural history of MS, they do not improve ongoing symptoms.

• Most patients have 1 or more active symptoms caused by MS, and most are undermanaged.

• Meaningful symptomatic management is a major factor in improving quality of life for MS patients.
What is fatigue?

- Defined as “a subjective lack of physical or mental energy that is perceived by the individual or caregiver to interfere with activities of daily living”

- Clinically, MS patients report fatigue as exhaustion, lack of energy, increased somnolence, or worsening of MS symptoms with fatigable weakness, exacerbated by activity and heat
Why is fatigue an important topic?

• Fatigue is considered to be one of the main causes of impaired quality of life among MS patients

• Among the most common symptoms, reported by at least 75% of MS patients at some point in their disease course

• For many, is considered to be the single most debilitating symptom, surpassing even pain or physical disability
Barriers to understanding/treating fatigue

• Subjective symptom without a unified definition
• No gold standard exists by which to measure fatigue
• Fatigue in MS patients may be multifactorial
Mechanisms of fatigue

• Inflammatory cytokines implicated in MS thought to be strong mediators of fatigue

• Possible endocrine contribution via dysfunction of the hypothalamo-pituitary-adrenal axis

• Could be related to brain lesions, cortical atrophy, axonal damage, hyper-activation of neural circuits

• SUMMARY: most likely represents a physiological adaptation of the MS patient to a weakened internal condition unable to meet external demands
Secondary causes: sleep disorders

- Restless legs syndrome/periodic limb movement disorder
- Sleep disordered breathing/sleep apnea
- Chronic insomnia (may arise secondary to pain, spasticity, depression, anxiety, nocturia, medication effects, or primary sleep disorders)
Secondary causes: depression

- Fatigue and depression are highly correlated
- Depressed MS patients have been found to have greater fatigue and symptoms such as lack of motivation and inability to complete tasks
- Fatigue is unlikely to improve if depression is present
- If depression is present, treatment with an anti-depressant is recommended
Secondary causes: iatrogenic, etc

• Medications used to treat symptoms of MS have the potential to cause fatigue: i.e. antispasmodics, pain medications, interferon beta

• May be more severe in patient with progressive MS rather than relapsing remitting MS
A diagnostic approach

• Labwork testing for common hematologic and metabolic conditions, iron studies, vitamin B12 and folate levels, thyroid studies, vitamin D level

• Screening for sleep disorders, depression, medication causes
Pharmacologic treatment: Amantadine

- Approved by the FDA for treatment of influenza
- Unknown how it works for MS-related fatigue, possible metabolic role
- Generally well tolerated and has a mild side-effect profile
- Usual dosage is 100 mg twice a day
- Is the most extensively studied medication for MS-related fatigue, but data has been mixed
Pharmacologic treatment: Modafinil

- Wake-promoting agent approved by the FDA for narcolepsy, shift-work sleep disorder, and sleep apnea with residual daytime sleepiness
- Generally safe and well tolerated, although increased risk of adverse psychiatric and cardiovascular effects have been reported
- Usual dosage of 200 mg in the morning, or 100 mg twice daily
- Studies have been mixed
Pharmacologic treatment: Methylphenidate

- Central nervous system stimulant used typically for ADHD
- Has been anecdotally reported to be useful in patients with MS, may also help with cognition
Non-pharmacologic treatments

• Cognitive behavioral therapy
• Relaxation therapy
• Aerobic exercise via a graded exercise program
• Energy conservation strategies
• Cooling devices, avoidance of hot humid conditions
• Low fat, low cholesterol diet supplemented with olive oil capsules
Pain in Multiple Sclerosis

• Pain and pain syndromes affect up to 86% of patients during their course of illness

• MS patients with pain more likely to report greater MS disease severity, poorer psychological functioning, and poorer health

• MS individuals with chronic pain have lower scores on quality of life measures, including psychological well-being and independent living
Pain in Multiple Sclerosis

- MS pain falls into 4 categories:
  - Neuropathic (central) pain
  - Pain indirectly related to MS
  - Pain related to MS treatment
  - Pain unrelated to MS
Neuropathic/Central Pain

- **Dysesthetic limb pain:**
  - manifests as chronic burning discomfort involving the arms, legs, or trunk
  - typically bilateral and more prominent in lower extremities
  - may result from lesions in the spinal nociceptive pathways

- **Trigeminal Neuralgia:**
  - occurs at 20x prevalence of general population
  - 31% is bilateral, uncommon in general population
  - due to lesions in the intrapontine trigeminal tract or root entry zone

- **Lhermitte phenomenon:**
  - paroxysmal sensory disturbance related to neck flexion felt centrally down the neck/back, usually involving the limbs
  - pain is brief, lasting seconds, “electrical” in nature
  - due to lesions in the cervical posterior column
Treatment of Neuropathic/Central Pain

• Dysesthetic limb pain-first line agents include:
  – tricyclic antidepressants (amitriptyline, nortriptyline)
  – anticonvulsants (gabapentin, pregabalin, lamotrigine)
  – serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine)

• Trigeminal neuralgia:
  – first line agents include carbamazepine or oxcarbazepine
  – second line agents include baclofen, gabapentin, lamotrigine
  – medically refractory treatment includes percutaneous gasserian rhizotomy or stereotactic gamma knife radiosurgery

• Lhermitte phenomenon:
  – gabapentin or carbamazepine can be used if symptoms are disruptive
Other Pain Types in MS

• Indirectly due to MS:
  – Spasticity
  – Musculoskeletal disturbances associated with limb weakness, immobility

• Related to MS treatment:
  – Injection site reactions from injectable immunomodulatory treatments
  – Headache secondary to interferon-beta

• Unrelated to MS:
  – Low back pain and headache are frequent in MS patients, though treatment is no different than the general population
Spasticity

- Defined as a state of increased muscle tone with velocity-dependent increased resistance to passive movement
- Can be manifested as symptoms of muscle tightness, spasms, cramping, or deep/aching pain
- Prevalence of 70-80% of MS patients
- Mechanism: interruption of descending pathways’ inhibitory control of group II spinal interneurons → overactivity of alpha motor neurons
- Therapeutic approach should be multidimensional:
  - PT/OT
  - Stretching, massage
  - Exercise
  - Pharmacotherapy
Pharmacologic treatment: Baclofen

- Mechanism: agonist of GABA receptors on spinal interneurons resulting in decreased alpha motor neuron activity
- Approved for spasticity in MS, demonstrated efficacy in various clinical trials
- Side effects: daytime sedation, increased muscle weakness that may have a negative impact on limb function and gait
- Short half life limits effectiveness to 3-4 hours
- Dosing: important to start low and go slow
Pharmacologic treatment: Tizanidine

- Mechanism: alpha 2 adrenergic agonist that reduces release of excitatory transmitters, effectively reducing muscle tone
- Approved for reducing spasticity and spasms; clinical trials showed efficacy without the limiting significant weakness
- Side effects: sedation, dizziness, hypotension (similar to clonidine in pharmacology)
- Dosing: start low and go slow
Pharmacologic treatment: Benzodiazepines

- Mechanism: bind to the benzodiazepine-GABA A receptor, increasing presynaptic inhibition of the spinal cord
- Diazepam or clonazepam are the formulations most commonly used
- Efficacy of diazepam assessed in several clinical trials, similar to baclofen effect
- Side effects: sedation, concerns for addictive potential
Pharmacologic treatment: Gabapentin

- Mechanism: Structural analog of GABA
- Not approved for spasticity, but efficacy has been suggested in small trials
- May be useful as an adjunctive therapy with other spasticity medications
- Relatively safe to take with other drugs
- Side effects: sedation, dizziness, weight gain
Pharmacologic treatment: Medical marijuana

- Has been difficult to study due to schedule 1 status, but some small studies have shown reduction in Ashworth scales as well as reduced pain

- Nabiximols is an oral mucosa spray that contains delta-9-THC and CBD in a 1:1 ratio, and is approved in 16 countries outside of the US for spasticity in MS

- Most likely the CBD component which is helpful

- Most common side effects reported by patients are dizziness and fatigue, though there are concerns about worsened cognitive function in MS

- Best used for refractory spasticity or as an adjunct therapy
Other therapies…

• Botulinum toxin:
  – Blocks presynaptic acetylcholine release at NMJ
  – Not approved for spasticity, but efficacy assessed in several trials
  – Main use in smaller muscles of hands and feet
  – Efficacy limited by size of muscle and dose required

• Baclofen pump:
  – Works by directly delivering liquid baclofen to the lower cord via CSF
  – Approved for spasticity, demonstrated efficacy in intractable cases
  – Efficacy sustained over time, not limited by sedation
  – Limitations can be muscle weakness and technical difficulties (i.e. kinking of catheter)
Neurogenic Bladder

- Bladder dysfunction present >70% of MS patients
- https://pollev.com/desiraeburkl966
- 10% at initial presentation

Physiologic micturition dependent on:
- Adequate bladder storage of urine
- Coordinated contraction of detrusor muscle
- Relaxation of external sphincter at appropriate times

Proper function requires integration of neuronal centers in cerebral hemispheres, pons, sacral spinal cord and their interconnections—lesions in these areas can cause dysfunction
Neurogenic Bladder Categories

- **Detrusor hyperreflexia**
  - Associated with suprasacral cord lesions or suprapontine cerebral lesions ➔ disinhibition of detrusor reflex
  - Results in poorly compliant bladder ➔ failure to store
  - Symptoms of urinary urgency, frequency, +/- urge incontinence

- **Detrusor sphincter dyssynergia (DSD)**
  - Associated with suprasacral cord lesions
  - Results in inadequate relaxation of external urinary sphincter during detrusor contraction ➔ urinary retention/failure to empty
  - Symptoms of urinary urgency, frequency, incontinence, urinary hesitancy, sensation of bladder fullness after voiding

- **Hypotonic bladder**
  - Associated with sacral cord lesions (least common)
  - Results in hypotonic, overly compliant bladder ➔ failure to empty
  - Symptoms of urinary frequency, overflow incontinence, signs of incomplete emptying
How to Assess Neurogenic Bladder

• Type of neurogenic bladder cannot be accurately determined by presenting symptoms

• Check UA to rule out UTI, treat with antibiotics if indicated

• Obtain postvoid residual (PVR) urine volume by ultrasound to differentiate failure-to-empty vs failure-to-store dysfunction
  – PVR volume < 100 ml= failure to store
  – PVR volume > 100 ml= failure to empty
Treatment of Neurogenic Bladder

• **Failure-to-store:**
  – Mainstay treatment with anticholinergic agents
  – Includes nonselective muscarinics, oxybutynin, tolterodine, trospium, fesoterodine
  – Alternatively, selective M2 or M3-antimuscarinics, darifenacin, solifenacin may be used
  – Common side effects: dry mouth, constipation
  – Contraindicated with angle-closure glaucoma, mechanical bladder outlet obstruction
  – Avoid non-selective agents in patients with cognitive dysfunction
  – Botox injections may reduce urinary urgency, frequency, and incontinence
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Treatment of Neurogenic Bladder

• **Failure-to-empty:**
  – Best treated with clean intermittent straight catheterization (CISC) ➔ perform at least once daily
  – Alpha adrenergic medication (i.e. tamsulosin) may reduce PVR urine volume
  – Patient with symptoms of both failure-to-store and failure-to-empty may benefit from combination of straight catheterization and anticholinergic agents
  – Indwelling catheter or suprapubic catheter may be indicated in patients who are refractory to CISC
Neurogenic Bowel

• Bowel dysfunction occurs in 39-73% of individuals with MS
• Symptoms can include constipation, fecal incontinence, or both
• Patients consider this equally as impacting as mobility on quality-of-life measures
• Function dependent on integrity of bowel transit, pelvic floor musculature, anorectal sensation, and executive control
• Lesion in frontal lobes, brainstem, and spinal cord can affect bowel function
• Spasticity, gait mobility, and fatigue can contribute to bowel dysfunction
• Anticholinergics, antispasticity medications, and antidepressants can exacerbate constipation
Treatment of Neurogenic Bowel

• **Conservative measures:**
  – Timed bowel evacuation
  – Dietary fiber
  – Bulk-forming agents
  – Biofeedback
  – Physical activity
  – Adequate hydration
Treatment of Neurogenic Bowel

• Medical therapies:
  – Stool softeners
  – Rectal stimulants (glycerol or bisacodyl suppositories)
  – Laxatives
  – Enemas
  – Manual disimpaction for fecal incontinence related to impaction
  – Antidiarrheal agents or anticholinergics for isolated fecal incontinence
Sexual Dysfunction

• Affects 50-90% of men and 40-85% of women

• Causes are multifactorial:
  – Lesions in the neuraxis causing physiologic disruption
  – Secondary to fatigue, spasticity, bladder dysfunction, depression, medication side effects

• Frequently unrecognized as patients and physicians reluctant to discuss these problems
Sexual Dysfunction in Men

- Symptoms include decreased libido, erectile dysfunction (ED), ejaculatory disturbance

- Pharmacologic treatment:
  - Directed at ED
  - Sildenafil citrate shown to improve both ED and quality of life in several trials
  - No studies for vardenafil or tadalafil, but similar mechanisms would predict equivalent efficacy

- Non-pharmacologic treatment:
  - Intracavernous vasodilator agents (papaverine, alpostadil)
  - Vacuum-based penile prostheses
Sexual Dysfunction in Women

- Symptoms include reduced libido, decreased vaginal lubrication, abnormal vaginal sensation, and anorgasmia
- No medical therapy approved for SD in women with MS
- Reliant on non-pharmacologic modalities:
  - Vaginal lubricants helps dryness, enhances perineal sensation
  - External vibratory stimulation may augment physiologic vasocongestion and orgasm
Tremor

• Pathophysiology presumably related to dysfunction in cerebellar efferent pathways
• May affect up to 80% of MS patients
• May be socially embarrassing or affect activities of daily living
Treatment of Tremor

• **Non-pharmacologic:**
  – Joint stabilization maneuvers
  – Limb weights
  – Large-handled, weighted utensils

• **Pharmacologic:**
  – Usually resistant to pharmacotherapy
  – Clonazepam, beta blockers (i.e. propranolol), primidone, gabapentin can be tried

• **Surgical:**
  – Stereotactic thalamotomy of ventral intermediate nucleus
  – Deep brain stimulation in ventral intermediate nucleus
Gait Impairment

• One of the most common and troubling impairments resulting from MS

• Historically not well addressed by drugs

• Dalfampridine (4-aminopyridine):
  – potassium channel blocker shown to result in a 25% increase in **walking speed** in 37% of patients
  – Contraindicated in patients with seizures or renal impairment

• Physical therapy with gait training and regular exercise may be the most beneficial measures
Case scenario #1

• A 52 yo woman with Multiple Sclerosis, HTN, and untreated anxiety/depression is being seen in follow up in clinic. She would like to address her fatigue symptoms at today’s visit as they are impacting her daily activities. Concomitant medications include dimethyl fumarate, lisinopril, vitamin D, and gabapentin 900 mg tid.
  – What other questions may you want to ask her?
  – What laboratory evaluations would be indicated?
  – What type of medication management could be considered?
Case scenario #2

- A 39 yo man with primary progressive Multiple Sclerosis presents to clinic with worsened function over the last month due to increased spasticity in his legs. He is still able to ambulate with a walker for 500 meters. He had been taking baclofen 20 mg tid, but had scaled back his dose to 20 mg qhs as he was not tolerating the sedation from the daytime doses. His recent labwork from 2 weeks ago did not show any evidence of infection. He reports not getting much exercise lately, and he has not done PT within the last year.
  - What nonpharmacologic approaches could be recommended?
  - What pharmacologic approaches could be considered?
References


