

MENOPAUSE MANAGEMENT IN MS



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YOUR PARTICIPATION IS IMPORTANT

90% women get MS prior to age 50



TALK OUTLINE

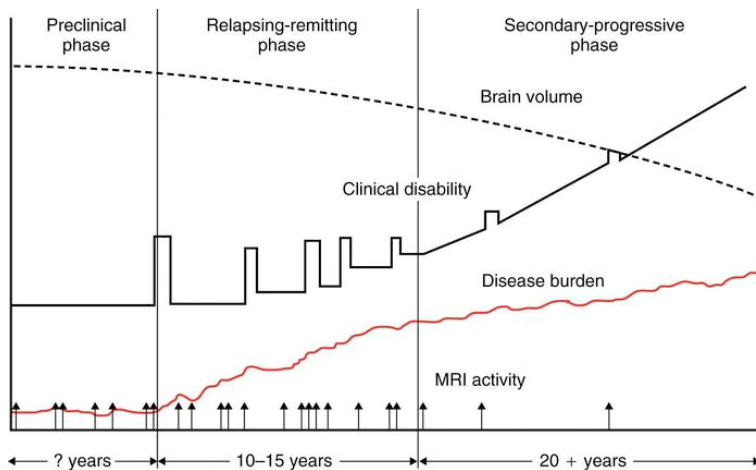
- Menopause overview
- MS and menopause: a relationship?
- Symptom management
 - Vasomotor symptoms
 - Hormonal therapies?
 - Other symptoms
 - “Overlap” - Bladder, mood, sleep
 - Other

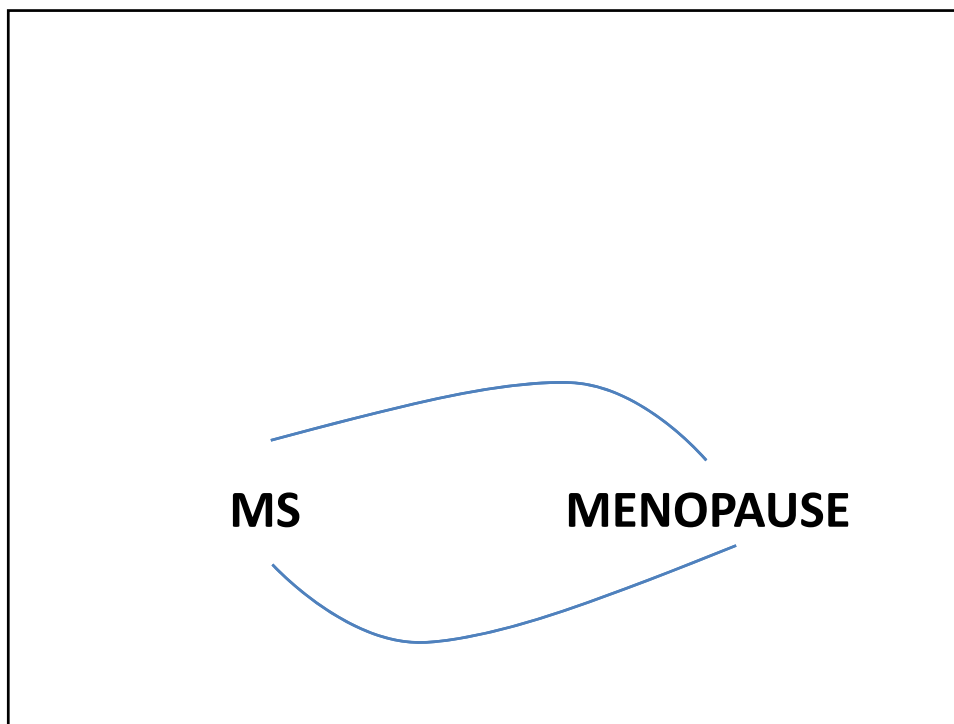
MENOPAUSE: AN OVERVIEW

Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	variable				variable	1-3 years	2 years (1+1)	3-6 years	Remaining lifespan	
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/Length	Variable Length Persistent ≥ 7 -day difference in length of consecutive cycles	Interval of amenorrhea of ≥ 60 days				
SUPPORTIVE CRITERIA										
Endocrine			Low	Variable* Low	Variable* Low	$\uparrow > 25$ IU/L**	Variable Low	Stabilizes Very Low		
FSH			Low	Low	Low	Low	Low	Very Low		
AMH Inhibin B			Low	Low	Low	Low	Very Low	Very Low		
Antral Follicle Count			Low	Low	Low	Low	Very Low	Very Low		
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms Likely	Vasomotor symptoms Most Likely	Increasing symptoms of urogenital atrophy		

blood draw on cycle days 2-3 = elevated
**Approximate expected level based on assays using current international pituitary standard⁶⁷⁻⁶⁹
 Stages of Reproductive Aging + 10 staging system for reproductive aging in women, *JCEM* 2012

MENOPAUSE AND MS – OFTEN COINCIDES WITH DISEASE PROGRESSION





MENOPAUSE: AN “OPPORTUNITY”

HEADACHES AND HOT FLASHES
HAIR BECOMES THINNER AND LOSES LUSTER



Children grown, out of house
Fewer career pressures
Media, scientific attention

An opportunity to:

- Tackle symptoms and improve well being
- Discuss meaningful QOL and priorities with patients

EFFECT OF MENOPAUSE ON MS: WIDE VARIABILITY IN PATIENT-REPORTED OUTCOMES

	Smith & Studd 1992	Holmqvist et al 2006	Wundes et al 2011 (abstract)
	All F "sufferers" at an annual MS mtg	All F with MS in 2 county registries	Mail survey of 591 pts w/ MS
N postmenopausal (HRT)	19 (8)	61 (30)	313 (160 approx)
Menopause	+ 2.15 disab score		
Worse	54%	HRT/No HRT 41%/30%	A few
No change	38%	55%/65%	Most
Better	8%	3%/7%	Rare
HRT	-2.88 disab score		
Worse	0%	7%	?
No change	25%	87%	75%
Better	75%	7%	?
	<i>J Roy Soc Med</i> 85	<i>Maturitas</i> 54	<i>Int'l J MS Care</i> 13(S3)

PRELIMINARY STUDIES: PATIENT VOICES

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THEME	Age (yr)
Perimenopausal onset of MS	
"I have never thought about the subject but my MS really flared after meno and that was when I was dx after being so sick for 15 years"	58
"Menopause and MS were pretty much simultaneous."	60
"My first MS attack occurred 3 months after my last menstrual period and right around the time I first started having hot flashes."	55
Effect of hot flashes on MS symptoms	
"I confused the two, especially hot flashes"	53
"About the time my menopause seemed to be bothering me (severe hot flashes) is when my MS symptoms really started to be intensified."	48
Overlap of MS, menopausal and aging symptoms	
"Please keep in mind that I was not officially dx'd when I had my complete hysterectomy. I also must mention that I was busy taking care of elderly ill parents constantly and had very little time to donate to myself or to think about my own health issues."	49
"I went through 2 surgeries, divorce and diagnoses all at the same time, hard to determine amount of stress, anxiety and depression and MS change."	45
Worsening of MS-related disability after menopause, particularly surgical	
"Before I stopped taking birth control pill's I was working and able to walk and houseclean etc. I had the surgery and I started to progress toward becoming completely wheelchair bound."	53
"Relapsing-remitting MS seemed more unstable; smaller flare-ups that the neurologist often called "decompensation" [...] Examples: numbness or tingling in hands or feet"	54
"My first noticeable relapse was July 1995, while still menstrating. In September 2010, after menopause, symptoms and lesions progressed rapidly."	49
Effect of HRT on MS symptoms	
"I truly believe that stopping the hormone therapy caused my MS to be much worse. I always wonder if I had been allowed to stay on the HRT I may not be disabled as much as I am."	61
"I am still on HRT and am afraid to go off of it even though I am 52 years old. I feel like I would rather risk the side affects of staying on it than take the risk of going off of it and have it mess with my MS."	52
"I am not taking any [estradiol] now because the insurance company refuses to pay for a more expensive brand that does help with my hot flashes which at times cause a lot of fatigue due to heat intolerance."	49
"[HRT was] beneficial as I believe the absence of hot flashes and increased sense of well-being improved my MS symptoms caused by heat and low energy."	48

Bove et al, under review

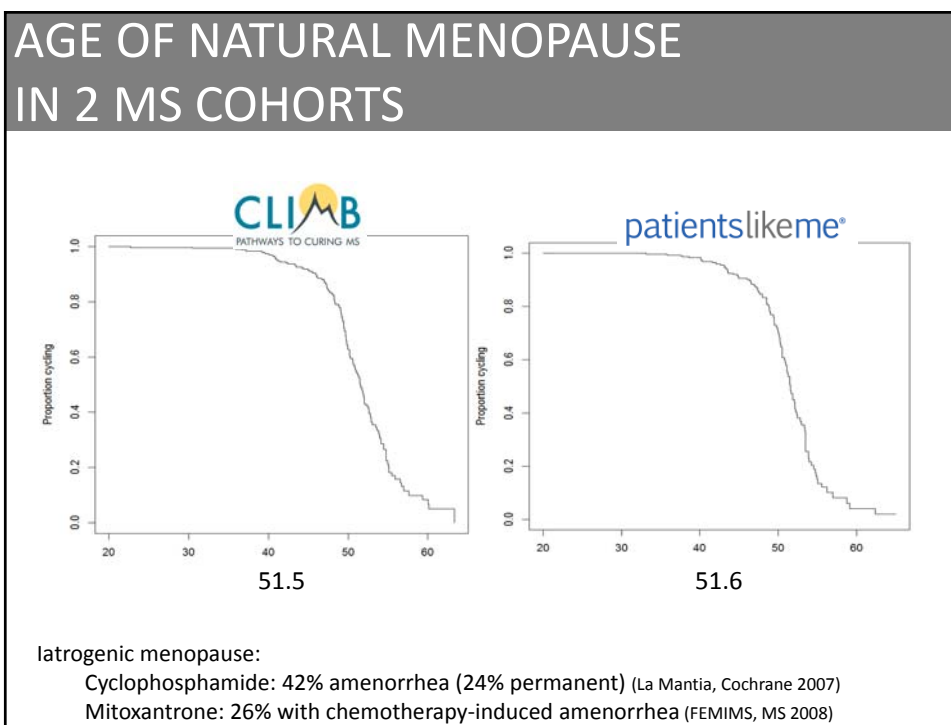
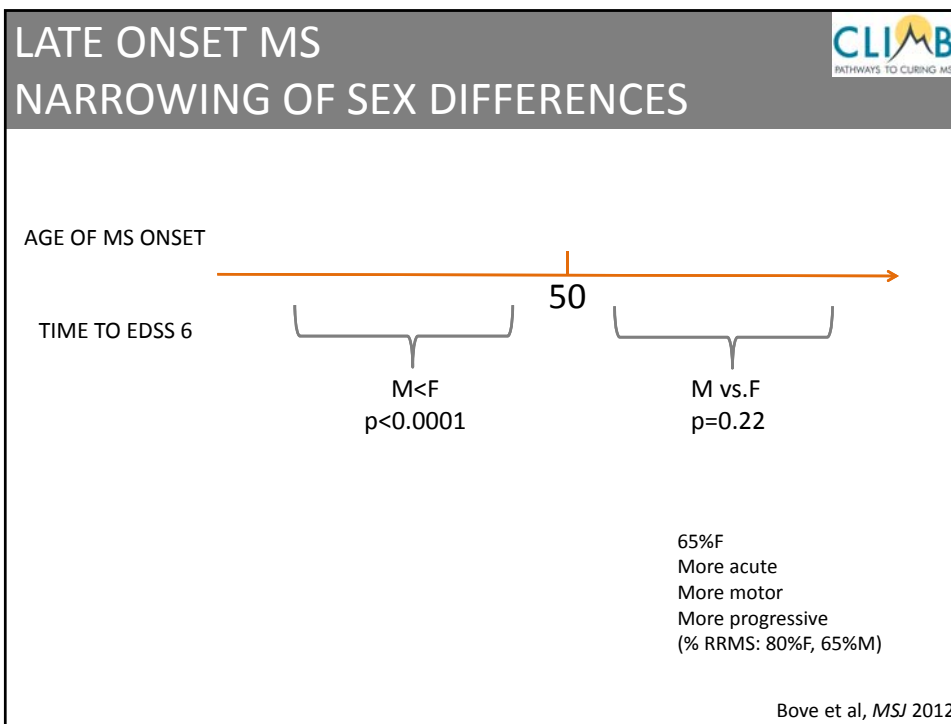
MENOPAUSE IN OTHER MODELS: SLE AND RA

	SLE (TH2)	RA (TH1)
Pregnancy	Worsens	Better
Late onset disease	Usu >50Y (16% pts) Lower F:M ratio (3.2:1 vs 13.3:1) Less frequent high titer anti-ds DNA/anti-Ro Milder course Lower incidence most symptoms More insidious: 5Y vs 3Y Less use of cytotoxic agents	Usu >60Y Lower F:M ratio (1:1) Less frequent RF Worse function More symptoms More acute onset Higher ESR
Age of menopause	Increased risk of SLE with earlier menopause, esp. surgical (RR 1.9)	Increased risk of RA with earlier menopause Milder disease course with earlier menopause
Disease course after menopause	Fewer flares Decreased SLEDAI Greater damage accrual in affected organs	Worse course More joint damage and physical disability
HRT	Case reports of worsening flares SELENA : No incr severe, modest incr mild-mod flares in stable pts; Incr thrombosis	?Maybe better WHI: non-significant improvements in joint pain scores and reduction in risk of RA

Bove, Clinical Immunology 2013

OBJECTIVE DATA: MINIMAL

	MS
Late onset disease	Well described in cohort studies
Age of menopause	?
Disease course after menopause	?
HRT	?



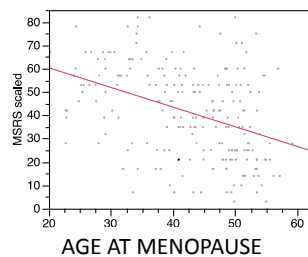
ONLINE COHORT

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EARLIER MENOPAUSE AND WORSE MSRS

SURGICAL (N= 103)	NATURAL (N= 99)
46.3	35.4
95% CI: 41.6-51.0	95% CI: 30.2-40.6

Multivariate regression adjusted for age, MS type and duration:
beta=10.4, p<0.001



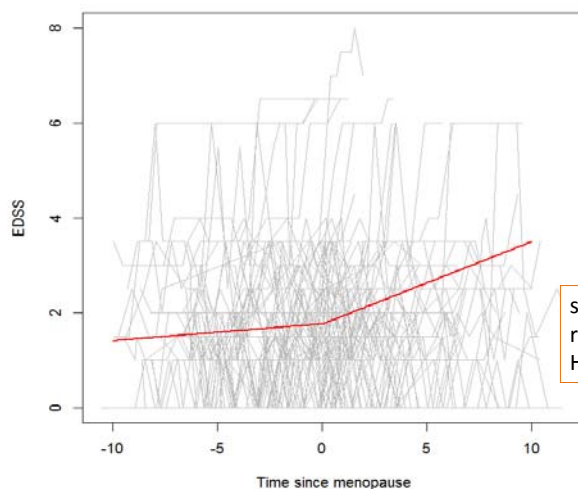
Multivariate regression adjusted for menopausal type
as well as age, disease type and disease duration (N=202)
beta=-1.68, p<0.001

Bove et al, MSARD 2015

CLINIC-BASED LONGITUDINAL ANALYSIS

CLIMB
PATHWAYS TO CURING MS

SLIGHT EDSS WORSENING AFTER MENOPAUSE



surgical menopause
relapses
HRT analyses

Change in EDSS trajectory at menopause (N=124, p=0.024)

(Bove et al, under review)

often, very general recommendations
evidence free zone

SYMPTOMS: OVERLAP AND MANAGEMENT

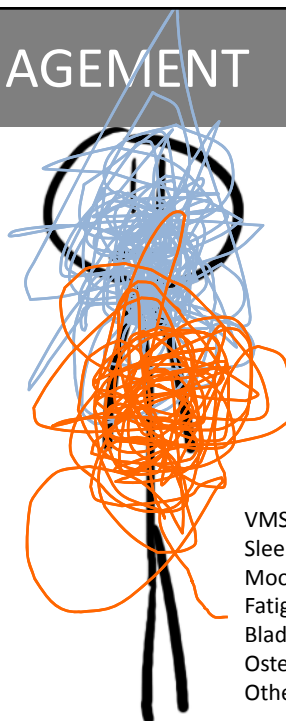
Bove et al, J Neurol 2013

SYMPTOM MANAGEMENT



"I'm falling apart"

"Something has to give"



- VMS
- Sleep
- Mood
- Fatigue
- Bladder
- Osteoporosis
- Other

VASOMOTOR SYMPTOMS

- **Manifestations**
 - Hot flashes (including night sweats)
 - Cold flashes
 - Vascular instability
 - Rapid heartbeat
- **Leading mechanistic explanation**
 - Abrupt hormone deprivation will result in loss of negative feedback over hypothalamic NA synthesis.
 - The proximity of the hypothalamic thermoregulatory centre to LHRH-producing areas may also be involved
- **Effects on MS**
 - Sleep disturbance, insomnia => impacts fatigue and mood
 - VMS => exacerbate symptoms (// Uthoffs)
 - Exacerbations, “pseudo-flares” => impacts MS decision-making

Joffe et al, Am J ObGyn 2010; Joffe et al, JCEM 2011;
Pinkerton et al, Menopause 2015; Ensrud et al, Sleep 2015

VASOMOTOR SYMPTOMS: APPROACH

- **HRT:**
 - Per NAMS, Estradiol therapy is most effective therapy
- **SSRIs, SNRIs**
 - venlafaxine: modest effects on sleep quality and insomnia
 - Has a generic extended release form, and few drug-drug interactions
 - 17β estradiol 0.5 mg/day (n = 97), venlafaxine XR 75 mg/day (n = 96), or placebo (n = 146) for 8 wks
 - escitalopram 10-20mg/day: effects on sleep quality and HR-QOL
 - paroxetine 7.5mg daily on sleep
 - eszopiclone 3mg daily: sleep parameters, depressive symptoms, anxiety symptoms, quality of life, and nighttime but not daytime hot flashes.
- Clonidine, gabapentin
- Placebo
- Lifestyle: AC, layers, cool rooms, cool drinks, cool packs, swimming
- CAM: omega 3, yoga, exercise, perhaps not effective

Joffe et al, Am J ObGyn 2010; Joffe et al, JCEM 2011
Pinkerton et al, Menopause 2015; Ensrud et al, Sleep 2015

TO HRT OR NOT HRT?



HRT: FORMULATIONS

Types:

- Estrogen therapy (ET)
- Combined estrogen–progestogen (EPT) therapy

Administered:

- Orally (ET and EPT)
- Vaginally (ET)
- Transdermally (low dose estrogen)

HRT: BENEFITS

- **Vasomotor symptoms**
 - Most effective treatment (ET with or without progestogen)
- **Urogynecological symptoms**
 - Vulvar and vaginal atrophy
 - Moderate-to-severe (local vaginal ET, systemic HRT)
 - Bladder
 - Overactive bladder (local ET; systemic HRT may provoke or worsen stress incontinence)
 - Reduces risk of recurrent UTIs (vaginal ET)
- **Bone health**
 - At low doses, maintains or improves bone mineral density (BMD)
 - At standard doses, reduces postmenopausal osteoporotic fractures even in women without osteoporosis.
- **Venous thromboembolism and stroke**
 - In observational studies at least (transdermal and low-dose ET)
- **Libido**
 - No report of significant improvement
 - Low dose local ET may improve vaginal symptoms such as lubrication, blood flow and sensation
- **HR-QOL in symptomatic menopausal women**

NAMS, Menopause, 2012

HRT: RISKS

- Unopposed systemic ET in postmenopausal women with an intact uterus is associated with increased endometrial cancer risk; concomitant progestogen recommended
- EPT initiated close to the onset of menopause may be associated with an increased risk of breast cancer; this increased risk has not been observed in ET.
- HRT use in breast cancer survivors may be associated with an increased risk of recurrence.
- EPT use for longer than 5–10 years may be associated with an increased risk of ovarian cancer, although the incidence rate is rare. There may also be increased risk of lung cancer, or of more aggressive lung cancer, particularly in smokers.
- Currently, HRT is considered primarily in women ages 50–59 years, within 10 years of menopause. In this age group, HRT used for menopausal symptoms is not felt to increase the risk of CHD events, and in fact ET initiated early postmenopausally may reduce coronary artery disease and CHD risk

NAMS, Menopause, 2012

HRT: A PRACTICAL APPROACH

- Individualized approach
- Communication with PCP
- Treat the symptoms
 - As low a dose as possible
 - As short duration as possible

... but ...

HRT: CONSIDERATIONS FOR NEURODEGENERATION

- Observational studies:
 - “Window of opportunity” (within 5 years of LMP) against AD
 - Beyond this, perhaps due to estrogen receptor down-regulation, HRT may even be harmful
 - increased risk of stroke and dementia
- Women’s Health Initiative Memory Study (WHIMS)
 - (1) unopposed estrogen and (2) EPT compared with placebo
 - HRT initiated in women aged 65 years or above was associated with an increased risk of dementia of any cause and of cognitive decline
- Need results from: longitudinal placebo-controlled trials of the effects of HRT, initiated within the “window of opportunity,” on long-term risk of cognitive decline

Rocca et al, Brain Res 2011; Craig et al, Lancet Neurol 2005;
Henderson J Ster Biochem Mol Biol 2013;

SYMPTOM: SLEEP

Primary triggers

- Vasomotor symptoms: frequent awakenings
- Bladder symptoms: frequent awakenings
- Sleep apnea: postmenopausal F rates approach M

- Mood disturbances (depression and anxiety)
 - Difficulty falling asleep; early rising
- Relational (interpersonal, co-sleeping habits)
- RLS
- Other (lifelong insomnia, family history)

?Impact on MS symptoms, mood, repair

Vousoura et al, Menopause 2015

SYMPTOM MANAGEMENT: SLEEP

- Identify and assess triggers
- Consider counseling and/or sleep consultation
- Pharmacological
 - Considerations:
 - 'get over the hump' vs. longer
 - Minimize doses in women
 - Sleep initiation vs. maintenance (need longer t1/2)
 - Comorbidities:
 - Anxiety -> antidepressant
 - RLS -> gabapentin
 - Classes:
 - Benzodiazepines
 - Non-benzodiazepine
 - TCAs, SSRI, SNRIs

SLEEP HYGIENE

- Determine time in bed (7-9 hrs), do not stay in bed longer
- Use bed for **sleep/intimacy** only
- Turn clock, so it is not visible from the bed
- Naps, if taken at all, should be early afternoon at latest
- Schedule regular wake times
- Cool room
- Allow ample amount of light during the day
- Allow dimmer light in the evening
- Moderate or limit caffeine - last intake at noon
- Moderate alcohol – best not close to bedtime

Courtesy Milena Pavlova, MD, BWH

SYMPTOM: MOOD

OVERLAP

- Late perimenopause especially: may experience an increase in depressive and anxiety symptoms
- Interpersonal and physical changes, self perception
- MS: Higher prevalence of anxiety and depression (50%)
 - May be under-diagnosed and under-treated
- Depression influences the severity of other MS symptoms
 - Strong predictor of cognitive and sexual dysfunction
 - Period of particular vulnerability to increased or more severe affective symptoms?

SYMPTOM MANAGEMENT: MOOD

- **Psychotherapy**
 - Optimize coping abilities, spousal/family/interpersonal support, sleep patterns, and other factors
- Antidepressants
 - (fluoxetine, sertraline, escitalopram, citalopram, venlafaxine, bupropion)
- Support groups
- Fatigue and sleep optimization
- Social work regarding employment stressors

SYMPTOM: COGNITION

Overlap

- With menopause, women may report:
 - Changes in attention, executive function, multi-tasking, word finding difficulties, memory
 - Particularly in the first year after FMP
- Approx ½ MS patients experience some degree of cognitive impairment.

Approach

- Neuro-cognitive testing may help to identify particular areas of dysfunction
- Cognitive rehabilitation (formal or informal) – increasing evidence for a positive effect
- Address: sleep issues (night sweats, restless leg syndrome), fatigue, mood and pain

SYMPTOM MANAGEMENT: BLADDER

Overlap

- Menopause:
 - Bladder irritability and incontinence (stress and urge).
 - Increased recurrent UTIs – from urologic changes, decreased mobility and perhaps immune suppression?
- MS: baseline bladder dysfunction may be magnified
 - MS relapses: typically have urgency/frequency/urge incontinence; more acute
 - Urodynamic testing

Approach

- **Lifestyle: fluid intake; weight loss**
- Bladder training, frequent voiding to keep bladder volume low
- Pelvic muscle exercises (Kegel's) - with referral to a therapist
- Biofeedback
- Perhaps: local estrogen, or antibiotic prophylaxis, in more disabled patients
- Botulinum injection
- Pharmacology
 - Antimuscarinics, TCAs, antispasmodics

SYMPTOM MANAGEMENT: PAIN SYNDROMES

Pain syndromes

- Pain tolerance may decrease
 - Arthralgias, myalgias, MSK pain
- MSK pain
 - Cervical and lumbar spondylosis, joint immobility, spasticity, deconditioning due to fatigue/weakness
- Neuropathic symptoms, paresthesias

Approach

- Pharmacology
 - Pain triggered by spasticity: baclofen (consider intrathecal for severe), diazepam, dantrolene, tizanidine
 - Neuropathic pain and paresthesias: phenytoin, carbamazepine, TCAs (amitriptyline and nortriptyline), gabapentin and pregabalin, duloxetine
- MSK pain: integrated approach at a pain center
- Weight loss, exercise
- Evaluation for osteopenia
- Evaluation for rheumatologic disorders
- PT, massage therapy to improve joint mobility and spasticity

SYMPTOM MANAGEMENT: FATIGUE

Overlap

- Common in MS
- Tends to increase in severity and frequency at menopause

Approach

- Rule out additional contributors, such as thyroid disease
- Contributing factors: sleep, mood, pain, spasms, bladder, hot flashes
- Daily schedule: space out work routines, intermittent rest breaks, maximize activities in cooler morning
- Mind-body techniques (relaxation and meditation practices): reduce stress and decrease fatigue
- Pharmacology:
 - Wakefulness promotion (modafinil, amantadine)
 - Stimulants (methylphenidate)

SYMPTOM: SEXUAL DYSFUNCTION

OVERLAP

MENOPAUSE

- Decreased libido/arousal
- Atrophic vaginitis
- Inadequate vaginal lubrication
- Occasionally - breast tenderness - masquerade as a thoracic sensory level

MS

- Effects of decreased self-esteem or body image, changes in physiologic function, concern about bladder symptoms, and decreased intimacy and inter-partner communication.
- Spinal cord lesions - disturbances in genital sensation, arousal, and orgasm

Foley et al, in Primer on MS 2011
Ben-Zacharia AB Mt Sinai J Med 2011

SYMPTOM MANAGEMENT: SEXUAL DYSFUNCTION

APPROACH

- Combination therapy to increase arousal, orgasmic response, intimacy, inter-partner communication
- Sexual therapy
- Couples therapy
 - mutual support, communication, stress and anger management
 - sexual feelings, attitudes that interfere with enjoyment (goal oriented sex, intimacy vs. sex), body image and (dys)function
- Patient education and guided counseling (bodymapping, pelvic floor techniques)
- Medical management
 - Parasthesias – neuropathic pain medications
 - Decreased sensation – vibrators, other devices may increase stimulation
 - Vaginal dryness – water-soluble lubricants

Foley et al, in Primer on MS 2011
Ben-Zacharia AB Mt Sinai J Med 2011

ASK ABOUT OTHER S/Sx

- Headaches
 - “estrogen withdrawal” headaches
- Epilepsy
 - 2% MS patients
 - Catamenial seizures: may increase peri-, decrease post-menopausally
- Gastrointestinal
 - Functional, dysmotility

OSTEOPOROSIS

OVERLAP

- Postmenopausal increase: fractures, morbidity and mortality
- MS:
 - Cumulative impact of steroid use (particularly if diagnosed pre-DMT), sedentarism and deconditioning
 - Balance, visual, strength or cognitive impairments=> gait issues, compound risk of falls

APPROACH

- Behavioral strategies: Ca, vitamin D intake; smoking cessation; avoid alcohol
- Fall precautions: home safety evaluation, PT for gait training, and eye evaluation
- Pharmacological therapy (NAMS recommendations)
 - Densitometric diagnosis (BMD testing by DXA of hip, spine and radius)
 - Therapy indicated in postmenopausal women with specific scores

NAMS, Menopause, 2012

OSTEOPOROSIS

Options

- Bisphosphonates: first line therapy
- Parathyroid hormone (PTH 1–34, teriparatide, *FORTEO*®) in severe osteoporosis.
- SERMs (mainly vertebral fractures)
- Monoclonal antibody denosumab.
- Calcitonin: 2nd line, recommended in women 5+Y from FMP
- Systemic HRT effective, with a 27 % reduction in fracture – consider in early menopause until reach age 51

NAMS, Menopause, 2012

OTHER NEEDS OF POSTMENOPAUSAL WOMEN (//aging)

- Co-Morbidities
- Diagnostic neglect, e.g. preventive cancer screening
 - Women with disabilities less likely to be up to date
 - Pap tests (even f/c demographic, geographic, SES)
 - Mammograms
 - Magnitude of disparities greater for women with complex limitations.
 - Lower cancer risk, but larger tumor size at diagnosis
 - Patient (e.g. discomfort) or physician (e.g. time, equipment) factors?
- Mortality
 - Elevated risk of death:
 - Cardiovascular diseases, suicide, infection and respiratory diseases
 - 10-year Framingham General Cardiovascular Disease Risk Score
 - Elevated in SPMS relative to RRMS
 - Correlates with EDSS and MSSS
 - Smoking, HTN, CVD: elevated in MS, correlate with brain atrophy and lesion burden

Horner-Johnson et al, Womens Health Issues 2014
Kingwell et al, JNNP 2012; Manouchehrinia et al, JNNP 2015
Kappus et al, JNNP 2015; Moccia et al, Eur J Neurol 2015

SUMMARY

- Many women living with MS are peri- or postmenopausal.
- Domino symptoms
 - Menopausal and MS symptoms may overlap; these may include sleep, affective and sexual complaints.
 - Hot flashes perimenopausally may exacerbate MS symptoms.
- The MS clinician may play an important role in managing these symptoms.
 - Anticipate
 - **RAISE THE QUESTIONS** (even if referring onwards for care)
 - Communicate with PCP
 - Consider referrals
 - Urology, sleep, social work, neuropsychology
- Interventions include lifestyle changes and pharmacologic treatments.
 - Polypharmacy should be avoided.
- Osteoporosis screening should be encouraged.

THANK YOU AND QUESTIONS