Women Veterans and MS: MS susceptibility and treatment considerations

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Birmingham VA Medical Center
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Disclosures

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• Grant research from BiogenIdec

PESG and PVA staff have no interest to disclose.

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Learning objectives

1. Examine the role of gender and sex hormones in MS susceptibility
2. Discuss differences in disease course between men and women
3. Review MS disease modifying drugs and their potential impacts on childbearing and fertility
Why should the DOD and the VA care about MS?

- MS is not that common
  - Prev. approx 1:1000
- MS affects mostly women
  - military mostly ♂
  - MS ratio ♀:♂: 2-3:1
- MS is less common in non-white minority groups
  - The military is increasingly diverse
Women’s Growing Presence, 1973-2010

Number of female enlisted, commissioned officers

- Enlisted
  - 12,750 in 1973
  - 42,278 in 1983
  - 195,532 in 2003
  - 166,729 in 2010

- Officers
  - 2.2% in 1973
  - 4.2% in 1983
  - 14.1% in 2003
  - 16.4% in 2010

Women’s Growing Share, 1973-2010

% of enlisted, commissioned officers who are women

Note: Middle data label for enlisted is the highest number of women, 1989. Trend for officers includes only commissioned officers, not warrant or non-commissioned officers.


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Women as veterans (2010 estimates)

- Total veterans
  - 22 million
  - 1.8 million women (8%)

- Post-9/11 veterans
  - 2.2 million
  - >400,000 women (19%)
  - Almost ¼ of total female veteran population

MS among military-connected women

- **Current active duty**
  - 201,400 women (1/2015)
  - 270-400 eventual MS

- **Post-9/11 veterans**
  - 800-1200 ♀ with MS

- **Total veterans**
  - 2400-3600 ♀ with MS
Gulf War cohort (1990-2007)

<table>
<thead>
<tr>
<th>Group</th>
<th>World War II and Korean Conflict adjusted case-control ratios</th>
<th>Vietnam and later adjusted case-control ratios</th>
<th>Gulf War era relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White males</td>
<td>1.00*</td>
<td>1.00*</td>
<td>1.00*</td>
</tr>
<tr>
<td>Black males</td>
<td>0.44</td>
<td>0.67</td>
<td>1.16 (1.03–1.30)</td>
</tr>
<tr>
<td>Other males</td>
<td>0.22</td>
<td>0.30</td>
<td>0.77 (0.65–0.92)</td>
</tr>
<tr>
<td>White females</td>
<td>1.79</td>
<td>2.99</td>
<td>3.54 (3.20–3.91)</td>
</tr>
<tr>
<td>Black females</td>
<td>1.28</td>
<td>2.86</td>
<td>3.62 (3.18–4.11)</td>
</tr>
<tr>
<td>Other females</td>
<td></td>
<td>(3.51)c</td>
<td>1.98 (1.52–2.58)</td>
</tr>
</tbody>
</table>

Why should the DOD and VA care about women and MS?

- Women comprise growing proportion of active duty military
- The prevalence of MS is increasing among women
- The Veterans Administration will be caring for an increasingly large number of female MS patients for years (decades) to come
- MS is a life-long disease, with high treatment costs
Why should we try and understand the differences in MS risk between men and women?
Why does female sex increase risk of MS?

- **Unmodifiable risk factors?**
  - Genetic predisposition
  - Hormonal differences

- **Modifiable risk factors?**
  - Behaviors: smoking
  - Exposures: combat stress, communal living
MS and female sex hormones

- MS risk equal among pre-pubescent boys and girls, increases for girls after menarche\(^1\)
- ♀:♂ ratio for late-onset MS declines after menopause (2.8:1 to 1.9:1)\(^2\)
- Late-onset MS in women more likely to be progressive, motor\(^3\)
- Symptom burden may increase after menopause\(^4\)

MS and pregnancy

McCombe and Greer, Mult Scler 2013; 19:392-402.
4 cohort studies (3 UK, 1 US) – OCP use not linked to increased MS rate

- OCP use + pregnancy may delay onset of MS
- Mixed results on OCPs effects on disease course

Prevention of ante- and post-partum relapses

- Definitive studies are lacking
- Approaches with limited evidence:
  - Monthly IV methylprednisolone (1g) x 6 resulted in >50% fewer relapses among 20 women compared to 22 untreated women
  - IVIG administered during pregnancy or post-partum may decrease relapse rates

FDA Drug Risk Classification for medications during pregnancy

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Controlled studies in humans show no risk to the fetus</td>
</tr>
<tr>
<td>B</td>
<td>No controlled studies have been conducted in humans; animal studies show no risk to the fetus</td>
</tr>
<tr>
<td>C</td>
<td>No controlled studies have been conducted in animals or humans</td>
</tr>
<tr>
<td>D</td>
<td>Evidence of human risk to the fetus exists; however, benefits may outweigh risks in certain situations</td>
</tr>
<tr>
<td>X</td>
<td>Controlled studies in both animals and humans demonstrate fetal abnormalities; the risk in pregnancy women outweighs any possible benefit</td>
</tr>
</tbody>
</table>
### MS therapeutics: pregnancy and childbearing

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Pregnancy category</th>
<th>Breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-interferons (β-1b, β-1a IM, β-1a SQ)</td>
<td>C</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>B</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>D</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>C</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>C</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>X</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>C</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>C</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
Beta-interferons

- Best-studied drug among pregnant MS patients (multiple international cohorts)
- No increased rate of fetal anomalies, low birth weight, pre-term or cesarean births
- Possible increased risk of spontaneous miscarriage

No evidence of harm found to date from several international observational cohorts

No increased risk found for low birth weight, congenital abnormalities, lower gestational age, preterm birth, or miscarriage

Fingolimod, dimethyl fumarate, natalizumab, alemtuzumab

- Insufficient or lacking data
Mitoxantrone

- Chemotherapeutic agent
  - Type II topoisomerase inhibitor, disrupts DNA synthesis and repair
- Risk of amenorrhea
- Teratogenic
Teriflunomide

- Blocks pyrimidine synthesis and thereby diminishing DNA synthesis; reduces activated T and B cells
- Teratogenic based on effects in rats, rabbits, and mice
- Women and men are advised to use contraception when taking Teriflunomide
- Clearance protocol
Teriflunomide clearance

- Pre-conception:
  - Long half-life (18-19 days); may take up to 2 years to reach concentrations <0.02 mg/L (recommended safe level for conception)

- Post-conception/accelerated clearance protocol:
  - Cholestyramine 8 grams orally tid x 11 days
  - Or 50 grams activated charcoal powder orally q 12 hours x 11 days
  - Verify drug concentration <0.02 mg/L x 2, 2 weeks apart
Conclusions

- Women will make up an increasing proportion of the VA MS population.
- Increasing evidence points to a role of sex hormones in MS susceptibility as well as a role for disease modification.
- The disease course in women is influenced by reproductive hormone cycles, pregnancy, and menopause.
- Use of DMTs during pregnancy is generally not advised; drugs with clear teratogenic potential such as mitoxantrone and teriflunomide should be avoided when pregnancy is a possibility.
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http://PVA.cds.pesgce.com
Women Veterans with MS Comorbidities & Wellness Interventions

Lynda Hillman, DNP, ARNP, MSCN
VA MS Center of Excellence – West

PVA Summit 8/31/2016
Disclosures

Dr. Hillman: no interest to disclose.

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Learning Objectives

1. Discuss common comorbidities of women MS Veterans and the issues associated with preventative care and modifiable risk factors.

2. Learn key interventions to improve overall health status of women MS Veterans.
1-Minute Version

- Comorbidities adversely impact MS.
- Communication with Primary Care is important.
- Interventions which help reduce comorbidities also help improve MS disease course.
Common Comorbidities of Women Veterans

- Alcohol Use Disorder
- Arthritis
- Cardiovascular Disease (HTN, Dyslipidemia, Diabetes Type 2)
- Depression/Anxiety
- Hip fractures
- Obesity
- Pain
- PTSD
- Pulmonary Disease
- Sedentary Lifestyle
- Smoking

(Bastian et al., 2016; McCauley et al., 2015, Reiber et al., 2016)
Symptom Overlap with Comorbidities & MS

- Anxiety
- Depression
- Fatigue
- Memory impairment
- Mobility deficits
- Pain/Sensory disorders
- SOB
Comorbidity
Speeds MS Disability Progression

- Vascular comorbidities significantly impact MS.
- Use of cane 6 years earlier.
- Increased risk of visual deficits.

(Marrie et al., 2010, 2011)
Autoimmune Comorbidities in MS

- Meta-analysis – limited data due to design quality and population size of studies.
- Most common: inflammatory bowel, uveitis, thyroid disorders and psoriasis.
- Prevalence ~5% or less of MS population studied.
- No clear increased risk for A-I d/o.

(Marrie et al., 2015)
# Health Screening Recommendations

(for women at average risk)

http://www.womenshealth.gov/ & U.S. Preventive Services Task Force (USPSTF)

<table>
<thead>
<tr>
<th>Screening</th>
<th>How often?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-woman visits</td>
<td>annually</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>every 1 - 2 yrs</td>
</tr>
<tr>
<td>Cervical cancer screening (Pap test)</td>
<td>age 21 – 39 every 3 yrs</td>
</tr>
<tr>
<td></td>
<td>age 40 – 64 every 5 yrs</td>
</tr>
<tr>
<td></td>
<td>(with HPV)</td>
</tr>
<tr>
<td>Human papillomavirus (HPV)</td>
<td>age 40 – 64 every 5 yrs</td>
</tr>
<tr>
<td></td>
<td>(with Pap test)</td>
</tr>
<tr>
<td>Screening</td>
<td>How often?</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Mammography</td>
<td>age 50 – 74 every 2 yrs</td>
</tr>
<tr>
<td>Bone mineral density</td>
<td>age 65</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>yearly thru age 24 if</td>
</tr>
<tr>
<td></td>
<td>sexually active or pregnant</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>age 50 - 74</td>
</tr>
<tr>
<td>fecal occult blood testing</td>
<td>yearly</td>
</tr>
<tr>
<td>sigmoidoscopy</td>
<td>every 5 yrs</td>
</tr>
<tr>
<td>colonoscopy</td>
<td>every 10 yrs</td>
</tr>
<tr>
<td>HIV</td>
<td>at least once, &amp; if pregnant</td>
</tr>
</tbody>
</table>
Persons with disabilities receive less health screening and care.

Why?

- Can’t drive safely.
- Unable to transfer.
- No lift available.
- Cognitive decline.
- Caregiver not available.
- Incontinence.
- Pain from spasticity.
- Visual deficits.
- Fatigue.
- Exam requires extended time.

(Horner-Johnson et al., 2014)
Fracture & Osteoporosis Risk in MS

- Danish MS Registry, n=2,963, majority female. No increased risk of fracture until EDSS 6+. Then 2.6 X risk hip/femur fracture.
- European study n=912, majority female, higher levels of osteoporosis in MS vs general population.
- Steroid use? Not significant unless long term.

The Most Important Modifiable Risk Factors for Fractures

- Falls.
- **Sedentary lifestyle** – insufficient *weight-bearing* exercise leads to:
  - Weakness.
  - Imbalance.
  - Poor proprioception.

(Karis et al., 2014; US HHS)
Modifiable Risk Factors for Osteoporosis

- Smoking.
- Excessive alcohol use.

(Karis et al., 2014; US HHS)
Interventions to Reduce Fracture & Fall Risk

- Active lifestyle with:
  - weight-bearing (bone-jarring) exercise.
  - resistance exercise.
- Smoking cessation.
- Moderate or no alcohol use.
- Healthy diet with sufficient nutrients.

USPSTF recommendations on Vit D and Ca+ supplementation are being updated.
Exercise is Medicine

Physical activity helps improve:

- CVD/Dyslipidemia/HTN/Diabetes
- Cognition
- Depression/Anxiety
- Fatigue
- Obesity
- Pain
- Weakness
Exercise is Medicine

Emerging research on brain-derived neurotrophic factor (BDNF)

- Thought to be neuroprotective.
- 21% lower in MS compared to healthy controls.
- Increases with endurance and resistance training over 24 wks in persons with MS.

(Szuhaney et al. 2014; Wens, 2016)
Healthy Diet and MS

• No clear evidence yet for particular diet which improves overall MS disease course.
• Fatigue improved with low-fat, plant-based diet.
• However – good evidence for diets which improve comorbidity risks in general population.

(Yadev, et al., 2016)
Diet & Cognition

“MIND diet slows cognitive decline with aging”

- Length of study: >4.7 yrs; $n = 960$.
- Components of Mediterranean & DASH diets which lower inflammation and risks of HTN, CVD, DM.
- Neuroprotective effects.
- MIND diet effect equivalent to ~7.5 years younger.

(Morris et al, 2015)
Comorbidities in MS

- Be aware of comorbidities and impact on MS.
- Educate about impact of comorbidities.
- PCPs and MS specialists – discuss who covers which conditions.
- “Multicondition models of care may be more effective than usual primary care.”

(Bastian et al., 2016)
Take-Home Points

- Comorbidities adversely impact MS.
- Communication with Primary Care is crucial.
- **3 best interventions for MS:**
  - physical activity.
  - smoking cessation.
  - healthy diet.
Thank you.


LaFleur, J. et al. Fracture Rates and Bone Density Among Postmenopausal Veteran and Non-Veteran Women From the Women’s Health Initiative. Gerontologist, 2016, (56) 1, S78-S90.


Weitlauf, J. C., et al. Who are the Women Veterans in the Women’s Health Initiative? *Gerontologist,* 2016, (56), S1, S6-S9.

CE/CME Credit

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Challenges in Addressing Sexual Health in Women Living with Multiple Sclerosis

Kathleen Burgess, MD, MS
Puget Sound Health Care Systems
Kathleen.burgess@va.gov
Intimacy, sexuality and quality of life
Disclosures

- Kathleen Burgess, MD, MS has no interest to disclose.
- This continuing education activity is managed and accredited by Professional Education Services Group in cooperative with PVA. PESG, PVA and all accrediting organization do not support or endorse any product or service mentioned in this activity.
CE/CME Credit

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Learning Objectives:

• At the conclusion of this activity, the participant will:
  • Use a model to characterize causes of sexual dysfunction in women living with MS
  • Identify common barriers to discussing sexual dysfunction between HCP and patients
  • Identify potential treatments for sexual dysfunction
Outline

- Challenge: Define the problem
- Model for characterizing the source of sexual dysfunction
- Challenges associated with discussing the topic
- Treatment
Challenge: Defining the problem
Sexual health: What is it?

- Sexual functioning
- Intimacy
- Satisfaction
- Sexual orientation
- Who defines it
- What if we disagree
- How do I recognize my biases
Sexual Dysfunction with MS

• NOT MS 44% of women 18 or older
• Prevalence of 40 to 80% of women with MS
• May be more prevalent with disease duration
• Can occur early in disease process

Normal sexual response: Masters and Johnson

Thomas and Thurston 2016
## Biopsychosocial model of sexuality

<table>
<thead>
<tr>
<th>Biology: physical health, physiology</th>
<th>Psychology: anxiety, depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociocultural: personal values, cultural norms</td>
<td>Interpersonal: life stresses, quality of relationship, past experiences</td>
</tr>
</tbody>
</table>

Thomas and Thurston 2016
The Challenge: Sexual Dysfunction Framework

- **Primary:** Due to MS related neurologic changes
- **Secondary:** Due to symptoms or treatment
- **Tertiary:** Due to cultural, psychological, emotional and social issues
Primary Sexual Dysfunction in Multiple Sclerosis

- Brain and spinal cord lesions:
  - affect genital sensation
  - affect transmission of nerve signals
- Brain lesions can affect libido
Primary Sexual Dysfunction Effects

- Decreased interest or arousal
- Decreased vaginal lubrication and engorgement
- Decreased vaginal muscle tone
- Sensory changes in the vaginal area
- Decreased intensity or frequency of orgasms

Orasanu B et al. 2013
Secondary Sexual Dysfunction

- Cognitive changes
- Fatigue
- Spasticity
- Bowel and bladder changes

- Tremor
- Medications
- Weakness
- Pain
Medications Associated with Sexual Dysfunction

- SSRIs-
- Antipsychotics
- TCA
- Trazodone
- Venlafaxine
- Beta blockers
- Anticholinergics

- Anti-lipids meds
- Hormonal meds for breast cancer
- Antihistamines
- Amphetamines
- Opiates
- H2 blockers

Buster 2013, Ward-Abel and Hall 2012
Secondary Sexual Dysfunction due to sx or tx NOT MS

- Diabetes
- Hypertension
- Obesity
- Hypopituatarism
- Hypothyroidism
- Breast cancer medications
- Substance abuse

Buster 2013
Secondary Sexual Dysfunction
NOT MS

- Depletion of estrogen
  - Insomnia
  - Mood swings
  - Depression
  - Irritability
  - Memory lapses
  - Atrophic vaginitis and dyspareunia
Tertiary Sexual Dysfunction

- Unhappy life events, finances
- Unsafe relationship vs stable
- Caregiver is also lover
- Past relationship experiences
- Self-esteem
- Body image
- Cultural norms
- Uncertainty about the future
Challenge: Why aren’t we talking about it?

• I have to talk about it?
The Challenge: Provider Associated Barriers

- Don’t understand importance of sex/intimacy
- Don’t know how to deal with the answers
- Single cause and single solution unlikely
- “Silent symptom”
- Lack of training
- Fear of offending the patient
- Uncomfortable with the topic
The Challenge: Patient Associated Barriers

- Sexual dysfunction is a part of aging
- No treatments available
- Fear of embarrassing the provider
- Cultural stereotypes
- Family members in the room
- Lack of time in clinic visit
Starting the conversation

Talking with Your MS Patients about Difficult Topics

Talking about Sexual Dysfunction

Frederick Foley, PhD
Putting it all together:

- Assess your biases and concerns
- Assess for primary, secondary and tertiary causes
- Sexual history, psychosocial/family history, couple’s interview
- Medication review
- Assess need for OB/Gyn eval
Treatments
Treatment for any issue with MS

- Communication
- Experimentation
- Set a goal
- Focus on what you can do: intimacy versus sexual intercourse
Treatments for Primary Sexual Dysfunction in MS

- Phosphodiesterase type 5 inhibitors not FDA approved for women
- Neuropathic pain medications for painful paresthesias
- Use of vibratory stimulators
- Water soluble lubricants
- Body mapping
Primary Sexual Dysfunction tx: Eros CTD
Txs for Secondary Sexual Dysfunction in Women with MS

- Transdermal estrogen, intravaginal estrogens
- Testosterone for women not yet FDA approved
- Catheter management
- Position changes to accommodate weakness or spasticity
Treatments for Secondary Sexual Dysfunction

- Minimize distractions and create ways to re-engage
- SSRI medication holiday for a day
- Try low dose bupropion
- Fatigue management strategies
Txs for Tertiary Sexual Dysfunction in MS

- Reassurance
- Counseling alone or with partner
- Cognitive behavioral therapy
- Stress management
- Support for care giver’s role
Summary

- Intimacy and sexual functioning are significant components to quality of life.
- Challenging to diagnose the problem.
- Challenging to start the discussion.
- Can be addressed over multiple visits.
- Treatment options are varied and available.
Thank you
references

- Thomas HN, Thurston RC. A biopsychosocial approach to women’s sexual function and dysfunction at midlife: A narrative review. Maturitas. 2016;87:49-60
Initiating the Conversation

- **When**
  - First visit, changes in meds, changes in function

- **How**
  - Many women experience decreased desire on this medication. Is that a problem for you?
  - Body posture, eye contact
  - Ask open ended questions and endure the silence
Initiating the conversation

- What
  - Normalization of the problem
  - Complexity of the problem
  - Your support
- Education
  - Face to face
  - Printed literature
  - videos