ACOFP Men's Health Issues Committee: Neurologic Differences Men vs. Women

Mark Klafter, DO
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Please check where applicable and sign below. Provide additional pages as necessary.
Name of CME Activity: 2015 AOA/ACOFP Osteopathic Medical Conference & Exposition (OMED)

Dates and Location of CME Activity: October 17 - October 21, 2015 Orange County Convention Center, Orlando, Florida
Topic: ACOFP Men's Issues Committee: Neurologic Differences Between Men vs. Women Tuesday, October 20, 2015, 3:00-4:00 pm
Name of Speaker/Moderator: Mark Klafter, DO

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- Others, please list:

Please indicate the name(s) of the organization(s) with which you have a financial relationship or interest, and the specific clinical area(s) that correspond to the relationship(s). If more than four relationships, please list on separate piece of paper:

<table>
<thead>
<tr>
<th>Organization With Which Relationship Exists</th>
<th>Clinical Area Involved</th>
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<tr>
<td>2. Teva Pharmaceuticals</td>
<td>2. Speaker's Bureau</td>
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<td>3. Allergan</td>
<td>3. Speaker's Bureau</td>
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*If you checked "Speakers' Bureau" in item B, please continue:
• Did you participate in company-provided speaker training related to your proposed topic?  Yes: No:
• Did you travel to participate in this training?  Yes: No:
• Did the company provide you with slides of the presentation in which you were trained as a speaker?  Yes: No:
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Various migraine preventatives and medications for encephalomalacia. For further use

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Signature: Mark Klafter, DO
Date: 9/1/15

Please fax this form to ACOFP at 866-328-1835, or e-mail to joank@acofp.org as soon as possible.
Deadline: Friday, September 11, 2015.

ACOFP Men’s Issues Meeting:
Neurologic Differences Between Men and Women

Mark J. Klafter, D.O.
Neurological Services of Orlando
Asst. Professor of Neurology University of Central FL
Courtesy Professor, University of Florida

Topics

• Differences in Brain Anatomy/Physiology
• Pathological Differences in Presentation, Progression of various disease processes
• Management Based on Various Factors: side effect differences (tolerability), practicality and efficacy
• Public Health implications (example: stroke)
Physiologic Gender Differences:

• *University of Pennsylvania* study in 2013: Using diffusion tensor imaging of 949 individuals aged 8–22 years, mapped difference in male and female neural wiring, found

A) **inter-hemispheric** connectivity was greater in women's and girls' brains

B) **intra-hemispheric** connectivity was greater in the brains of men and boys. The effect was reversed in **cerebellar** connections

? multi-tasking vs. focus?

? analysis vs. coordinated action?


Cognitive approach - functionality

• Example: Studies using the **Iowa gambling task**, or Iowa Card Task, have examined cognitive reasoning and decision-making in males and females. A study in which participants of various age groups who were asked to perform the Iowa Card Task produced data showing that males and females differ in their decision making processes on the neurological level.

• A) decision-making in **females** may be guided by avoidance of negativity

• B) decision making in **males** is mainly guided by assessing the **long term outcome** of a situation.

(they also found that males outperformed females in the Iowa Card Task)

**MANY** studies show that females remember rote lists and objects, with males memory being 3 dimensional or visual/spacial-based

Anatomical Differences:

• Amygdala
• Hippocampus
• Limbic system
• Orbital pre-frontal cortex
• Grey/white matter ratios – and rate of grey matter loss with development of neurological disorders

Disease processes will include:

• Alzheimer’s and other dementias
• Parkinson’s, Essential tremor
• Epilepsy
• Migraine and other headache conditions
• PNS (peripheral nervous system) topics to include neuropathies and myasthenic syndromes
• Stroke: prevention and life expectancy
• Other topics, Q & A
ALZHEIMER’S DISEASE
Gross Brain at Autopsy
• Note the generalized cerebral cortical atrophy.

ALZHEIMER’S DISEASE
Microscopic Disease

• Photomicrograph of entorhinal cortex in Alzheimer's disease. The neuritic plaque is composed of an amyloid core surrounded by dystrophic neurites. The dark flame-shaped fibrillar structures are neurofibrillary tangles, which are chiefly made up of paired helical filaments.
ALZHEIMER’S DISEASE (AD)

– Clinical:
Subtle memory loss followed by slowly progressive dementia

• Aphasia may be prominent, starting with word finding
• Apraxias present - performing sequential tasks (dressing etc)
• Delusions are common LATER, with occasional hallucinations (early hallucinations suggest Lewy Body dementia)

– Genetics: Four different “susceptibility” genes: apolipoproteins (apolipoprotein E4 homozygous: HIGH risk)

ALZHEIMERS DISEASE

Treatment

- ANTICHOLINESTERASE – results in increase in acetylcholine in brain:
  Aricept (donepezil)
  Razadyne (galantamine)
  Exelon (rivastigmine) – GI side effects generally less in men, and now rivastigmine available in patch

- NMDA ANTAGONIST - Namenda (memantine) – well tolerated, adjunctive, occasionally stimulating
  (recently available is combination memantine/donepezil combination)
  Axona – medical food relying on alternative source via ketone bodies (proprietary formulation of coconut oil)
Risk factors beyond Apolipoproteins: 

— **AGE**: Incidence: 10% of pts > 70 yrs old; 40% if > 80 yrs old *(greatest risk factor is age)*

**GENDER**: Women have a higher rate of AD, even when correcting for age and matching with Apoliprotein type

As presented at AAIC (Alzheimer’s Association International Conference), July, 2015 —

A) Women with MCI (Mild Cognitive Impairment) decline dramatically faster in cognition, function and brain size.^[^]

B) This is exacerbated post-surgically.^^

• ^ Lin, Duke University ADNI study, unpublished
• ^^Schenning, Oregon Health & Science, unpublished
• (data available through the Alzheimer’s Association)

**AD management implications re: gender**

Should men and women be treated differently pharmacologically, or by other means (dietary, activities, etc.)

More questions than answers at this stage regarding neuropharmacology, but INDIVIDUALIZING patient/family needs at forefront. Understand behavioral implications:

Driving and other safety concerns, disinhibition, mood/affect
PARKINSON’S DISEASE

• An isolated **Lewy body**, a distinctive eosinophilic cytoplasmic inclusion body found in the substantia nigra of Parkinson's disease

• Known to be more common in **men** – especially the bradykinetic form

PARKINSON’S DISEASE

• Syndrome of a combination of
  • **Tremor at rest** – relatively slow
  • **Rigidity**
  • **Bradykinesia**
  • **Characteristic disturbance of gait and posture** (ABOVE ARE “CARDINAL” SIGNS)
    • Flexed posture of neck, trunk and limbs
    • Loss of postural reflexes
    • Freezing
  • Also **dysautonomia** (constipation, orthosatic bp drops, erectile dysfunction, flushing, etc.)
PARKINSON’S DISEASE  Treatment

• **Levodopa** (L-DOPA) = precursor of Dopamine
  – Best for bradykinesia – more common presentation in men
  – Need a dopa decarboxylase inhibitor (*carbidopa*) as L-DOPA will be metabolized otherwise
    • “Sinemet” is a combination of this inhibitor and Levodopa
    • While motor fluctuations prominent over time, **better tolerability with higher dosing better in men** (particularly GI)

PARKINSON’S DISEASE  Treatment

• COMPLICATIONS OF L - DOPA
  – Wearing off effect - transient deterioration shortly before the next dose
  – ON - OFF Phenomenon - abrupt but transient fluctuations that occur during day without warning
    • Reduce dose intervals
    • Take Sinemet 1 hr prior to meals
    • Restrict dietary protein diet (do reduce competition by various amino acids for the same carrier proteins that levodopa uses)
      – C-OMT (catechol O-methyltransferase inhibitor) useful when taken with SINEMET
Role of Dopamine in the CNS

- Dopamine modulates various brain functions
  - Mood
  - Cognition
  - Motor function
  - Drive
  - Aggression
  - Motivation

PARKINSONS DISEASE Treatment

• *Dopamine agonists* – Good for mild to moderate Parkinson’s especially less than 70 yr old
  – Pramipexole (MIRAPEX), Ropinirole (REQUIP), Rotigotine (NEUPRO)
  *** addictions most problematic to men: gambling, internet activities – dopamine stimulation pertains to pleasure-seeking

*MAO-B inhibitors* (esp. Azilect): efficacy fair to good, excellent tolerability, some interactions

*Amantadine* – MOA still not well understood, but helps some with motor fluctuations:

*Anticholinergic Drugs* – Cognitive, urological and other side effects so recommended for under 65 – helps tremor only

ALL of the above (except Azilect) have higher rate of hallucinations than levodopa

Essential Tremor

• No Parkinsonian features (no slowness or rigidity or gait disturbance)
• Faster than Parkinson’s tremor
• Bilaterally nearly symmetrical men’s greater predilection: hand involvement
• Can also involve the head and even voice: F>>M
  (Parkinson’s can involve jaw, however).
Essential Tremor Treatment

- Many patients need none, as it is a condition, as opposed to a disease
- Beta Blockers like propranolol (non-selective preferred in women, but men? – ED possible)
- Anti-convulsants such as mysoline (start with $\frac{1}{2}$ of a 50mg pill at night and increase slowly), and even topamax

Migraine Prevalence Compared With Other Neurologic Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence</th>
</tr>
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<tbody>
<tr>
<td>MS</td>
<td>0.09%</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0.71%</td>
</tr>
<tr>
<td>PD+HD</td>
<td>0.96%</td>
</tr>
<tr>
<td>Stroke</td>
<td>1%</td>
</tr>
<tr>
<td>AD</td>
<td>6.7%</td>
</tr>
<tr>
<td>Migraine</td>
<td>12.1%</td>
</tr>
</tbody>
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MS = multiple sclerosis; PD+HD = Parkinson disease + Huntington disease; AD = Alzheimer’s disease.

Migraine Is a Highly Prevalent Medical Disorder

28 million US migraine sufferers

1-yr prevalence of migraine in the US 1999 (%)

Overall 12.6% Females 18.2% Males 6.5%


Lifetime incidence of migraine: closer to even later in life

Figure 1. Migraine prevalence by age. Prevalence increased from 12 to 38 years of age in both females and males; the peak was considerably higher among females.
**International Headache Society**

**Criteria for Migraine**

**Migraine Is an Episodic Recurrent Headache**

**Lasting 4-72 Hours with:**

- **Any 2 qualities:**
  - unilateral pain
  - throbbing pain
  - pain worsened by movement

- **Any 1 of these:**
  - nausea
  - vomiting
  - photophobia and phonophobia

- **moderate or severe pain**

**IMPORTANTLY,** tension-like features such as posterior head and neck pain can also be present in a headache that meets IHS criteria for migraine.


**Migraine: A Common Episodic Headache Disorder**

- **Neurologic disorder**
  - Strong genetic component (up to 50%)

- **Global prevalence:**
  - Women: 15%–17%
  - Men: 6%–9% **AND lower rate of diagnosis (misdiagnosis with cluster)**

- **2 major subtypes**
  - Without aura (~75%)
  - **With aura (~25%) – occasionally without headache - later in life**

- **Burden**
  - Among the world’s 20 most disabling diseases (WHO)
  - Indirectly costs employers up to $13 billion per year
  - Direct medical costs exceed $1 billion per year

WHO = World Health Organization.


The Migraine Process: Activation of the Trigeminal Nucleus Caudalis

Current treatment options: drug

<table>
<thead>
<tr>
<th>Acute therapy: OLD</th>
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<tbody>
<tr>
<td><strong>Migraine non-specific</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td><strong>Migraine “specific”</strong></td>
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<table>
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<tr>
<th><strong>ACUTE TX: NEW</strong></th>
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<tr>
<td>Triptans such as sumatriptan, naratriptan, rizatriptan, zolmitriptan, almotriptan, eletriptan, combination suma/naproxen,</td>
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<tr>
<td>Also - remember injections - suma, nasal spray (suma and zolmi), dissolving (riza, zolmi), and newly released iontophoretic patch: suma (ZECUITY)</td>
</tr>
<tr>
<td><em><strong>with men, always keep ‘transportability’ in mind</strong></em></td>
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</tbody>
</table>
Current treatment options: drug

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th></th>
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<tbody>
<tr>
<td><strong>b-blockers</strong></td>
<td>propranolol - beware in men (ED)</td>
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<thead>
<tr>
<th>TCAs</th>
<th>amitriptyline, nortriptyline – wt gain, sedation</th>
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<tbody>
<tr>
<td>CCBs</td>
<td>verapamil – ** if aura</td>
</tr>
<tr>
<td>Other</td>
<td>sodium valproate – OK in men</td>
</tr>
<tr>
<td></td>
<td>topiramate (cognition, wt loss)</td>
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Becker (1999); Bartleson (1999)

Sexual Dysfunction: pharmacologic categories relevant to neurology and psychiatry

- **Tricyclic Antidepressants (TCAs)**
  - Stimulation of 5HT2A receptors
  - Inhibits erection > ejaculation (Reduction of lubrication in women)

- **Selective Serotonin Reuptake Inhibitors (SSRIs)**
  - Increases serotonin levels in both sexes
  - Decreases sex drive
  - Impairs orgasm (primarily delay)
  - 5HT2A Agonist
Substances Related to Sexual Dysfunction (various neurological and psychiatric conditions)

- **Antidepressants**
- Lithium
- Sympathomimetics
- $\alpha$ and $\beta$ - adrenergic antagonists
- **Anticholinergics**
- Antihistamines
- Anti-anxiety agents
- Alcohol
- Opioids
- Hallucinogens
- Cannabis
- Barbiturates
- Sedative hypnotics

Cluster Headaches

- Brief (almost always less than an hour)
- Almost always **male**
- Unilateral
- Most frequently at **night**, often after etoh or tob
- “Clustering” pattern
- Similar prophylaxis to migraines, but consider mini-prophylaxis with steroids
- **Injectable sumatriptan** (imitrex) FDA approved, and **home oxygen** sometimes used to treat an attack
SEIZURES/ EPILEPSY

Gender differences in presentation and prognosis for epilepsy

• Women have a higher rate of generalized epilepsies

• Men have a higher incidence of status epilepticus, sudden unexpected death in epilepsy (SUDEP), prognosis and mortality for any reason related to epilepsy/seizures

• Source: McHugh JC, Delanty N., Int Rev Neurobiol 2008; 83:11-26
SEIZURES
Status Epilepticus

• CAUSES OF STATUS
  – Anticonvulsant withdrawal
  – Medical Noncompliance
  – Metabolic Disturbance
  – Drug Toxicity
  – CNS Infection or tumors
  – Refractory epilepsy
  – Head trauma

Anticonvulsant choices:
Special Issues Related to Gender

Contraception:
phenytoin, carbamazepine, lamotrigine all lower estrogens

Non- issue in men
Anti-epileptic RX

GENERALIZED: Valproic Acid (contraindicated in women of childbearing age due to neural tube defects) – but studies show it to be the most effective for primary generalized epilepsies such as tonic-clonic convulsions.

Excellent choice for men. Side effects include dose-related tremor and thinning of hair

(NOTE: ethosuximide an alternative for absence epilepsy, which is also a generalized epilepsy)

Partial-onset (+/- secondary generalization):
phenytoin, carbamazepine, lamotrigine,
*levetiracetam, gabapentin, pregabalin, topiramate, and oxcarbazepine

*levetiracetam (Keppra) has gained in popularity tremendously in recent years due to safety, efficacy and minimal Rx interactions – BUT behavioral issues of irritability need to be taken into account.
MULTIPLE SCLEROSIS

• Characteristics
  – Most common young adult neuro disability (after trauma)
  – Presentation: Weakness (35%) Optic neuritis, (36%) Sensory Disturbance, (37%) Ataxia (11%) Diplopia (15%)

  – Familial Preponderance
  – Whites > other ethnic races (esp. northern European, Irish)
  – Location/Risk: Increased in temperate climate

  – Females = incidence is 2 x Males, but primary progressive and transition to secondary progressive: male predilection.
  – Relapsing forms more common in women – stakes are higher in treating, as meds likely to make more of a difference.

What this means to men? Less “up-side” in immunomodulatory Rx: of men.

MULTIPLE SCLEROSIS

Reduce attack frequency and disease burden w/immunomodulatory agents.

Interferons Beta-1-a (Avonex once/wk IM) (Rebif T.I.W. sq)
Beta-1-b (Betaseron every other day)

Glatiramer Acetate (daily Copaxone)

Tysabri, Aubagio**, Gilenya and other chemotherapeutics being developed (Lemtrada just approved)

**the teratogenicity of this category X product and others of no concern for men.
Diabetes and Diabetic Polyneuropathy

1. Type 2 diabetic polyneuropathy develops at a younger age in male patients than female patients (average age 63 vs 67).*

2. Male patients less likely to be diagnosed with type 2 DM**

* Aaberg, etal, J diabetes complications, 2008, Mar-Apr


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Therefore, in neuropathy

- Look for DM assertively in men who present with foot numbness, considering OGTT’s
- Always consider ETOH us hx spanning across a lifetime, with implications on other nutritional aspects (of course B12).
- American Academy of Neurology (AAN) 2009 recommendations:
  ”The tests with the highest yield of abnormality are blood glucose, serum B12 with metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis (Class III). Patients with distal symmetric sensory polyneuropathy have a relatively high prevalence of diabetes or prediabetes (impaired glucose tolerance), which can be documented by blood glucose or GTT (Class III).”

MYASTHENIA GRAVIS

- **Etiol:** - RECEPTOR ANTIBODIES
  – Decreased numbers of acetylcholine receptors due to autoimmune destruction

- **Epidemiology**
  – **Bimodal** peak of incidence in younger women (second and third decades) and older men (fifth and sixth decades).

- **THYMUS:**
  – **Surgical removal** associated with improvement in disease severity in young patients (>50)
  – Thymic abnormalities are either hyperplastic or neoplastic.
  – Neoplasms occur in about 12 percent of patients-locally invasive epithelial cell tumors (thymomas) – prompting surgery even in older patients
MYASTHENIA GRAVIS

- **History**
  - Diplopia, ptosis, weakness
  - Fluctuation in fatigue worse with repetition and better with rest

- **Differential diagnosis of ALS** (somewhat more common in men), Lambert-Eaton Myasthenic Syndrome (much more common in men), and myopathies (gender variation based on type)

- **DIAGNOSIS**
  - Edrophonium chloride (Tensilon) injection, Clinical Suspicions
  - Anti–AchR radioimmunoassay
    - A Positive test is Dx, A neg test does not exclude disease
  - Repetitive Nerve Stimulation: look for decremental (fatigue) response
  - Single Fiber electromyography

- **TREATMENT**
  - Acetylcholinesterase inhibitors (mainly *pyridostigmine*)
  - Thymectomy
  - Corticosteroids
  - Cytotoxic Therapies → *Azathioprine*, cyclosporine
  - Plasma exchange and intravenous pooled immune globulin (IVIg) for urgencies

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**Stroke**

- Ischemic 85%
- Cryptogenic 26%
- Atherosclerotic 17%
- Cardioembolic 17%
- Lacunar 21%
- Subarachnoid
- Intraparenchymal
Stroke

- Can a higher rate of consultation with physicians (such as primary care wellness visits) have an favorable impact on a disorder with high morbidity and mortality?

Gender differences started to be referenced in studies around 2000:

Three times as many men as women had not seen a doctor in the previous year (24% vs. 8%). One of three men had no regular doctor, compared with one of five women (33% vs. 19%).

Uninsured men were at least three times as likely as insured men not to have gotten care when needed, filled a prescription because of the cost, or seen a specialist (28% vs. 9%).

Among men age 50 and older, 60 percent had not been screened for colon cancer and 41 percent had not been tested for prostate cancer in the year prior to the survey.

2013 study: men's consultation rates were over 30% lower than women's age 16-60

- there was very little difference in childhood and older age, and much higher rates of consulting in women than men during the reproductive and mid-life years.

- consultations for reproductive reasons only partially explained the large gap in consulting between men and women in mid-life

- The gender difference in consulting also varied by deprivation status, reflecting a socioeconomic gradient in consulting rates among women but not men


Annual rate of all first-ever strokes by age, sex and race (GCNKSS: 1999).
source: GCNKSS unpublished data. Note: rates for ages 45-54 for black men and women and for black men 75 and over, are considered unreliable.
CVD and other major causes of death: males (United States: 2006). Source: NCHS and NHLBI.

Estimated direct and indirect costs (in billions of dollars) of major cardiovascular diseases and stroke (United States: 2010). Source: NHLBI.
Stroke rates (and other cardiovascular diseases) and gender life-expectancy gap: implications of differences in the rate of consultation?

Summary

• Men and women present differently with neurological disorders

• Treatment options, of course, need to be tailored to needs – and this includes gender differences

• We have a responsibility as physicians and leaders to foster patients’ use of resources to maximize health. This benefits individuals and families, and will hopefully favorably impact public health
THANKS!!
Questions.....