VASOMOTOR SYMPTOMS: IMPACT ON SLEEP, MOOD AND QUALITY OF LIFE AND METHODS OF MEASUREMENT

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Learning Objectives

- At the end of this presentation, the learner is expected to:
  - Frame the two basic models for how hot flashes and other menopausal symptoms affect daily function and impact quality of life
  - Evaluate common menopausal symptoms using a variety of tools appropriate for the research and clinical settings

Disclosures

- Bayer, Inc: investigator-initiated grant support
- Menogenix: stock options

Who Gets Hot Flashes?

- Eventually, just about everyone: up to 85% of women report ever having a hot flash and a large proportion will report moderate to severe hot flashes
- Hot flashes interact with other menopause associated difficulties such as sleep, adverse mood (depression and anxiety), and overall quality of life
The ‘Cascade’ Model of Hot Flash Disruption

- Hot flashes lead to sleep disruption, which leads to mood disturbance.

Evidence for the ‘Cascade’ Model

- Sleep disruption is increased in the second half of the night in women with hot flashes who report poor sleep (Freedman).
- Treating hot flashes often appears to prevent or improve pre-morbid sleep and mood conditions.
- Women with hot flashes are more likely to develop depression (Cohen, Arch Gen Psych 2006; 63:385).
- Perimenopausal women with adverse mood note improved sleep before their mood lifts (Joffe JCEM 2011; 96:1044).

The ‘Cumulative Burden’ Model

- Protective Factors
- Decompensating Factors
- Hot Flashes
- Adverse Mood
- Poor Sleep

Evidence for a ‘Cumulative Burden’ Model

- There are parallel, bidirectional avenues by which patients may acquire bothersome menopausal symptoms:
  - Depression may cause abnormal sleep patterns
  - Abnormal sleep patterns may cause depression
  - Adverse QOL may be a sign of symptom sensitivity, which is related to higher hot flash reporting
  - When the total sum of bothersome symptoms become too much, treatment is sought.
SOME KNOWN INTERACTIONS

Factors Linked in Time to Increasing Severity of Hot Flashes, Mood or Sleep (Association)

VMS Increase Across the Transition

<table>
<thead>
<tr>
<th>Stage</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Early Peri</td>
<td>1.86</td>
<td>1.47, 2.34</td>
</tr>
<tr>
<td>Late Peri</td>
<td>6.64</td>
<td>4.80, 9.20</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>4.96</td>
<td>3.51, 7.01</td>
</tr>
</tbody>
</table>

Gold EB, AJPH 2006; 96:1226

Associations Between Sleep Characteristics and MS

<table>
<thead>
<tr>
<th>PSG-Assessed Sleep</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor sleep efficiency</td>
<td>1.40</td>
<td>1.04-1.89</td>
</tr>
<tr>
<td>NREM</td>
<td>1.45</td>
<td>1.08-1.95</td>
</tr>
<tr>
<td>AHI</td>
<td>1.73</td>
<td>1.26-2.37</td>
</tr>
<tr>
<td>Sleep Duration</td>
<td>0.93</td>
<td>.71-1.22</td>
</tr>
</tbody>
</table>

Adjusted for race, menopausal status, education, health complaints, sleep medications, smoking, exercise, obesity

Hall MH et al, Sleep 35:783, 2012

Sleep Difficulty Across the Menopausal Transition (Kravitz Obstet Gyn Clin NA 2011; 38:567)
FACTORS CAUSALLY LINKED TO HOT FLASHES, MOOD AND SLEEP

Hot Flashes Worsen Sleep

- 20 healthy premenopausal women receiving GnRHa
- 80% concordance between subjective/objective VMS (sVMS/oVMS)
- Sleep efficiency (polysomnography) worse with oVMS, quality worse with sVMS (questionnaire)

Joffe H, Menopause 2013 PMID 23481119


- Figure 3
- Induced Hot Flashes Interrupt Sleep

SOME FACTORS AFFECTING PERCEPTION AND RECORDING OF SYMPTOMS

Subjective Influences May Contribute to Either Model
Adjusted OR for CES-D > 16 Across Visits 00-05 by Menopausal Status (p=.005)

Poverty and Life Events
- Low SES-Bronx-based cohort (N=536), 50% HIV infected and 50% uninfected, aged 45+-5yrs
- 89% reported psychological symptoms
- CES-D score >23 associated with:
  - Menopausal symptoms (OR 1.8 [1.5, 2.3])
  - >3 negative life events (OR 2.1 [1.5, 2.8])

Miller et al, Menopause 2005; 12:348

How To Measure Hot Flashes
- Count them
  - How frequently: must balance burden against need to capture adequate data
  - Over what time period?—perimenopause may require longer time period for assessment
- Measure 'bothersomeness' or severity
  - Specific scales exist, good agreement with frequency
- Use an 'objective' measure (sternal skin conductance)
Counting Hot Flashes

- Reasonable completion rates for daily diaries in most studies (Sloan)
- Retrospective reporting is more common than one would like (Johannes)
- Balancing of data capture vs participant burden is important to consider
- Can also capture severity
- Hot flash ‘scores’, frequency and sternal skin conductance all yield similar data

Measuring ‘Bothersomeness’

- HFRDIS (Carpenter): measures interference of hot flashes with daily life
- Provides a commonly applicable index for severity of hot flashes
- Does not seem to add much helpful information beyond frequency and severity determination

‘Objective’ Measurements

- Sternal skin conductance
  - Good agreement with diary data in optimal settings
  - Higher reporting than subjective hot flashes in outpatient settings due to distraction
  - Overall performance is best in laboratory or controlled settings
  - Burdensome to wear and carry for more than 24hrs

Validations

- Sloan, J Clin Oncol 2001; 19:4280 (N=968)
  - Daily diaries with >90% completion rates
  - Subjective frequency and severity assessments derived from patient self-reports
  - Total # hot flashes/day
  - Severity (mild, moderate, severe, very severe)
  - Hot flashes correlated with insomnia, sweating and sleepiness on QOL cross correlation
Recommendations

  - Both a subjective and an objective assessment is desirable
  - Sternal skin conductance remains the best standardized measurement
  - Yet an individual woman's subjective experience is what drives treatment

VMS Studies: Principles from MSFLASH
(Menopause 2014; 21:45)

- To decrease PBO response
  - Diary run-in—3 weeks
  - Eliminate women with very variable symptoms
  - Diary not necessary to do daily
  - 8-12 week duration of treatment/PBO
  - Usefulness of objective monitor—does not appear overall critical to outcomes
  - VMS frequency well below FDA guidance was still able to be evaluated

Measuring Sleep

- Best method: polysomnography
- Requires overnight stay in sleep lab
  - Most expensive and disruptive
- Second best: sleep actigraphy
  - Can be done at home
  - Can assess sleep stages but less accurately than EEG
- Third best: self reported sleep
  - Reasonable correlations with actigraphy and EEG when sleep disturbance is significant, overall less sensitive

Measuring Sleep by Survey

- ISI: Insomnia Severity Index
- PSQI: Pittsburgh Sleep Quality Index
- FSS: Fatigue Severity Scale
- Eppenworth Sleepiness Scale: easy to use in office setting
- Good agreement with each other and overall helpful for clinical studies; less sensitive than PSG or actigraphy
Ways to Measure Symptoms: Menopause QOL Scales

**Advantages**
- Highly specific to the menopausal experience
- May be easier for participants to complete
- Captures breadth of well known and less well known menopausal symptoms

**Disadvantages**
- 'Blunt instrument' for highly specific comorbidities (e.g., anxiety + depression)
- May fail to capture the nuances of individual syndromes
- Sacrifice of accuracy for speed

Measuring Mood

- Specific instruments exist to measure multiple psychiatric symptoms
  - CES-D: depressive symptoms
  - PHQ, Hamilton, BDI: depression, anxiety and other disorders
  - SCID: most complete (but lengthiest)
- Do these symptoms differ in menopausal women such that additional instruments are needed?
- Important to capture other aspects of mood that will affect symptoms (e.g. symptom sensitivity)

Putting Them All Together...

- Climacteric scales developed and validated for use in menopausal women:
  - Greene Climacteric Scale
  - Utian Climacteric Scale
  - MENQOL
  - Kupperman Index
  - Menopause Rating Scale

Comparison of Scales

<table>
<thead>
<tr>
<th>Scale</th>
<th>Items</th>
<th>Domains</th>
<th>Scaling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utian</td>
<td>23</td>
<td>Occupational, health, emotional, sexual</td>
<td>5-point Likert</td>
</tr>
<tr>
<td>MenQOL</td>
<td>29-32</td>
<td>VMS, Psychosocial, Physical, Sexual</td>
<td>6-point Likert scale with opt-out</td>
</tr>
<tr>
<td>Kupperman</td>
<td>11 items, self report and physician ratings</td>
<td>VMS, paresthesia, insomnia, mood, vertigo, arthralgias</td>
<td>4 point Likert, weighted</td>
</tr>
<tr>
<td>Greene</td>
<td>21</td>
<td>Psychological, somatic, VMS</td>
<td>4-point Likert</td>
</tr>
<tr>
<td>MRS</td>
<td>11 items</td>
<td>Derived from Kupperman but includes vaginal symptoms</td>
<td>5-point Likert</td>
</tr>
</tbody>
</table>
Summary and Recommendations

- In clinical studies, self-reported hot flash frequency and severity should be measured
  - Subsampling for sternal skin conductance may have some advantages
- Subjective sleep scales are reasonably accurate
  - Actigraphy and EEG when sleep is the primary outcome
- Many assessments for mood and QOL exist
  - Balancing participant burden vs data quality