Sleep Disturbance, Hot Flashes, and Urinary Frequency in Prostate Cancer Patients Treated with Androgen Deprivation Therapy

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ADT, Testosterone, and Prostate Cancer

- Androgen deprivation therapy (ADT) (i.e., goserelin, leuprolide) used to treat prostate cancer at intermediate or high risk of recurrence or local metastasis
- Eliminates testosterone, which slows the growth of cancer
- Associated with a number of side effects, including hot flashes and fatigue
Testosterone, Sleep, and ADT

- Testosterone may help to modulate sleep
  - Prostate cancer patients treated with ADT report sleep disturbance (Stephens et al. BJU International 2007; 99: 310-310)
  - Demonstrate average of 5.9 hours of sleep per night, frequent awakening, and report daytime sleepiness (Hanisch et al. Eur J Cancer Care 2011; 20: 549-554)

- Extent to which these problems are specific to ADT treatment is unclear
  - Sleep disturbance also common in aging men
Study Aims

• To compare objective sleep disturbance in prostate cancer patients treated with ADT and matched controls
  – Prostate cancer patients treated with prostatectomy
  – Men with no cancer history

• To examine symptoms of ADT which may mediate sleep disturbance
  – Hot flashes
  – Nocturia
Methods: Study Design

• Substudy of a larger study of quality of life in men treated with ADT for prostate cancer
  – Patients recruited on or before day of ADT initiation

• 3 groups of men:
  • Diagnosed with prostate cancer undergoing ADT (ADT+)
  • Diagnosed with prostate cancer treated with surgery only (ADT-)
  • Non-cancer controls (CA-)

• Matched on:
  • Age (within 3 years)
  • Education (3 levels)
  • Time since diagnosis (ADT+ & ADT-)

• ADT+ participants assessed 6 months after initiation of ADT/recruitment to larger study
### Methods: Eligibility Criteria

#### All participants
- ≥ 18 years of age
- ≥ 6\textsuperscript{th} grade education
- Able to speak/read English
- Able to provide informed consent

#### ADT-
- Diagnosed with non-metastatic prostate cancer
- No other treatment besides a prostatectomy
- No testosterone supplementation

#### ADT+
- Diagnosed with non-metastatic/asymptomatic metastatic prostate cancer
- Scheduled to be treated with ADT for at least 12 months
- No previous ADT treatment

#### CA-
- No history of a cancer diagnosis besides non-melanoma skin cancer
- No testosterone supplementation
Methods: Measures

- Objective sleep disturbance was assessed using actigraphy
  - Actiwatch Score (MiniMitter, Bend, OR)
  - Worn on non-dominant wrist continuously for three consecutive days
  - Measures intensity of motion in one minute intervals
  - Validated measure of sleep
    (Morgenthaler et al. Sleep 2007; 30: 519-529)
  - Real time assessment of hot flashes
Methods: Measures

- Daily diary of bedtime, rising time, urinary frequency

![Daily Diary Table]

<table>
<thead>
<tr>
<th>Day: Sunday</th>
<th>Date: Nov 26</th>
<th>Notes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rising time:</td>
<td>Number of times you urinated during the day:</td>
<td></td>
</tr>
<tr>
<td>7:30</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Bed time:</td>
<td>Number of times you urinated at night:</td>
<td></td>
</tr>
<tr>
<td>11:30</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
Methods: Statistical Analyses

• Sociodemographic and clinical comparisons
  – One-way ANOVA and chi-square

• Comparisons of objective sleep disturbance, hot flashes, and nocturia
  – One-way ANOVA with LSD post-hoc tests

• Relationship among symptoms
  – Pearson correlations

• Mediation
  – Linear regression in accordance with Baron and Kenny (1986)
  – Sobel tests of indirect effects
### Results: Participants

<table>
<thead>
<tr>
<th></th>
<th>ADT+ (n=32)</th>
<th>ADT- (n=31)</th>
<th>CA- (n=28)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: mean (range)</td>
<td>68 (49-90)</td>
<td>67 (56-82)</td>
<td>69 (55-90)</td>
<td>.79</td>
</tr>
<tr>
<td>College graduate</td>
<td>41%</td>
<td>42%</td>
<td>54%</td>
<td>.55</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>2.68</td>
<td>4.52</td>
<td>--</td>
<td>.11</td>
</tr>
<tr>
<td>Caucasian</td>
<td>94%</td>
<td>97%</td>
<td>93%</td>
<td>.78</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3%</td>
<td>7%</td>
<td>4%</td>
<td>.76</td>
</tr>
<tr>
<td>Annual household income (≥$40k)</td>
<td>52%</td>
<td>70%</td>
<td>65%</td>
<td>.39</td>
</tr>
</tbody>
</table>
Actigraphy Data

ADT+ participant

ADT- participant

CA- participant
## Results: Group Differences in Symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>ADT+ (n=34)</th>
<th>ADT- (n=32)</th>
<th>CA- (n=28)</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in bed at night</td>
<td>496.67</td>
<td>478.34</td>
<td>478.82</td>
<td>.65</td>
</tr>
<tr>
<td>Nighttime activity</td>
<td>37.73</td>
<td>31.04</td>
<td>26.60</td>
<td>2.38</td>
</tr>
<tr>
<td>Sleep onset latency</td>
<td>23.51</td>
<td>17.00</td>
<td>26.20</td>
<td>1.38</td>
</tr>
<tr>
<td>WASO</td>
<td>77.16&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60.70&lt;sup&gt;b&lt;/sup&gt;</td>
<td>54.29&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.23**</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>75.05&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80.16&lt;sup&gt;b&lt;/sup&gt;</td>
<td>80.00&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.65*</td>
</tr>
<tr>
<td>Nighttime hot flashes</td>
<td>.06</td>
<td>.00</td>
<td>.01</td>
<td>1.00</td>
</tr>
<tr>
<td>Nighttime urinary frequency</td>
<td>3.34&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.60&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.48&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10.64**</td>
</tr>
</tbody>
</table>

Note: Differing subscripts indicate statistically significant group differences

*p<.05, **p<.01
## Results: Relationships Among Symptoms in ADT Patients

<table>
<thead>
<tr>
<th></th>
<th>WASO</th>
<th>Sleep efficiency</th>
<th>Nighttime hot flashes</th>
<th>Nighttime urinary frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>WASO</td>
<td>1.00</td>
<td>-0.70**</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>-0.70**</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nighttime hot flashes</td>
<td>0.04</td>
<td>0.05</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Nighttime urinary frequency</td>
<td>0.55**</td>
<td>-0.50**</td>
<td>-0.03</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**p < 0.01
Results: Mediation models

- Because WASO and sleep efficiency were highly correlated in ADT+ patients ($r^2=.70$), we selected one (i.e, WASO) to test in mediation model.
- Compared ADT+ to ADT-, ADT+ to CA-
- Models tested: Group $\rightarrow$ Nocturia $\rightarrow$ WASO
Results: Mediation models

ADT+ vs. ADT-

Nocturia

WASO

c = -.26*, c’ = -.04 (ns)
b = .54**
a = -.41**

Sobel = -2.85, p < .01

ADT+ vs. CA-

Nocturia

WASO

c = -.37**, c’ = -.20 (ns)
b = .44**
a = -.42**

Sobel = -2.55, p = .01
Summary of Findings

- Patients treated with ADT displayed significantly greater WASO, worse sleep efficiency, and more nocturia than patients treated with prostatectomy and men without cancer.
- No differences were found among groups in real-time assessment of hot flashes.
- Greater sleep disturbance was associated with greater nocturia but not hot flashes.
- Nocturia mediated the relationship between ADT treatment and sleep disturbance.
Discussion

- Findings on poor sleep, nocturia among patients treated with ADT consistent with previous literature (Hanisch et al. Eur J Cancer Care 2011; 20: 549-554)
  - First study to our knowledge comparing these symptoms in ADT patients to matched controls
  - Suggests that symptoms are not the result of cancer itself or normal aging
- Suggests that poor sleep is not the result of hot flashes
  - Consistent with self-report measures of sleep and hot flashes in the same study
  - Limitations of real-time hot flash data collection
- Patients should be educated regarding sleep disturbance and nocturia as side effects of cancer
  - Treatment for urinary frequency (e.g., tolterodine, oxybutynin) may improve sleep in patients treated with ADT
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