Psychostimulants for Fatigue

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“In my experience with psychostimulants for the treatment of fatigue…”

Wise Practitioner, MD, NP
Palliative Care Provider Extraordinaire
Learning Objectives

By the end of this presentation, you will take pride in your ability to

- Define fatigue
- Appreciate the impact of cancer-related fatigue
- Appraise the value of methylphenidate and other psychostimulants in the treatment of fatigue, particularly when cancer-related
Fatigue – Definition

Fatigue…

- relates to an overwhelming lack of energy and a feeling of exhaustion that is associated with impaired physical and/or cognitive function but which does not lead to sleep
- has physical, affective, and cognitive components
- can be either central or peripheral
  - Central fatigue is related to mood, emotion and psychological arousal, and is associated with increased serotonin release
  - Peripheral fatigue is related to mechanisms such as neuromuscular transmission and impulse propagation, dysfunction of the sarcoplasmic reticulum, and other metabolic factors that disrupt energy provision and muscle contraction
Fatigue – Definition

Cancer-Related Fatigue (CRF) is...

- a feeling of weakness and inability to perform tasks, decreased motivation and low mood, and difficulty in thinking clearly
  - It differs from fatigue felt by healthy individuals in that it is of greater magnitude, disproportionate to the level of exertion, and incompletely relieved by rest
- distress/functional impairment for 2 weeks, almost every day, not d/t depression or other psychiatric d/o
- persistent in 30% of cancer survivors
- not etiologically understood
Fatigue – Causes

For what diagnoses have you observed fatigue to be an issue?

- Cancer/Cancer treatments
- Neuro disorders
- Depression
- Sleep disorders
- Endocrine disorders
- Inflammatory Bowel Disease
- Renal failure

- COPD
- Arthritis
- Autoimmune diseases
- Fibromyalgia
- Infection
- Tachyarrythmias (e.g., Afib)
- Liver failure
Fatigue – Causes

What are some conditions contributing to fatigue?

- Pain
- Anemia (specifically during chemo)
- Sleep-Wake disturbances
- Medication side-effects (esp. Antihistamines, Benzodiazepines, Antiepileptics, and Opioids)
Fatigue – Hospitalization

Hospitalization disrupts sleep

- Procedures performed at night
- Staff conversations
- Telephones
- Televisions
- Increased sympathetic stimulation causing increased arousal levels
- Bright light
- Exhaustion
- Affects melatonin levels causing desynchronisation of circadian rhythms
- Lack of control
- Separation from parents
- Unfamiliar environment
- Loss of normal routine
Fatigue – Prevalence

Fatigue is common in adult Palliative Care patients, esp. cancer

- Fatigue (84%), weakness (66%), and lack of energy (61%) are in the top five most common symptoms
- Fatigue is present in >75% of cancer patients
- Fatigue has the greatest negative impact on QOL by self-report
Fatigue – Prevalence

Cancer-Related Fatigue (CRF) is common in all children

- Of 158 children receiving IV antineoplastic therapy, 80% suffered from symptoms of fatigue
- Children have reported fatigue to be the most distressing of their treatment-related symptoms
- Related to disrupted sleep patterns
  - Adult patients experiencing restless sleep at night also experienced more intense daytime fatigue, increased daytime napping and were less active
- Significantly increased during treatment, with medical procedures and the hospital environment identified as major causative factors
Fatigue – Non-Pharmacologic Interventions

Hugs before drugs

- Address the underlying cause
- Exercise/Activity
  - Moderate and high-intensity programs
    - 60-85% max heart rate
    - >=3 time per week
  - Aerobic and/or strength training
Fatigue – Non-Pharmacologic Interventions

Hugs before drugs

- Cognitive Behavioral Therapy (CBT)
- Energy expenditure planning
- Insomnia treatments
  - Bright White Light (open the curtains, perhaps?)
Fatigue – Drugs

Psychostimulants

- Methylphenidate - (more later)
- Modafinil (and R-Modafinil) – (more later)
- Caffeine
  - Well-supported for improving exercise tolerance and other parameters in healthy athletes
  - Only one study for CRF
    - Prostate cancer survivors had increased exercise capacity with no change in resulting post-exercise fatigue
Fatigue – Drugs

Others with at least one positive study result

- Amantadine (MS)
- Steroids (CRF)
  - Dexamethasone for outpatients with advanced cancer
  - Likely to respond within one week when a response occurs
- L-Carnitine (Cancer chemotherapy)
- Hematopoietic stimulants (CRF)
  - May be helpful if anemia is clearly established
  - Not routinely helpful
  - Associated with increased risk of thrombotic events in one study
Fatigue – Drugs

Probably NOT helpful

- Donepezil
- Paroxetine
- Sertraline
Fatigue – Botanicals

Limited evidence supports

- **American Ginseng**
  - Recent RCT showed small positive results
    - CRF excluding CNS disease
    - 2000mg PO BID (breakfast and lunch)
    - Many exclusions
      - Opioids
      - Other moderate to severe symptoms (e.g., pain, insomnia)
      - Changes in cancer treatment
  - Negative results in another trial for MS
Fatigue – Methylphenidate

Cochrane on Methylphenidate in adult cancer patients

- Only two studies met inclusion criteria
- Methylphenidate was slightly better than placebo in improving FACIT-Fatigue scores

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Methylphenidate Mean</th>
<th>SD</th>
<th>Total</th>
<th>Placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference IV, Fixed, 95% CI</th>
<th>Std. Mean Difference IV, Fixed, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Bruera 2006</td>
<td>9.6</td>
<td>9.8</td>
<td>52</td>
<td>7.5</td>
<td>11.3</td>
<td>53</td>
<td>0.20 [-0.19, 0.58]</td>
<td></td>
</tr>
<tr>
<td>Butler 2007</td>
<td>6.5</td>
<td>2.28</td>
<td>20</td>
<td>2.8</td>
<td>2.66</td>
<td>21</td>
<td>1.46 [0.76, 2.16]</td>
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</tr>
<tr>
<td>Total (95% CI)</td>
<td>72</td>
<td></td>
<td>74</td>
<td>100.0%</td>
<td></td>
<td>0.49 [0.15, 0.83]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 9.71, \text{df} = 1 (P = 0.002); I^2 = 90\%

Test for overall effect: \( Z = 2.86 \) (\( P = 0.004 \))

FACIT-Fatigue Scale
Fatigue – Methylphenidate

Another meta-analysis for Methylphenidate in adult cancer

- Five studies (overlap with Cochrane), 2 different fatigue scales
Fatigue – Methylphenidate and Modafinil

Yet another meta-analysis in adult cancer (again with overlap)

- **Methylphenidate**
  - Improved fatigue (7 studies, p<0.0005)
  - Had no effect on quality of sleep (2 studies)
  - Trended toward *worsening* depression and QOL (2-3 studies)

- **Modafinil**
  - Trended toward improving fatigue (3 studies)
  - Had no effect on quality of sleep, depression, or QOL (1-2 studies)
Fatigue – Methylphenidate

May be more effective…

• Over time

Short

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<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
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</thead>
<tbody>
<tr>
<td>1.8.1 short-time</td>
<td>-9.6</td>
<td>9.8</td>
<td>52</td>
<td>-7.5</td>
<td>11.3</td>
<td>53</td>
<td>35.8%</td>
<td>-2.10 [-6.14, 1.94]</td>
</tr>
<tr>
<td>Butler et al, 2007</td>
<td>-6.5</td>
<td>10.16</td>
<td>20</td>
<td>-2.8</td>
<td>13.08</td>
<td>21</td>
<td>11.4%</td>
<td>-3.70 [-10.85, 3.45]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>72</td>
<td>47.2%</td>
<td>74</td>
<td>-2.49 [-6.01, 1.03]</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.39 (P = 0.17)

1.8.2 long-time

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<tr>
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<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower et al, 2009</td>
<td>-10.5</td>
<td>8.82</td>
<td>54</td>
<td>-6.8</td>
<td>9.97</td>
<td>69</td>
<td>52.8%</td>
<td>-3.70 [-7.03, -0.37]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>54</td>
<td>52.8%</td>
<td>69</td>
<td>-3.70 [-7.03, -0.37]</td>
<td></td>
<td></td>
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</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 2.18 (P = 0.03)

Total (95% CI)

<table>
<thead>
<tr>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>126</td>
<td>143</td>
<td>100.0%</td>
<td></td>
<td>-3.13 [-5.55, -0.71]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.62). I² = 0%

Favours [experimental] Favours [control]

• In combination with antidepressants (more in a minute…)

• With more severe fatigue and more advanced disease
Fatigue – Methylphenidate

May help with post Traumatic Brain Injury fatigue

- Small adult study
- Dose-dependent effect on mental fatigue as measured by the Mental Fatigue Scale
Psychostimulant Side Effects

Generally mild and uncommon

- **Short-Term**
  - Cardiovascular (Tachyarrythmias, Hypertension)
  - Vertigo
  - Nausea
  - Anxiety
  - Appetite suppression

- **Long-Term**
  - Modest reduction in BMI, no change in height (for children)
Psychostimulant Side Effects

One meta-analysis of adult studies showed insignificant trend towards more overall side effects with methylphenidate (MPH).

- The subset of vertigo, anxiety, anorexia and nausea were (significantly) slightly more common.

A 2nd meta-analysis of adult studies showed no more severe/life threatening side effects (grade 3 or 4) with MPH or modafinil.
Fatigue and Depression

Fatigue and depression are correlated
Fatigue and Depression

Psychostimulants may improve mood in fatigued cancer patients

- Modafinil given to adult cancer patients reduced depressive symptoms
  - Fatigued patients became more depressed during treatment
  - Fatigue and depression were correlated
  - Impact of modafinil was primarily on positive affect and NOT somatic symptoms, negative affect, or interpersonal subscales

  **BUT**

- Two earlier meta-analyses did *not* show a beneficial effect of methylphenidate or modafinil on depression in adult cancer patients
Fatigue and Depression

Methylphenidate + Mirtazepine = Magic?

- In an 88 patient RCT, methylphenidate (MPH) given to adult cancer patients in addition to mirtazepine (MTZ) led to more rapid onset of clinically significant reduction in depression
  - Larger improvement (statistically, than MTZ alone) by day 3
  - Significantly larger number of patients had a significant response (>50% reduction) by day 14 (and nearly by day 9: p<0.07)
  - Nervous system adverse events (psychosis, agitation, insomnia, tremor and seizure) more common with MPH (9/44 vs. 4/44), and all were manageable
“In the future, I plan to use psychostimulants for the treatment of fatigue…”

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