Supportive Care in Cancer - Fatigue

Professor Paddy Stone
Overview

- Definition
- Measurement
- Prevalence
- Screening
- Pathophysiology
- Management
  - Non-drug treatments
  - Drug treatments
- Guidelines
Overview

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• Measurement
• Prevalence
• Screening
• Pathophysiology
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Cancer-related fatigue is...

Fatigue that;
- Is persistent
- Is not the result of exertion
- Is not relieved by rest
- Results in reduced functioning
- Is associated with poor memory or concentration
- Is associated with unrefreshing sleep

As a result of;
- Cancer
- Cancer treatment

Berger et al CA Cancer J Clin 2015;65:190-211
Cella’s diagnostic criteria for Cancer Related Fatigue Syndrome

A1 Significant fatigue
A2 – A11 5 other associated symptoms
B Fatigue impact
C Due to cancer or cancer treatment
D Not due to co-morbid psychopathology
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Fatigue scales

• Single items
• Uni-dimensional
• Multi-dimensional
• CRFS
Single item instruments

- NCCN guidelines (http://www.nccn.org)
- How would you rate your fatigue on a scale of 0-10 over the past 7 days?
  - None to mild (0 – 3)
  - Moderate (4 – 6)
  - Severe (7 – 10)
A systematic review of the scales used for the measurement of cancer-related fatigue (CRF)

Unidimensional scales

• FACIT-F*
• EORTC QLQc30*
• Brief Fatigue Inventory
• FSS
• POMS
FACIT-F

- I feel fatigued
- I feel weak all over
- I feel listless ("washed out")
- I feel tired
- I have trouble starting things because I am tired
- I have trouble finishing things because I am tired
- I have energy

- I am able to do my usual activities
- I need to sleep during the day
- I am too tired to eat
- I need help doing my usual activities
- I am frustrated by being too tired to do the things I want to do
- I have to limit my social activity because I am tired
EORTC QLQc30

- Did you need to rest?
- Have you felt weak?
- Were you tired?
Multi-dimensional scales

- Chalder Fatigue Scale* (mental and physical)
- EORTC QLQ-FA13 (physical, emotional and cognitive)
- Fatigue Symptom Inventory
- Lee Fatigue Scale
- Multi-dimensional assessment of Fatigue
- Multi-dimensional Fatigue Inventory
- Multi-dimensional Fatigue Symptom Inventory
- Revised Piper Fatigue Scale
- Schwartz cancer fatigue scale
- Wu cancer fatigue scale
Table 6. Final EORTC QLQ-FA13 phase III module

<table>
<thead>
<tr>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have you lacked energy?</td>
</tr>
<tr>
<td>2. Have you felt exhausted?</td>
</tr>
<tr>
<td>3. Have you felt slowed down?</td>
</tr>
<tr>
<td>4. Did you feel sleepy during the day?</td>
</tr>
<tr>
<td>5. Did you have trouble getting things started?</td>
</tr>
<tr>
<td>6. Did you feel discouraged?</td>
</tr>
<tr>
<td>7. Did you feel helpless?</td>
</tr>
<tr>
<td>8. Did you feel frustrated?</td>
</tr>
<tr>
<td>9. Did you have trouble thinking clearly?</td>
</tr>
<tr>
<td>10. Did you feel confused?</td>
</tr>
<tr>
<td>11. Did you have trouble completing things?</td>
</tr>
<tr>
<td>12. Did tiredness interfere with your daily activities?</td>
</tr>
<tr>
<td>13. Did you feel that your tiredness is (was) not understood by the people close to you?</td>
</tr>
</tbody>
</table>
Chalder Fatigue Scale

- Have you had problems with tiredness?
- Have you needed to rest more?
- Have you felt sleepy or drowsy?
- Have you had problems starting things?
- Have you been lacking in energy?
- Have you had less strength in your muscles?

- Have you felt weak?
- Have you had difficulty concentrating?
- Have you had problems thinking clearly?
- Have you made slips of the tongue when speaking?
- Have you had any difficulties with your memory?
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Prevalence

- 40% at diagnosis
- 60-90% of those on treatment
- 30-75% of cancer survivors
- 84% of palliative care patients

Berger et al CA Cancer J Clin 2015;65:190-211
Pawlikowska et al. 1994


n = 15283
Prevalence (%) of "Severe fatigue" among different populations

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Screening

- NCCN and ASCO guidelines
  - Level of fatigue in last week
  - 0 = no fatigue
  - 10 = worst fatigue you can imagine
- Score 0 – 3; none to mild
- Score 4 – 6; moderate
- Score 7 – 10; severe
## Screening for CRFS with ChFS

<table>
<thead>
<tr>
<th></th>
<th>CRFS case</th>
<th>Non-case</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFS &lt; 11</td>
<td>5</td>
<td>74</td>
<td>79</td>
</tr>
<tr>
<td>(negative test)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BFS ≥ 11</td>
<td>55</td>
<td>66</td>
<td>121</td>
</tr>
<tr>
<td>(positive test)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>140</td>
<td>200</td>
</tr>
</tbody>
</table>

Sensitivity = \( \frac{55}{60} = 91.7\% \)
Specificity = \( \frac{74}{140} = 52.9\% \)
PPV = \( \frac{55}{121} = 45.5\% \)
NPV = \( \frac{74}{79} = 93.6\% \)

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Causes of fatigue in the general population?

- Depression
- Sleep disturbance
- Anxiety
- Stress
- Somatisation
Causes of fatigue in other chronic illnesses

- Psychological distress
- Deconditioning
- Anaemia
- Cachexia
- Metabolic disturbances
- Multiple symptomatology
Causes of fatigue specific to cancer patients?

- Muscle dysfunction?
  - Accumulation of metabolites
  - ATP dysregulation
- Erythrocyte dysfunction?
- Neuro-Endocrine dysfunction?
  - Central serotonin sensitivity
  - HPA axis dysfunction
  - Hypogonadism
- Autonomic dysfunction?
  - Autonomic reflex loss of muscle tone
- Cytokine effects?
- Circulating “asthenins”?
Causes of fatigue – unifying hypothesis?

Altered HPA-axis activity?

- Bower et al 2002 – decreased morning serum cortisol in patients with CRF compared to controls
Figure 1. Mean salivary free cortisol levels before, during, and after experimental psychologic stress in fatigued and nonfatigued breast cancer survivors. The stressor occurred during the first 30 minutes indicated on the graph. Error bars represent 1 standard error. *p < .05.
Altered 5HT metabolism?

- Serotonin hypothesis of depression
- Effects of 5HT
  - Decreased somatomotor drive, modified HPA function, sensation of decreased capacity for physical work
- Effects of exercise
  - Increased tryptophan, increased 5HT in hypothalamus and brain stem
Fig. 4 – Possible association between serotonin (5-HT) levels and fatigue.
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Exercise for cancer-related fatigue

- 56 studies, 4068 participants
- SMD -0.27, [95% CI -0.37 to -0.17]
- Benefits of exercise on fatigue were observed for interventions delivered during or post-adjuvant cancer therapy
- Benefits of exercise on fatigue for breast and prostate cancer but not for those with haematological malignancies
- Aerobic exercise significantly reduced fatigue but resistance training and alternative forms of exercise failed to reach significance
Psycho-social interventions

- 7/27 studies reported a significant effect of the intervention
  - Effect sizes varied between 0.17 to 1.07
- Interventions specific for fatigue
  - 4/5 (80%) positive
- Interventions not specific for fatigue
  - 3/22 (14%) positive
- Brief interventions: 3 individual sessions provided by oncology nurses

Goedendorp MM et al. Psychosocial interventions for reducing fatigue during cancer treatment in adults. Cochrane database of systematic reviews 2009; Issue 1
Non-drug treatments

<table>
<thead>
<tr>
<th>Interventions Identified as Likely to Be Beneficial by the NCCN (NCCN 2015⁴), ONS (ONS 2014⁷), CPAC/CAPO (HOWELL 2013⁹), and ASCO (BOWER 2014¹⁰)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address treatable contributors to fatigue</td>
</tr>
<tr>
<td>Manage concurrent symptoms</td>
</tr>
<tr>
<td>Physical activity/exercise</td>
</tr>
<tr>
<td>Rehabilitation</td>
</tr>
<tr>
<td>Psychoeducation</td>
</tr>
<tr>
<td>Meditation, mindfulness-based stress reduction, and cognitive-behavioral stress management</td>
</tr>
<tr>
<td>Relaxation</td>
</tr>
<tr>
<td>Cognitive-behavioral therapy for fatigue, depression, and pain</td>
</tr>
<tr>
<td>Cognitive-behavioral therapy for sleep</td>
</tr>
<tr>
<td>Yoga</td>
</tr>
</tbody>
</table>

Berger AM et al CA Cancer J Clin 2015; 65: 190 - 211
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Erythropoietin

Methylphenidate Trials

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Psychostimulant</th>
<th>Placebo</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Auret 2009</td>
<td>-1.07</td>
<td>1.85</td>
<td>21</td>
</tr>
<tr>
<td>Bruera 2006</td>
<td>-9.6</td>
<td>9.8</td>
<td>56</td>
</tr>
<tr>
<td>Bruera 2013</td>
<td>-5.5</td>
<td>6</td>
<td>68</td>
</tr>
<tr>
<td>Butler 2007</td>
<td>-3.8</td>
<td>9</td>
<td>26</td>
</tr>
<tr>
<td>Lower 2009</td>
<td>-11.8</td>
<td>12.6</td>
<td>75</td>
</tr>
<tr>
<td>Mar Fan 2008</td>
<td>-3.3</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>Moaraska 2010</td>
<td>-1.9</td>
<td>3.4</td>
<td>69</td>
</tr>
<tr>
<td>Roth 2010</td>
<td>-3.5</td>
<td>2.9</td>
<td>13</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>355</td>
<td>358</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.01; \) Chi\(^2 = 7.79, \) df = 7 (\( P = 0.35; \) I\(^2 = 10\% \))

Test for overall effect: Z = 2.71 (\( P = 0.007 \))

Minton O et al. Psychostimulants for the management of cancer-related fatigue: a systematic review and meta-analysis. JPSM 2011; 41: 761-7
Modafinil: US trial

- N=877 mixed solid tumours on chemotherapy
- Mid cycle 4 fatigue score change
- Beneficial effect only seen in severe fatigue (based on a 0-10 scale) 8-10 only

Modafinil: UK trial

- Multicentre
- Randomized, double-blinded
- Placebo-controlled
- N = 207

Treatment effect by subgroup – Spathis et al

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Size of Subgroup</th>
<th>Treatment Effect</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>20</td>
<td>5.83</td>
<td>-5.42 to 17.08</td>
</tr>
<tr>
<td>1</td>
<td>113</td>
<td>-0.45</td>
<td>-5.41 to 4.52</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>-0.62</td>
<td>-7.30 to 6.05</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIa</td>
<td>20</td>
<td>-4.31</td>
<td>-18.57 to 9.95</td>
</tr>
<tr>
<td>IIIb</td>
<td>46</td>
<td>-5.31</td>
<td>-13.21 to 2.60</td>
</tr>
<tr>
<td>IV</td>
<td>130</td>
<td>2.59</td>
<td>-2.09 to 7.28</td>
</tr>
<tr>
<td>Recurrent</td>
<td>11</td>
<td>-4.15</td>
<td>-20.06 to 11.76</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>103</td>
<td>-0.86</td>
<td>-6.19 to 4.48</td>
</tr>
<tr>
<td>Female</td>
<td>104</td>
<td>1.30</td>
<td>-3.99 to 6.59</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>62</td>
<td>0.68</td>
<td>-5.89 to 7.25</td>
</tr>
<tr>
<td>65–74</td>
<td>82</td>
<td>1.34</td>
<td>-4.49 to 7.17</td>
</tr>
<tr>
<td>≥ 75</td>
<td>64</td>
<td>-3.16</td>
<td>-10.44 to 4.11</td>
</tr>
<tr>
<td>Baseline NRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate fatigue</td>
<td>98</td>
<td>1.39</td>
<td>-4.06 to 6.84</td>
</tr>
<tr>
<td>Severe fatigue</td>
<td>109</td>
<td>-0.66</td>
<td>-5.99 to 4.67</td>
</tr>
</tbody>
</table>

Paroxetine

### Progestational steroids

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Progestational steroid Mean (SD)</th>
<th>N</th>
<th>Placebo Mean (SD)</th>
<th>N</th>
<th>SMD (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Sub-category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simons 1996</td>
<td>3.60 (1.96)</td>
<td>103</td>
<td>7.00 (2.51)</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Bruera 1998</td>
<td>-0.40 (1.50)</td>
<td>65</td>
<td>0.30 (2.10)</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>De Conno 1998</td>
<td>-2.00 (3.00)</td>
<td>21</td>
<td>5.00 (0.10)</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Westman 1999</td>
<td>1.30 (4.50)</td>
<td>128</td>
<td>-3.90 (2.20)</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>3.17</td>
<td></td>
<td></td>
<td>316</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 146.61, df = 3 (P &lt; 0.00001), I² = 98.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.78 (P = 0.44)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 Megestrol acetate alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruera 1998</td>
<td>-0.40 (1.50)</td>
<td>65</td>
<td>0.30 (2.10)</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>De Conno 1998</td>
<td>-2.00 (3.00)</td>
<td>21</td>
<td>5.00 (0.10)</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Westman 1999</td>
<td>1.30 (4.50)</td>
<td>128</td>
<td>-3.90 (2.20)</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>214</td>
<td></td>
<td></td>
<td>213</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: Chi² = 130.94, df = 2 (P &lt; 0.00001), I² = 98.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.67 (P = 0.51)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ginseng for cancer-related fatigue

- Placebo-controlled
- Wisconsin Ginseng 2000mg daily
- N = 364
- Primary outcome; fatigue at 4 and 8 weeks

Barton et al JNCI 2013
All patients

![Graph showing MFSI-SF general subscale change from baseline for Ginseng and Placebo groups at 4 weeks and 8 weeks. The p-values are 0.07 and 0.003, respectively.]
Patients on treatment vs patients after treatment

- **4 Weeks**
  - During treatment: **Ginseng** (P = .02) vs **Placebo** (P = .86)

- **8 Weeks**
  - During treatment: **Ginseng** (P = .01) vs **Placebo** (P = .07)
  - After treatment: **Placebo** (P = .07)
Reduction of Cancer-Related Fatigue With Dexamethasone: A Double-Blind, Randomized, Placebo-Controlled Trial in Patients With Advanced Cancer


See accompanying article on page 3056

ABSTRACT

Purpose
Cancer-related fatigue (CRF) is the most common symptom in patients with advanced cancer. The primary objective of this prospective, randomized, double-blind, placebo-controlled study was to compare the effect of dexamethasone and placebo on CRF.

Patients and Methods
Patients with advanced cancer with ≥ three CRF-related symptoms (i.e., fatigue, pain, nausea, loss of appetite, depression, anxiety, or sleep disturbance) ≥ 4 of 10 on the Edmonton Symptom Assessment Scale (ESAS) were eligible. Patients were randomly assigned to either dexamethasone 4 mg or placebo orally twice per day for 14 days. The primary end point was change in the Functional Assessment of Chronic Illness-Fatigue (FACIT-F) subscale from baseline to day 15. Secondary outcomes included anorexia, anxiety, depression, and symptom distress scores.

Results
A total of 84 patients were evaluable (dexamethasone, 43; placebo, 41). Mean (± standard deviation) improvement in the FACIT-F subscale at day 15 was significantly higher in the dexamethasone than in the placebo group (9 [± 10.3] vs. 3.1 [± 9.59]; P = .008). The improvement in FACIT-F total quality-of-life scores was also significantly better for the dexamethasone group at day 15 (P = .03). The mean differences in the ESAS physical distress scores at day 15 were significantly better for the dexamethasone group (P = .013, respectively). No differences were observed for ESAS overall symptom distress (P = .22) or psychological distress score (P = .76). Frequency of adverse effects was not significantly different between groups (41 of 62 vs. 44 of 58; P = .14).

Conclusion
Dexamethasone is more effective than placebo in improving CRF and quality of life in patients with advanced cancer.

J Clin Oncol 31:3076-3082. © 2013 by American Society of Clinical Oncology
Table 2. Change in Symptom Scores at Day 8 and Day 15

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Dexamethasone (n = 43)</th>
<th>Placebo (n = 41)</th>
<th>Day 8 From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACIT-F subscale</td>
<td>9.0 (10.30)</td>
<td>3.1 (9.59)</td>
<td>0.008</td>
</tr>
<tr>
<td>FACIT physical</td>
<td>5.25 (6.11)</td>
<td>1.32 (5.52)</td>
<td>0.002</td>
</tr>
<tr>
<td>FACIT social/family</td>
<td>-0.05 (5.50)</td>
<td>0.2 (4.77)</td>
<td>0.820</td>
</tr>
<tr>
<td>FACIT emotional</td>
<td>1.85 (4.93)</td>
<td>1.18 (4.49)</td>
<td>0.490</td>
</tr>
<tr>
<td>FACIT functional</td>
<td>1.3 (6.21)</td>
<td>1.51 (5.17)</td>
<td>0.820</td>
</tr>
<tr>
<td>FACIT-F total score</td>
<td>18.16 (22.88)</td>
<td>7.87 (19.93)</td>
<td>0.030</td>
</tr>
<tr>
<td>ESAS pain</td>
<td>-1.35 (3.11)</td>
<td>-0.17 (2.66)</td>
<td>0.09</td>
</tr>
<tr>
<td>ESAS fatigue</td>
<td>-2.70 (2.85)</td>
<td>-1.61 (2.69)</td>
<td>0.158</td>
</tr>
<tr>
<td>ESAS nausea</td>
<td>-1.08 (2.95)</td>
<td>-0.36 (3.17)</td>
<td>0.32</td>
</tr>
<tr>
<td>ESAS depression</td>
<td>-0.89 (2.58)</td>
<td>-0.80 (2.67)</td>
<td>0.54</td>
</tr>
<tr>
<td>ESAS anxiety</td>
<td>-0.72 (2.81)</td>
<td>-1.17 (2.45)</td>
<td>0.77</td>
</tr>
<tr>
<td>ESAS drowsiness</td>
<td>-1.59 (3.46)</td>
<td>-0.89 (2.94)</td>
<td>0.35</td>
</tr>
<tr>
<td>ESAS shortness of breath</td>
<td>-2.16 (2.92)</td>
<td>-0.89 (2.40)</td>
<td>0.06</td>
</tr>
<tr>
<td>ESAS appetite</td>
<td>-2.19 (3.78)</td>
<td>-0.63 (3.11)</td>
<td>0.06</td>
</tr>
<tr>
<td>ESAS sleep</td>
<td>-0.22 (3.22)</td>
<td>-0.14 (2.93)</td>
<td>0.91</td>
</tr>
<tr>
<td>ESAS feeling of well-being</td>
<td>-0.32 (3.03)</td>
<td>-1.22 (3.38)</td>
<td>0.24</td>
</tr>
<tr>
<td>ESAS physical</td>
<td>-10.86 (9.55)</td>
<td>-4.78 (10.86)</td>
<td>0.013</td>
</tr>
<tr>
<td>ESAS psychological</td>
<td>-1.48 (4.67)</td>
<td>-2.08 (4.73)</td>
<td>0.65</td>
</tr>
<tr>
<td>ESAS symptom distress</td>
<td>-12.2 (13.49)</td>
<td>-8.86 (15.91)</td>
<td>0.15</td>
</tr>
<tr>
<td>HADS anxiety</td>
<td>-0.66 (3.45)</td>
<td>1.00 (3.54)</td>
<td>0.75</td>
</tr>
<tr>
<td>HADS depression</td>
<td>-1.39 (3.59)</td>
<td>-0.31 (3.90)</td>
<td>0.29</td>
</tr>
<tr>
<td>FAACT</td>
<td>6.82 (8.95)</td>
<td>1.95 (8.54)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Abbreviations: ESAS, Edmonton Symptom Assessment Scale; FAACT, Functional Assessment of Cancer Therapy–Anorexia-Cachexia; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; HADS, Hospital Anxiety Depression Scale; SD, standard deviation.
Efficacy of Methylprednisolone on Pain, Fatigue, and Appetite Loss in Patients With Advanced Cancer Using Opioids: A Randomized, Placebo-Controlled, Double-Blind Trial

Ornulf Pausen, Pål Klepstad, Jan Henrik Rosland, Nina Aass, Eva Alberi, Peter Fayers, and Stein Kaasa

See accompanying editorial on page 3210; listen to the podcast by Drs Vardy and Agar at www.jco.org/podcasts

Abstract

Purpose
Corticosteroids are frequently used in cancer pain management despite limited evidence. This study compares the analgesic efficacy of corticosteroid therapy with placebo.

Patients and Methods
Adult patients with cancer receiving opioids with average pain intensity ≥ 4 (numeric rating scale [NRS], 0 to 10) in the last 24 hours were eligible. Patients were randomly assigned to methylprednisolone (MP) 16 mg twice daily or placebo (PL) for 7 days. Primary outcome was average pain intensity measured at day 7 (NRS, 0 to 10); secondary outcomes were analgesic consumption (oral morphine equivalents), fatigue and appetite loss (European Organisation for Research and Treatment of Cancer–Quality of Life Questionnaire C30, 0 to 100), and patient satisfaction (NRS, 0 to 10).

Results
A total of 592 patients were screened; 50 were randomly assigned, and 47 were analyzed. Baseline opioid level was 269.9 mg in the MP arm and 160.4 mg in the PL arm. At day-7 evaluation, there was no difference between the groups in pain intensity (MP, 3.60 v PL, 3.68; P = .88) or relative analgesic consumption (MP, 1.19 v PL, 1.20; P = .95). Clinically and statistically significant improvements were found in fatigue (−17 v 3 points; P = .003), appetite loss (−24 v 2 points; P = .003), and patient satisfaction (5.4 v 2.0 points; P = .001) in favor of the MP compared with the PL group, respectively. There were no differences in adverse effects between the groups.

Conclusion
MP 32 mg daily did not provide additional analgesia in patients with cancer receiving opioids, but it improved fatigue, appetite loss, and patient satisfaction. Clinical benefit beyond a short-term effect must be examined in a future study.

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Paulsen O et al J Clin Oncol 32:3221-3228
Overview

• Definition
• Measurement
• Prevalence
• Screening
• Pathophysiology
• Management
  – Non-drug treatments
  – Drug treatments
• Guidelines
Guidelines

• National Comprehensive Cancer Network (NCCN) Clinical practice guidelines
• Oncology Nursing Society
• Canadian Partnership Against Cancer and Canadian Association of Psychosocial oncology
• American Society of Clinical Oncology (ASCO)
NCCN guidelines

• Consensus statement
  – First published 2000, revised annually

• Evidence-based when possible

• Category 1 consensus
  – There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate

• Category 2a consensus
  – There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate
## Interventions for Patients at the End of Life

**Patient/Family Education and Counseling**

- Information about known pattern of fatigue during and following treatment
  - Expected end-of-life symptom
  - May vary in intensity

**General Strategies for Management of Fatigue**

- Energy conservation
  - Set priorities
  - Pace
  - Delegate
  - Schedule activities at times of peak energy
- Labor-saving and assistive devices (including wheelchairs, walkers, and commodes)
- Eliminate nonessential activities
- Structured daily routine
- Attend to one activity at a time
- Conserve energy for valued activities
- Use distraction (eg, games, music, reading, socializing)
- Find meaning in current situation
  - Emphasis on meaningful interactions
  - Promote dignity of patient

**Nonpharmacologic**

- Activity enhancement
  - Optimize level of activity with careful consideration of the following constraints:
    - Bone metastases
    - Thrombocytopenia
    - Anemia
    - Fever or active infection
    - Assessment of safety issues (ie, risk of falls, stability)
  - Psychosocial interventions

**Pharmacologic**

- Consider psychostimulants (methylphenidate or modafinil) after ruling out other causes of fatigue
- Consider corticosteroids (prednisone or dexamethasone)
- Treat for pain, emotional distress, and anemia as indicated per NCCN Guidelines (See appropriate NCCN Guidelines for Supportive Care)
- Optimize treatment for sleep dysfunction and comorbidities

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**Footnotes:**

- See Discussion for information on differences between active treatment, post-treatment, and end-of-life treatment. (See MS-1)
- Examples include use of reachers for grasping items beyond arm’s length, sock aids for pulling on socks, rolling carts for transporting items, escalators and elevators for traveling between building floors, and electrical appliances for performing common household tasks (eg, opening cans).
- Pharmacologic interventions should be culturally specific and tailored to the needs of patients and families along the illness trajectory, because not all patients may be able to integrate these options due to variances in individual circumstances and resources.
- Psychostimulants remain investigational, but have been reported to improve symptoms of fatigue in some patients. There is more evidence for methylphenidate and less for modafinil. These agents should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterized or excluded. Optimal dosing and schedule have not been established for use of psychostimulants in cancer patients.
- Also See NCCN Guidelines for Palliative Care.

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**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Summary

- Cancer-related fatigue is common and debilitating
- Screen patients for fatigue
- Treat reversible causes
- Consider
  - Aerobic exercise
  - Psycho-educational approaches
  - Methylphenidate / Methylprednisolone
  - Ginseng