Exhausted? Let’s *Stimulate* the Discussion on Cancer-Related Fatigue!

Pharmacotherapy Rounds

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**Learning Objectives**

1. Explore the incidence and complications of cancer-related fatigue
2. Identify risk factors for cancer-related fatigue
3. Evaluate literature for evidence in psychostimulants and cancer-related fatigue
4. Summarize recommendations regarding psychostimulant use in cancer-related fatigue
Cancer-Related Fatigue (CRF)

I. Epidemiology
   a. Nearly 13 million people have a history of cancer in the United States
      i. 1.6 million people will be diagnosed this year
      ii. Approximately 66.1% will survive at least 5 years after diagnosis
      iii. Fatigue is the most common symptom patients experience with cancer with prevalence rates above 60% to 90%
   b. CRF affects quality of life, physical and psychosocial functioning, and decreases adherence to chemotherapy
   c. Reported as the most distressing symptom associated with cancer and its treatment, more than pain, nausea, or vomiting

II. Definition
   a. “Unusual, persistent, subjective sense of tiredness related to cancer and cancer treatment that interferes with usual functioning” per the National Comprehensive Cancer Network (NCCN)

III. Diagnosis
   a. Fatigue must be persistent with increasing need for rest, limb heaviness, diminished concentration, inertia, emotional lability, and post-exertional malaise with cancer or treatment for cancer serving as underlying cause

<table>
<thead>
<tr>
<th>Table 1. International Classification of Diseases (10th edition) Criteria7</th>
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</thead>
<tbody>
<tr>
<td>Symptoms have been present every day or nearly every day during the same 2-week period in the past month</td>
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<tr>
<td>• Significant fatigue, diminished energy or increased need of rest, disproportionate to any recent change in activity level</td>
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<tr>
<td>• Plus five (or more) of the following</td>
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<tr>
<td>o Complaints of generalized weakness or limb heaviness</td>
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<td>o Diminished concentrations or attention</td>
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<td>o Decreased motivation or interest in engaging in usual activities</td>
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<td>o Insomnia or hypersomnia</td>
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<td>o Experience of sleep as unrefreshing or nonrestorative</td>
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<tr>
<td>o Perceived need to struggle to overcome inactivity</td>
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<tr>
<td>o Marked emotional reactivity (sadness, frustration, or irritability) to feeling fatigued</td>
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<tr>
<td>o Difficulty in completing daily tasks attributed to feeling fatigued</td>
</tr>
<tr>
<td>o Perceived problems with short-term memory</td>
</tr>
<tr>
<td>o Post-exertional malaise lasting several hours</td>
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</tbody>
</table>

   • The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning
   • There is evidence from history, physical examination, or laboratory findings that symptoms are a consequence of cancer or cancer-related therapy
   • The symptoms are not primarily the consequence of comorbid psychiatric disorders, such as major depression, somatization disorder, somatoform disorder or delirium

IV. Mechanism of CRF
   a. Not well understood
Figure 1. Mechanisms in CRF²³
HPA: Hypothalamic-pituitary—adrenal axis; ATP: adenosine triphosphate; CRF: cancer-related fatigue

V. Etiology of CRF²⁷,⁸

VI. Contributory comorbid conditions²³,⁹

<table>
<thead>
<tr>
<th>Table 2. Comorbidities</th>
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<tbody>
<tr>
<td>Type</td>
</tr>
<tr>
<td>Anemia</td>
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<tr>
<td></td>
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<tr>
<td>Cachexia/Nutritional disorders</td>
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<td></td>
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<td></td>
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<tr>
<td>Sleep Disorders</td>
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<tr>
<td>Depression</td>
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</tbody>
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Figure 2. Causes of Fatigue⁸
Management

I. Non pharmacological
   a. Energy conservation and activity management (ECAM)\textsuperscript{10,11}
      i. Allows patients to find ways to decrease effort required to perform, to eliminate, and to
         alternate rest and activity with tasks
      ii. ECAM has been found to have a modest benefit in patients with cancer undergoing
           cancer treatment
   b. Cognitive-behavioral therapy (CBT)\textsuperscript{12}
      i. Increase cognitive control through cognitive restructuring, relaxation, imagery, visualization, attention diversion
      ii. May be beneficial in improving cancer-related symptoms of pain, sleep disturbance, as well as fatigue
   c. Acupuncture\textsuperscript{10,13}
      i. In a randomized controlled trial 302 patients were evaluated with 6 weeks of acupuncture vs usual care, and found improvements in fatigue
      ii. Further study needed to conclude benefits with this intervention
   d. Psychosocial interventions\textsuperscript{10}
      i. Management of anxiety, stress, depression through support groups, education, and counseling, guided imagery
      ii. Three meta-analyses showed that psychosocial interventions had a small to moderate effect on CRF
   e. Exercise\textsuperscript{10}
      i. Meta-analyses have found exercise effectively reduces fatigue\textsuperscript{12}
         1. Moderate effect on fatigue, however, fatigue was not used as a criteria for study entry in trials
         2. Type of exercise range from aerobic to home programs that reduce CRF
      ii. Mixed effects are reported for resistance exercise
      iii. Guidelines from the American College of Sports Medicine (ACSM) recommend patients with cancer engage in at least 150 minutes of moderate aerobic activity each week
      iv. Fatigue may serve as barrier to participate in exercise interventions in which other strategies may be appropriate

II. Pharmacological treatments
   a. Minton et al (2010) conducted meta-analysis of total of 50 studies (only 31 studies suitable for analysis) evaluating CRF\textsuperscript{14}
      i. Psychostimulants: lead to an observable improvement in fatigue
      ii. Erythropoietin: provides significant reduction in fatigue
      iii. Darbepoietin: fatigue reduced but not clinically significance
      iv. Paroxetine: trials demonstrate an improvement in mood without associated improvement in fatigue
      v. Progestational steroids: no superiority over placebo for this class of drugs
      vi. Conclusion: further randomized control trials needed, but psychostimulants may be helpful in CRF
b. Erythropoietin-stimulating agents (ESA)\textsuperscript{15}
   i. Corrects anemia with hemoglobin $<$10 g/dL to decrease fatigue
   ii. Adverse drug reaction: Increased risk of thrombotic events, hypertension, tumor growth, decreased survival
   iii. ESAs are not indicated for use of CRF treatment and should only be used for anemia treatment

c. Antidepressants
   i. Paroxetine\textsuperscript{6}
      1. Mechanism of action: selective serotonin reuptake inhibitor
      2. Studies evaluating effectiveness of paroxetine in treating fatigue during and post-cancer treatment resulted in no beneficial effect on fatigue
   ii. Sertraline\textsuperscript{16}
      1. Mechanism of action: selective serotonin reuptake inhibitor
      2. No improvement in symptoms, well-being, or survival in patients with advanced cancer without major depression
   iii. Bupropion\textsuperscript{17,18}
      1. MOA: primarily dopaminergic and noradrenergic
      2. Some potential as an effective pharmaceutical agent for treating CRF

d. Donepezil\textsuperscript{19}
   i. Mechanism of action: long-acting selective acetylcholinesterase inhibitor
   ii. In a prospective, double-blind, placebo, randomized, controlled trial to evaluate the effectiveness of donepezil vs placebo on fatigue with patients with advanced cancer, no benefit found

e. Thyreoliberin\textsuperscript{20}
   i. Mechanism of action: thyrotropin-releasing hormone [TRH] regulating thyroid axis and may produce mood elevating effects
   ii. Proof-of-concept study suggest benefits with TRH in the treatment of CRF

f. Levocarnitine\textsuperscript{1}
   i. Mechanism of action: micronutrient important for the processing of long-chain fatty acids and energy production in mammalian cells
   ii. Conclusions from studies treating CRF limited by small sample size and study design, but results encourage further study


g. Ginseng\textsuperscript{20,21}
   i. Mechanism of action: reduce cytokines related to inflammation and to help regulate cortisol levels
   ii. American ginseng product safe and potentially effective at 2000 mg daily for 8 weeks
   iii. More research is needed to confirm findings that this agent is beneficial
   iv. One major disadvantage of ginseng is lack of regulation, potentially allowing dosing inconsistencies and contamination

h. Guarana (\textit{Paullinia cupana})\textsuperscript{23}
   i. Mechanism of action: stimulates sympathetic neurons
   ii. Improved CRF in women undergoing chemotherapy for breast cancer
i. Corticosteroids
   i. Yennurajalingam et al\textsuperscript{24}
      1. 84 patients with advanced cancer treated with dexamethasone 4 mg or placebo twice daily for 14 days
      2. Found improvement in FACIT-F score (Appendix A) without differences in adverse effects

j. Psychostimulants

\textbf{Methylphenidate}\textsuperscript{14,20}

\textbf{Indications/Uses:}
- Approved for the treatment of attention deficit hyperactivity disorder and narcolepsy

\textbf{Mechanism of action}
- Inhibits dopamine and norepinephrine reuptake into cell
- Stimulates neurotransmitter production resulting in increased dopamine levels to bind active receptors

\textbf{Adverse events (AE):}
- Irritability, anorexia, insomnia, mood lability, nausea, tachycardia, potential cardiovascular effects, growth restriction

\textbf{Modafinil}\textsuperscript{25,26}

\textbf{Indications/Uses:}
- Wake promoting agent, obstructive sleep apnea, narcolepsy, Parkinson’s disease, multiple sclerosis

\textbf{Mechanism of action}
- Affects histamine, epinephrine, \greekgamma-aminobutyric acid (GABA), and glutamate
- Enhances catecholamine signaling and decreases GABA release by binding directly to dopamine/norepinephrine receptors

\textbf{AE:}
- Headache, infection, nausea, nervousness, anxiety, and insomnia

\textbf{Clinical Question: What is the role of psychostimulants in cancer-related fatigue?}

I. Literature evaluation
   a. Methylphenidate (MPH)
      i. Systematic review: Gong et al 2014
      ii. Lower et al 2009
      iii. Bruera et al 2013
   b. Modafinil
      i. Jean-Pierre et al 2010
      ii. Spathis et al 2014
### Purpose

To evaluate use, efficacy, and safety of MPH in the treatment of CRF

### Included Trials

- Bruera et al 2006
- Butler et al 2007
- Lower et al 2009
- Moraska et al 2010
- Roth et al 2010

### Outcomes

- Primary outcome: fatigue scores with FACT-F and BFI

### Results

- Subgroup analyses showed efficacy of MPH improved with longer treatment duration
  - $-3.70$ (95% CI $(-7.03$ to $-0.37)$; $p = 0.03$) for long-time group ($>4$ weeks)
  - $-2.49$ (95% CI $(-6.01$ to $1.03)$; $p = 0.17$) for short-time group ($<4$ weeks)
- More reported vertigo, anxiety, anorexia, and nausea in MPH vs PB but no statistically significant risk ratio for study discontinuation ($p=0.17$)

### Critique

#### Strengths

- Variety of cancers (breast, prostate, lung, genitourinary, gastrointestinal, hematologic, brain tumor) investigated
- Randomized trials chosen
- Separated FACT-F and BFI scales

#### Limitations

- Few studies available
- Numbers of patients were very small
- Heterogeneity with BFI scale
- Did not define psychiatric conditions

### Conclusion

- Limited evidence for the use of MPH to treat CRF but may be effective for management

### Take Home Points

- Long term treatment ($>4$ weeks) may be beneficial over short term treatment ($<4$ weeks)

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<thead>
<tr>
<th>Purpose</th>
<th>To evaluate use, efficacy, and safety of MPH in the treatment of CRF</th>
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| Included Trials | - Bruera et al 2006  
- Butler et al 2007  
- Lower et al 2009  
- Moraska et al 2010  
- Roth et al 2010 |
| Outcomes | Primary outcome: fatigue scores with FACT-F and BFI |
| Results | |
| Critique | Strengths  
- Variety of cancers (breast, prostate, lung, genitourinary, gastrointestinal, hematologic, brain tumor) investigated  
- Randomized trials chosen  
- Separated FACT-F and BFI scales |
| | Limitations  
- Few studies available  
- Numbers of patients were very small  
- Heterogeneity with BFI scale  
- Did not define psychiatric conditions |
| Conclusion | Limited evidence for the use of MPH to treat CRF but may be effective for management |
| Take Home Points | Long term treatment ($>4$ weeks) may be beneficial over short term treatment ($<4$ weeks) |

BFI: Brief Fatigue Inventory; CRF: cancer-related fatigue; FACT-F: Functional Assessment of Cancer Therapy for Fatigue; MPH: methylphenidate; PB: placebo

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To determine if dexmethylphenidate (D-MPH) will reduce fatigue vs placebo after chemotherapy in cancer patients</th>
</tr>
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<tbody>
<tr>
<td>Design</td>
<td>Multicenter, randomized, placebo-controlled, parallel-group study</td>
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</table>
| Population | • Inclusion: men or women aged 18–70 years with cancer, previously treated with ≥4 cycles chemotherapy completed ≥2 months, life expectancy of >6 months, ECOG ≤2, MMSE ≥20, BDI-II <18 (no greater than moderate depression), CGI-S score ≥3 (mildly impaired)  
  • Exclusion: concurrent treatment with anticancer therapies (biological and/or radiation therapy), history of major psychiatric illness, prior treatment with MPH/D-MPH, use of monoamine oxidase inhibitors within 30 days, seizure disorder or drug/alcohol abuse |
| Methods | • 5 mg D-MPH twice a day (10 mg/day) vs PB twice a day up to 50 mg daily  
  • Subjects seen weekly for efficacy and safety assessments |
| Outcomes | • Primary: change from baseline in the FACIT-F total score at Week 8  
  • Secondary: cognitive function |
| Statistical Analysis | • Required 60 subjects per group to detect a 15% relative difference with 80% power  
  • ANCOVA for primary analysis  
  • T test for continuous variables, Fisher’s exact test for categorical measures, Cochran-Mantel-Haenszel test for categorical variables |
| Results | • Baseline characteristics: well matched except D-MPH-treated subjects had lower screening ECOG performance status scores  
  • N=154 (breast and ovarian cancers, post chemotherapy)  
  • Most commonly reported AEs were headache, nausea, and dry mouth; higher rate of AEs in the D-MPH treatment group  
  • 11% vs 1.3% (D-MPH vs PB) had AEs that led to study discontinuation (p=0.02) |
| Efficacy outcomes | D-MPH | PB | P Value |
| FACIT-F score at Week 8 [mean(SEM)] | -10.5 (1.2) | -6.8 (1.2) | 0.02 |
| CGI-S score of 1, 2, or 3 at Week 8 [n(%)] | 54 (72) | 45 (58.4) | 0.02 |
| CGI-I score of 1, 2, or 3 at Week 8 [n(%)] | 58 (77) | 52 (68) | 0.06 |
| HSCS overall score [mean(SEM)] | 12.2 (1.8) | 9.0 (1.7) | 0.18 |
| Modified SNAP score [mean(SEM)] | 8.7 (0.9) | 8.4 (0.9) | 0.81 |

<table>
<thead>
<tr>
<th>Select Adverse Events</th>
<th>% D-MPH (n=76)</th>
<th>% PB (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>40.8</td>
<td>33.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>27.6</td>
<td>7.7</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>26.3</td>
<td>12.8</td>
</tr>
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<table>
<thead>
<tr>
<th>Critique</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Randomized, double-blinded</td>
<td>• Almost all female with breast cancer/ovarian cancer</td>
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<td></td>
<td>Excluded psychiatric disorders</td>
<td>• Stage of disease not reported</td>
</tr>
<tr>
<td></td>
<td>Defined CRF from proposed ICD 10 criteria</td>
<td>• Considerably younger (mean age 53)</td>
</tr>
<tr>
<td></td>
<td>Longer follow up</td>
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| Conclusion | D-MPH produced significant improvement in fatigue but no reduction in cognitive impairment |
| Take Home Points | • More AE seen with D-MPH vs placebo  
  • May provide improvement in women with breast/ovarian cancer during chemotherapy |

ADD: attention deficit disorder; BDI-II: Beck Depression Inventory-ll; CGI-I: Clinical Global Impression- Improvement; CGI-S: Clinical Global Impression-Severity; D-MPH: dexmethylphenidate; ECOG: Eastern Cooperative Oncology Group; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue Subscale; HSCS: High Sensitivity Cognitive Screen; MMSE: mini-mental status examination; PB: placebo; SEM: standard error of mean; SNAP: Swanson, Nelson Pelham Attention Deficit/Hyperactivity Scale

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To compare the effects of methylphenidate vs placebo on CRF</th>
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<tbody>
<tr>
<td>Design</td>
<td>• Randomized, placebo-controlled, phase II trial</td>
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<tr>
<td></td>
<td>• 5mg MPH every 2 hours PRN up to 20 mg daily vs PB for 14 days + NTI calls 4-6 times over 2 weeks</td>
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<tr>
<td></td>
<td>• 5 mg every 2 hours PRN up to 20 mg daily vs PB for 14 days + CTI calls 4-6 times over 2 weeks</td>
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<tr>
<td>Population</td>
<td>• Inclusion: advanced cancer, ≥ 4 on ESAS scale, ≥24 on MMSE, Hgb ≥8 g/dL, no history of tachycardia, arrhythmia, uncontrolled hypertension, glaucoma, severe anxiety disorders, major depression, substance abuse; not currently taking monoamine oxidase inhibitors, tricyclic antidepressants, clonidine, warfarin, or erythropoietin</td>
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<tr>
<td></td>
<td>• Exclusion: pregnant, lactating</td>
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<tr>
<td>Outcomes</td>
<td>• Primary: median difference in FACIT-F fatigue at day 15</td>
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<tr>
<td></td>
<td>• Secondary: anxiety, depression, sleep</td>
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<tr>
<td>Statistical Analysis</td>
<td>• Wilcoxon two-sample test</td>
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<td>• Kruskal-Wallis test</td>
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<td>• Signed ranked test</td>
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<td></td>
<td>• Chi-square test for adverse events</td>
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<td></td>
<td>• Two-sided tests with p&lt;0.05 considered statistically significant</td>
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<tr>
<td>Results</td>
<td>• Baseline characteristics: No statistically significant differences, well matched</td>
</tr>
<tr>
<td></td>
<td>• N=141</td>
</tr>
<tr>
<td>FACIT-F Score</td>
<td>ESAS Fatigue Score</td>
</tr>
<tr>
<td>Treatment</td>
<td>Median Day 15</td>
</tr>
<tr>
<td>MPH</td>
<td>5.5</td>
</tr>
<tr>
<td>PB</td>
<td>6</td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
</tr>
<tr>
<td>NTI</td>
<td>6</td>
</tr>
<tr>
<td>CTI</td>
<td>5.5</td>
</tr>
<tr>
<td>All groups</td>
<td></td>
</tr>
<tr>
<td>MPH + NTI</td>
<td>4</td>
</tr>
<tr>
<td>MPH + CTI</td>
<td>7</td>
</tr>
<tr>
<td>PB + NTI</td>
<td>8.5</td>
</tr>
<tr>
<td>PB + CTI</td>
<td>5</td>
</tr>
<tr>
<td>• Grade ≥ 3 adverse events between groups was not statistically significant (p= 0.06)</td>
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</tbody>
</table>

### Critique

#### Strengths
- Randomized, placebo-controlled trial
- Inclusion/exclusion

#### Limitations
- Underpowered
- Stage of cancer/tumor type/chemotherapy not reported
- Low dose of MPH
- Short duration of treatment

### Conclusion
- MPH, NTI, or combination were not superior to PB in CRF improvement

### Take Home Points
- Several cancer-related symptoms were significantly improved in the nursing telephone intervention group compared with those receiving the control telephone intervention
- Absence of methylphenidate effect might have been due to benefit from the nursing intervention showing more benefit than methylphenidate

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CRF: cancer-related fatigue; CTI: control telephone intervention; ESAS: Edmonton Symptom Assessment Scale; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue Subscale; MMSE: mini-mental status examination; MPH: methylphenidate; NTI: nursing telephone intervention

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To evaluate modafinil in cancer patients undergoing chemotherapy</th>
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<tbody>
<tr>
<td>Design</td>
<td>Multicenter, randomized, double-blind, placebo-controlled Phase III clinical trial</td>
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<tr>
<td>Population</td>
<td>Inclusion: at least 18 years old, life expectancy &gt;6 months, initial cancer treatment of at least four planned cycles of chemotherapy at least two weeks apart Exclusion: previous modafinil or psychostimulant use within 30 days, pregnant, nursing, uncontrolled anemia, cardiac disease, uncontrolled hypertension, alcohol or drug abuse, severe headaches, seizure disorder, narcolepsy, Tourette’s syndrome, other psychiatric disorders</td>
</tr>
<tr>
<td>Methods</td>
<td>200 mg daily of modafinil vs PB Treatment began on Day 5 of Cycle 2 and ended after Day 7 of Cycle 4 Medication was discontinued if chemotherapy was discontinue/delayed &gt; three weeks</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary: CRF was assessed using Item 3 of the BFI Secondary: daytime sleepiness, depression</td>
</tr>
<tr>
<td>Statistics</td>
<td>Analyses were performed on an intent-to-treat basis Analysis of covariance (ANCOVA) was used to address the primary objective 586 participants would provide 90% power to detect a difference of 0.75 points between groups, based on an alpha-level of 0.05</td>
</tr>
<tr>
<td>Results</td>
<td>Baseline characteristics: 67% females; baseline cancer: breast 35%; alimentary 25%; lung 16% N=867; 631 with evaluable data</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Change in outcome for modafinil vs placebo at median baseline</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFI-3 (Fatigue)</td>
<td>-0.33</td>
<td>0.08</td>
</tr>
<tr>
<td>ESS (Sleepiness)</td>
<td>-1.03</td>
<td>0.002</td>
</tr>
<tr>
<td>CESD (Depression)</td>
<td>0.34</td>
<td>0.6</td>
</tr>
<tr>
<td>POMS-DD (Depression)</td>
<td>-0.04</td>
<td>0.87</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Fatigue severity at baseline</th>
<th>Difference between modafinil vs placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>0.74</td>
<td>0.09</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.2</td>
<td>0.411</td>
</tr>
<tr>
<td>Severe</td>
<td>-0.44</td>
<td>0.033</td>
</tr>
<tr>
<td>Maximum Fatigue</td>
<td>-0.76</td>
<td>0.01</td>
</tr>
</tbody>
</table>

| Author’s Conclusion | Study supports the use of modafinil as an effective treatment for severe CRF in patients undergoing chemotherapy |
| Critique | Strengths Limitations |
|---|---|---|
| Blinded | Single item fatigue measure potential susceptible to bias |
| Study design | Mostly female patients |
| Intent to treat | Characterized the severity level of CRF |
| Heterogeneous sample | |

| Take Home Points | Modafinil shown to reduce excessive daytime sleepiness Although the difference between the group adjusted means was statistically significant this small change is unlikely to be of clinical significance May be helpful in severely fatigued patients No difference in alleviating depression |

AE: adverse events; BFI: Brief Fatigue Inventory; CES-D: Center for Epidemiologic Studies Depression; CRF: cancer-related fatigue; ESS: Epworth Sleepiness Scale; PB: placebo; POMS: Profile of Mood States Depression Dejection

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To establish its efficacy and tolerability in fatigued patients with advanced non-small cell lung cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Placebo-controlled, double-blind, randomized-controlled trial.</td>
</tr>
<tr>
<td>Population</td>
<td>Inclusion: adult outpatients with stage 3a/3b/4 NSCLC, WHO performance status of 0 to 2, numeric rating scale score of ≥ 5. Exclusion: received radiotherapy or chemotherapy within the last 4 weeks; blood transfusion, steroids, or antidepressants in the last 2 weeks; major psychiatric illness; uncontrolled hypertension; history of arrhythmia; left ventricular hypertrophy.</td>
</tr>
<tr>
<td>Methods</td>
<td>Modafinil 100 mg days 1-14 and 200 mg days 15-28 vs PB. Assessments in clinic/telephone on days 0, 14, and 28.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary: fatigue measured by FACIT. Secondary: daytime sleepiness, depression, and quality of life.</td>
</tr>
<tr>
<td>Statistics</td>
<td>Required sample size of 206 to have 80% power. Modified intention-to-treat (ITT) analysis. Changes in FACIT-Fatigue score at day 28 from baseline compared using ANCOVA. Secondary outcomes analyzed by ANCOVA or Mann-Whitney U test.</td>
</tr>
</tbody>
</table>

### Results

#### Difference Between Treatments

<table>
<thead>
<tr>
<th>Scale</th>
<th>∆ in Modafinil arm</th>
<th>∆ in PB arm</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACIT-F 28 days</td>
<td>5.29</td>
<td>5.09</td>
<td>0.92</td>
</tr>
<tr>
<td>FACIT-F 14 days</td>
<td>5.78</td>
<td>4.33</td>
<td>0.33</td>
</tr>
<tr>
<td>ESS</td>
<td>-1.84</td>
<td>-1.78</td>
<td>0.94</td>
</tr>
<tr>
<td>HADS-Depression</td>
<td>-1</td>
<td>0</td>
<td>0.39</td>
</tr>
<tr>
<td>QOL-LAS</td>
<td>0</td>
<td>0</td>
<td>0.60</td>
</tr>
</tbody>
</table>

#### Adverse Effects

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Modafinil</th>
<th>PB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>22.1%</td>
<td>24.3%</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>15.4%</td>
<td>19.4%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>8.7%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Other</td>
<td>43.3%</td>
<td>34%</td>
</tr>
<tr>
<td>Any</td>
<td>55.8%</td>
<td>54.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Exploratory analyses showed no difference across subgroups defined by stage of disease, performance status, age, sex, and severity of baseline fatigue.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More withdrew from the modafinil than PB group (modafinil, n=30; PB, n=16; p &lt;0.02)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Author's Conclusion

There is insufficient evidence to prescribe modafinil for patients with CRF outside of a clinical trial.

#### Critique

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-blind trial</td>
<td>Speaking on phone may serve as benefit</td>
</tr>
<tr>
<td>Largest trial with modafinil</td>
<td>Attrition rate of 22%</td>
</tr>
<tr>
<td>Sample size met power</td>
<td>No baseline depression score</td>
</tr>
<tr>
<td>Intent-to-treat analysis</td>
<td></td>
</tr>
<tr>
<td>Frequent follow up assessments</td>
<td></td>
</tr>
</tbody>
</table>

#### Take Home Points

- Clinically significant placebo effect found in this trial is an important finding.
- Patients with severe fatigue did not show benefit.
- Modafinil had a greater dropout rate vs placebo.
- Safety of modafinil has not been established.

ANCOVA: analysis of covariance; CRF: cancer-related fatigue; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; ESS: Epworth Sleepiness Scale; HADS: Hospital Anxiety and Depression Scale; ITT: intent to treat; NSCLC: non-small cell lung cancer; PB: placebo; QOL-LAS: Quality of life linear analog scale; WHO: World Health Organization.
Summary

Concerns with Trials in CRF and Psychostimulants

I. Overall concern with trials
   a. Potential heterogeneity of study populations
   b. No consensus defining CRF
   c. Small number of patients
   d. Patients suffer from concomitant conditions attributable to fatigue
   e. Short term treatment
   f. Safety data for long term use is unavailable in CRF
   g. CRF includes patients with very different potential causes of fatigue
   h. Open-label designs without placebo
   i. Baseline fatigue assessment difficult

Safety Concerns

I. Methylphenidate
   A. In 2006, safety concerns reported with MPH as treatments for ADHD regarding cardiovascular safety
   B. MPH may increase blood pressure, heart rate, headache, insomnia, decrease appetite, mucosal dryness, and some neurological symptoms
   C. Schelleman et al (2012) found initiation of MPH associated with a 1.8 fold risk in sudden death or ventricular arrhythmia but may be due to chance
   D. Lasheen et al (2013) found MPH in advanced cancer (n=62), is well tolerated with some agitation, insomnia, and dry mouth in a retrospective analysis

II. Modafinil
   A. Insomnia, irritability, muscle tension, headache, appetite suppression seen in < 20% of patients
Conclusion and Recommendations

I. Current National Comprehensive Cancer Network (NCCN) guidelines (2014) and American Society of Clinical Oncology (ASCO) guidelines (2014) recommend physical activity, psychosocial interventions, management of co-morbidities, and possible use of psychostimulants.\textsuperscript{5,37}

II. Should we be using psychostimulants in our CRF patients?
   a. Modafinil should not be considered at this time due to mixed effectiveness and lack of robust studies
   b. Methylphenidate has mixed data regarding effectiveness, but due to adverse effects seen in trials, should not be considered at this time
Reference:


Sen
46. Smarr KL, Kiefer AL. Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). Arthritis Care Res. 2011;63(5):5454-66.
## Appendices

### Appendix A. Select Fatigue Measures

**Brief Fatigue Inventory (BFI)**[^3][^38]
- Uni-dimensional
- Evaluates fatigue over 24 hours
- ≥ 7 correlates with severe fatigue
- 9 items:
  - 3 items: current, usual, and worst fatigue in the past 24 hours
  - 6 items: extent fatigue interferes with different aspects of life (work or social) during the preceding 24 hours

**Edmonton Symptom Assessment Scale (ESAS)**[^39]
- Multi-dimensional
- Assesses 9 symptoms on a visual analogue scale
  - Pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, anorexia, well-being
- Valid/reliable for assessing intensity of symptoms in patients with cancer

**Functional Assessment of Cancer Therapy for Fatigue (FACT-F)**[^40][^41]
- Multi-dimensional
- General quality of life with 28 questions and an additional 13 questions on fatigue (the ‘fatigue’ subscale)
- Two to three point change is the clinically significant difference reported for this scale

**Fatigue Symptom Inventory (FSI)**[^42]
- Multi-dimensional
- 13-item self-reported instrument that was designed to measure the intensity and duration of fatigue and its interference with the individual's ability to participate fully in life in last 7 days
- Validated measure of both overall fatigue and of how fatigue might interfere with activities of daily living

**MD Anderson Symptom Inventory (MDASI)**[^43]
- Uni-dimensional
- 13-item symptom common across all cancer types (pain, fatigue, nausea, disturbed sleep, being distressed, shortness of breath, difficulty remembering, lack of appetite, feeling drowsy, dry mouth, feeling sad, vomiting, and numbness or tingling)

**Multidimensional Fatigue Symptom Inventory (MFSI)**[^41]
- Multidimensional
- Evaluates global, somatic, affective, cognitive and behavioral symptoms of fatigue
- 83-item questionnaire
- Items are rated on a 5-point scale

**Multidimensional Fatigue Symptom Inventory Short Form (MFSI-SF)**[^44]
- Multidimensional
- 30-item measure evaluating general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor
- Reliable and valid scale in cancer patients

### Appendix B. Other Measures

**Beck Depression Inventory (BDI)**[^45][^46]
- Measures depression
- Examine both somatic and cognitive aspects of depression
- The BDI is a 21-item self-reporting scale

**Beck Depression Inventory II**[^46]
- Indicates severity of depression
- 21-item scale
- Revision of BDI (above)
### Center for Epidemiology - Depression (CES-D)\(^{47}\)
- Measures depression in past week
- 20-item measure
- >16 cutoff = at risk for depression

### Clinical Global Impression Scale\(^{48}\)
- Easy to use and applicable to all psychiatric disorders
- **Clinical Global Impression Severity Scale (CGI-S)**: symptoms, behavior, and function in the past seven days
- **Clinical Global Impression Improvement Scale (CGI-I)**: measure at baseline and then compare the patient’s overall clinical condition to the one week period just prior to the initiation of medication
- No universally accepted scoring guidelines for the seven anchor points; designed to be based solely on clinical judgment

### Eastern Cooperative Oncology Group (ECOG)\(^{49}\)
- Assesses functional status in cancer correlating with patient survival
- Score 0: fully active, carry all pre-disease performance without restriction
- Score 5: dead

### Epworth Sleepiness Scale (ESS)\(^{31}\)
- Measures daytime sleepiness
- Differentiates between average sleep issues that require intervention

### High Sensitivity Cognitive Screen (HSCS)\(^{9}\)
- Tests six cognitive domains (memory, language, visual-motor, spatial, attention/concentration, self-regulation/planning)
- Sensitive in detecting subtle cognitive impairment

### Hospital Anxiety and Depression Scale (HADS)\(^{45}\)
- Detects depression and anxiety in outpatient clinic
- Identifies patients requiring further psychiatric evaluation and assistance, not for diagnosis

### Mini-Mental State Exam (MMSE)\(^{50}\)
- Assesses cognitive function (screen, severity of impairment)
- Scores 0-30 (30 means normal, 0 means impaired)

### Quality of Life Linear Analog Scale (QOL-LAS)\(^{51}\)
- Measures quality of life
- Single-item measure comparable to multi-item global measures
- Recommended in lung cancer trials

### Profile of Mood States (POMS)\(^{52}\)
- Assesses transient, fluctuating affective mood state
- 65 item scale
- Measures six identifiable mood/affective states: Tension-Anxiety (T), Depression-Dejection (D), Anger-Hostility (A), Vigor-Activity (V), Fatigue-Inertia (F), and Confusion-Bewilderment (C)

### Swanson, Nelson Pelham Attention Deficit/Hyperactivity Scale (SNAP)\(^{28}\)
- Assesses inattention and hyperactivity/impulsivity in children
- Modified scale may be used to assess behavioral symptoms in adults

### Appendix C. Medication Review\(^{39,34}\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Excretion</th>
<th>Half Life</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate (Ritalin, Concerta)</td>
<td>2.5 mg/day up to 54 mg/day; administer 30-45 minutes prior to meals</td>
<td>Urine</td>
<td><em>d</em>-MPH: 6 hours; <em>l</em>-MPH: 1-3 hours</td>
<td>Cardiovascular events, peripheral vasculopathy, priapism, visual disturbance, hypertension, psychiatric disorder, seizures disorder, abuse potential</td>
</tr>
<tr>
<td>Dexmethylphenidate (Focalin)</td>
<td>2.5 mg/day up to 27 mg/day</td>
<td>Urine</td>
<td>2-4.5 hours</td>
<td>CNS effects, dermatologic effects, hypersensitivity disorders, headache, decreased appetite</td>
</tr>
<tr>
<td>Modafinil (Provigil)</td>
<td>50 mg up to 200 mg daily</td>
<td>Urine</td>
<td>15 hours</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Intervention/Scale Used</td>
<td>Conclusion</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------------</td>
<td>----------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
</tr>
</tbody>
</table>
| Morrow 2005<sup>55</sup>  
N=51; completed breast cancer treatment | OL study               | Modafinil 200 mg daily for 4 weeks | Patients with fatigue persisting two years post cancer treatment showed benefit with modafinil |
| Morrow 2006<sup>56</sup>  
N=82 women with breast cancer | OL study               | Modafinil 200 mg daily for 4 weeks | Modafinil reduced CRF in breast cancer patients for whom fatigue persisted up to two years post chemotherapy |
| Blackhall 2009<sup>57</sup>  
N=27 | OL, pilot study         | Modafinil 100 mg weeks 1-2, 200 mg weeks 3-4 BFI | Study showed modafinil improved BFI score by end of 4 weeks |
| Spathis 2009<sup>58</sup>  
N=20; NSCLC | OL, pilot study         | Modafinil 100 mg for one week up to 200 mg in second week BFI | Modafinil showed decreased fatigue scores during 14 day study period |
| Boele 2013<sup>59</sup>  
N=37; glioma or meningioma | Multicenter, DB, PB, crossover study | Modafinil 200 mg daily up to 400 mg daily vs placebo for 6 weeks CIS | Study did not find beneficial effects of modafinil on fatigue, depression, overall HRQOL, or cognitive functioning vs placebo |
| Hovey 2014<sup>60</sup>  
N=83; metastatic prostate/ breast cancer undergoing docetaxel chemotherapy (every 21 days; minimum dose 50 mg/m<sup>2</sup>) | Phase III, multicenter, R, DB, PB study | Modafinil 200 mg daily vs PB for 15 days MDASI | Study found trend towards improvement of docetaxel-related fatigue with modafinil. Complications included nausea and vomiting |

BFI: Brief Fatigue Inventory; CIS: Checklist Individual Strength; DB: double-blind; FACT-F: Functional Assessment of Cancer Therapy for Fatigue; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; LHRH: luteinizing hormone releasing hormone; NSCLC: non-small cell lung cancer; OL: open-label; PB: placebo; R: randomized
# Appendix E. Methylphenidate trials and CRF

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention/Outcome measure used</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| Sarhill 2001<sup>60</sup>  
N=9 with advanced cancer treated with methylphenidate | Prospective, OL, pilot trial | Methylphenidate 10 mg BID | Methylphenidate relieves fatigue in advanced cancer with few side effects |
| Sugawara 2002<sup>61</sup>  
N=14; advanced cancer | Pilot study | Methylphenidate 5-10 mg daily  
VAS | Improved fatigue after 7 days but without a validated fatigue instrument |
| Bruera 2003<sup>62</sup>  
N=31 | Prospective, OL study | Methylphenidate 5 mg up to 20 mg daily for 7 days | Methylphenidate administration improved fatigue, appetite, anxiety, and insomnia |
| Bruera 2006<sup>63</sup>  
N=112 | R, DB, PB trial | Methylphenidate 5 mg up to 20 mg daily vs placebo for 7 days  
FACIT-F | Both methylphenidate and placebo resulted in symptom improvement, but methylphenidate was not superior to PB; methylphenidate was not significantly superior to placebo after 1 week of treatment |
| Hanna 2006<sup>64</sup>  
N=37, with breast cancer (moderate to severe fatigue) | Phase II trial | Methylphenidate 5 mg BID for 6 weeks  
BFI | Women with breast cancer suffering from moderate to severe fatigue may benefit from methylphenidate |
| Butler 2007<sup>65</sup>  
N=68, primary brain tumor patients undergoing radiotherapy | Phase III, prospective, R, trial | D-methylphenidate 5 mg BID up to 15 mg daily vs placebo for 8 weeks  
FACT-F | High dropout rate over time and final analysis conducted on smaller sample size than original one; study did not show improvement in fatigue |
| Mar Fan 2008<sup>66</sup>  
N=57 women | R, PB, DB trial | D-Methylphenidate 5 mg BID up to 10 mg BID vs PB for 12 weeks  
FACT-F | No benefit on fatigue or cognitive dysfunction. However, study lacked power to determine difference |
| Johnson 2010<sup>67</sup>  
N=32 women, gynecologic cancer | OL trial | Methylphenidate 5 mg to 10 mg BID over a 8-week period  
FSI | This study supports use of methylphenidate in active treatment for recurrent gynecologic cancer |
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Cancer Type/Condition</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moraska 2010&lt;sup&gt;58&lt;/sup&gt;</td>
<td>148</td>
<td></td>
<td>Phase III, R, DB, PB study</td>
<td>Methylphenidate (target dose, 54 mg/d) or placebo for 4 weeks</td>
<td>Trial was unable to support long-acting methylphenidate in decreasing CRF. Subset showed patients with more severe fatigue and more advanced disease did have some fatigue improvement</td>
</tr>
<tr>
<td>Roth 2010&lt;sup&gt;59&lt;/sup&gt;</td>
<td>32</td>
<td>Advanced prostate cancer</td>
<td>R, DB PB study</td>
<td>Methylphenidate 5 mg up to 30 mg vs placebo for 6 weeks</td>
<td>Methylphenidate is effective in treating fatigue in men with prostate cancer; however, 37.5% participants had to discontinue methylphenidate because of clinically significant increase in blood pressure or tachycardia</td>
</tr>
<tr>
<td>Cueva 2012&lt;sup&gt;60&lt;/sup&gt;</td>
<td>10</td>
<td>Breast cancer patients treated with docetaxel</td>
<td>Pilot study</td>
<td>Methylphenidate 10 mg BID with one cycle of docetaxel</td>
<td>Pilot study concludes methylphenidate may improve fatigue and quality of life</td>
</tr>
<tr>
<td>Escalante 2014&lt;sup&gt;44&lt;/sup&gt;</td>
<td>42</td>
<td>Lymphoma, myeloma, or breast, gastrointestinal, or lung cancer (no men)</td>
<td>R, DB, PB crossover trial</td>
<td>Methylphenidate 18 mg daily followed by placebo for 4 weeks OR placebo followed by methylphenidate for 4 weeks</td>
<td>This trial included several cancer types, and a majority had advanced disease but did not show improvement in CRF</td>
</tr>
<tr>
<td>Richard 2014&lt;sup&gt;9&lt;/sup&gt;</td>
<td>24</td>
<td>Prostate cancer treated with LHRH agonist (minimum of six months)</td>
<td>Single center, R, DB, PB trial</td>
<td>Methylphenidate up to 10 mg daily for 10 weeks</td>
<td>Methylphenidate arm demonstrated a statistically significant improvement of fatigue</td>
</tr>
<tr>
<td>Siu 2014&lt;sup&gt;72&lt;/sup&gt;</td>
<td>25</td>
<td>Palliative patients</td>
<td>Prospective study</td>
<td>Methylphenidate 5 mg daily for 8 days up to 10 days in 29 days as tolerated</td>
<td>One-third of the patients complained of intolerable side effects and stopped treatment before day 8; no significant improvement seen with methylphenidate</td>
</tr>
</tbody>
</table>

BFI: Brief Fatigue Inventory; DB: double-blind; FACT-F: Functional Assessment of Cancer Therapy for Fatigue; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; LHRH: luteinizing hormone releasing hormone; NSCLC: non-small cell lung cancer; OL: open-label; PB: placebo; R: randomized; VAS: visual analog scale