STRATEGIES TO IMPLEMENT PHARMACOLOGICAL, NUTRACEUTICAL, AND PHYTO-PHARMACEUTICAL INTERVENTIONS TO MANAGE CANCER RELATED FATIGUE

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CONFLICT OF INTEREST

• RESEARCH FUNDING: BAYER, GENENTECH, HELSINN, AMERICAN CANCER SOCIETY, NATIONAL INSTITUTE OF HEALTH (NCI, NINR)

• CONSULTANSHIP: (PFIZER)
OBJECTIVES

• INTRODUCTION
• METHODS
• RESULTS
• FUTURE RESEARCH / PROMISING THERAPIES
• IMPLEMENTATION OF THE GUIDELINES
KEY CONTRIBUTORS

• SRIRAM YENNU MD,MS
• FAUSTO RIOLA MD
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• ZHANNI LU DR PH
• YIMIN GENG (LIBRARIAN)
## Symptom Prevalence, Summarized from the Palliative Symptom Grid

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Cancer</th>
<th>AIDS</th>
<th>Heart disease</th>
<th>COPD</th>
<th>Renal Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>35–96%</td>
<td>63–80%</td>
<td>41–77%</td>
<td>34–77%</td>
<td>47–50%</td>
</tr>
<tr>
<td>Depression</td>
<td>3–77%</td>
<td>10–82%</td>
<td>9–36%</td>
<td>37–71%</td>
<td>5–60%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>13–79%</td>
<td>8–34%</td>
<td>49%</td>
<td>51–75%</td>
<td>39–70%</td>
</tr>
<tr>
<td>Confusion</td>
<td>6–93%</td>
<td>30–65%</td>
<td>18–32%</td>
<td>18–33%</td>
<td>–</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32–90%</td>
<td>54–85%</td>
<td>69–82%</td>
<td>68–80%</td>
<td>73–87%</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>10–70%</td>
<td>11–62%</td>
<td>60–88%</td>
<td>90–95%</td>
<td>11–62%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>9–69%</td>
<td>74%</td>
<td>36–48%</td>
<td>55–65%</td>
<td>31–71%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6–68%</td>
<td>43–49%</td>
<td>17–48%</td>
<td>–</td>
<td>30–43%</td>
</tr>
<tr>
<td>Constipation</td>
<td>23–65%</td>
<td>34–35%</td>
<td>38–42%</td>
<td>27–44%</td>
<td>29–70%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3–29%</td>
<td>30–90%</td>
<td>12%</td>
<td>–</td>
<td>21%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>30–92%</td>
<td>51%</td>
<td>21–41%</td>
<td>35–67%</td>
<td>25–64%</td>
</tr>
</tbody>
</table>

Minimum-maximum range of prevalence (%) is shown
- Joao Paulo Sobrinho, et al
Ontario’s cancer system Data: trajectory of Edmonton Symptom Assessment System (ESAS) symptom scores for Patients With Cancer During the Last Six Months of Life

Hsien Seow et al. Clinical Oncology 29, no. 9 (March 2011) 1151-1158.
DEFINITION
[VERSION 1:2010]

• CANCER-RELATED FATIGUE IS A DISTRESSING PERSISTENT, SUBJECTIVE SENSE OF PHYSICAL, EMOTIONAL, AND/OR COGNITIVE TIREDNESS OR EXHAUSTION RELATED TO CANCER OR CANCER TREATMENT THAT IS NOT PROPORTIONAL TO RECENT ACTIVITY AND INTERFERES WITH USUAL FUNCTIONING.

JCCN 2015 +
FATIGUE

- Deconditioning
- Cachexia
- Mood Disorders
- Renal/Hepatic/Heart Disease
- Bioimmunotherapy/
- Chemotherapy/
- Radiotherapy
- Dehydration
- Infection
- Tumor Byproducts
- Anemia
- Cancer-related symptoms
- Inflammation/Cytokine
- Drugs (including opioids)
Cancer

Individual

Impairment of Mitochondrial/Metabolic Function
IGF, C-peptide, adiponectin, 5'-nucleotidase

Immune Response
Dysregulation
CD3+/CD69+, HLA-DR+/CD11c+/CD14

Dysregulation of Hypothalamic-Pituitary Adrenal (HPA) Axis
Cortisol, adrenocorticotropic hormone, epinephrine, and norepinephrine

Associated Genes
IL-6-174, TNFα-308, PLODI, NPCD1, UGTL1

Inflammation
TNFα, IL-6, IL-1Ra, TGF, sTNF-RII, C-Reactive Protein

Endocrine Function
Testosterone, free and total estradiol, tri-iodothyronine, thyroid-binding and sex-hormone-binding globins

Cancer Related Fatigue

Cancer Treatment
- Cytotoxic Therapy
- Target Therapy
- Hormonal Therapy
- Radiation Therapy

Patient Factors
Age, gender, socioeconomic status, comorbid conditions

Cognitive and Behavioral Symptoms
Anxiety/Depression/Anorexia/Cognitive Dysfunction/Sleep Quality

Impairment of Physical Function/Activity

Anorexia-Cachexia Syndrome
Fat/Muscle Loss

Saligan et al JSCC 2015
MATERIALS AND METHODS

- We reviewed reports of pharmacological, nutraceutical, and phytopharmaceutical interventions effects in adult cancer patients on cancer related fatigue receiving treatment or post-treatment. To be eligible to be included in the guidelines and recommendations they have to meet the following eligibility criteria:

**INCLUSION**

- English language publications
- Indexed in either Medline, Embase, Cinahl, Psycinfo, Cochrane Library, or Pubmed
- Pharmacological, nutraceutical, and phytopharmaceutical interventions in human subjects only
- Use randomized clinical trial phase II or III design
- Timeline – from 1947 to May 15, 2019
- Use a valid and acceptable fatigue measure that assesses both presence of fatigue and severity of fatigue
- Cancer related fatigue should be a primary or secondary outcome

**EXCLUSION**

- Assessment of fatigue using treatment toxicity only using the common terminology criteria for adverse events (CTCAE) or equivalent was not acceptable
- Combinations treatments, (e.g. combination treatment of Coenzyme-Q, N acetyl Carnitine)
- HemoPoietin growth factors
- We used Pedro quality scoring systems to evaluate the quality of the articles
SEARCH TERMS

• FATIGUE AND CANCER (PRIMARY/ BROAD)

• FATIGUE AND CANCER AND METHYLPHENIDATE, OR FATIGUE AND CANCER AND PSYCHOSTIMULANTS; CANCER AND FATIGUE AND TREATMENT; FATIGUE AND CANCER AND DEXMETHYLPHENIDATE; DEXTROAMPHETAMINE, FATIGUE AND CANCER AND MODAFINIL; FATIGUE AND CANCER AND ARMODAFINIL; FATIGUE AND CANCER AND PEMOLINE, FATIGUE AND CANCER AND AMANTADINE; FATIGUE AND CANCER AND DEXAMETHASONE, FATIGUE AND CANCER AND METHYLPHREDINSONE, FATIGUE AND CANCER AND PROGESTATIONAL STEROIDS; FATIGUE AND CANCER AND ERYTHROPOIETIN; FATIGUE AND CANCER AND DARBEPOETIN; FATIGUE AND CANCER AND FLUOXETINE; FATIGUE AND CANCER AND PAROXETINE; FATIGUE AND CANCER AND ADENOSINE TRIPHOSPHATE; FATIGUE AND CANCER AND TESTOSTERONE; FATIGUE AND CANCER AND ETANERCEPT; FATIGUE AND CANCER AND THYROLIBERIN (TRH); FATIGUE AND CANCER AND DONEPEZIL; FATIGUE AND CANCER AND GINSENG; FATIGUE AND CANCER AND GUARANA (PAULLINIA CUPANA); FATIGUE AND CANCER AND FISH OIL/ DHA; FATIGUE AND CANCER AND VITAMIN D; FATIGUE AND CANCER AND LEVO CARNITINE; FATIGUE AND CANCER AND MISTLETOE; FATIGUE AND CANCER AND ANTIMEOPLASTIC AGENTS, FATIGUE AND PLACEBO, FATIGUE AND CANCER AND ANTI CYTOKINE THERAPY
RESULTS

- THE LITERATURE SEARCH IDENTIFIED 855 ARTICLES
- 178 ARTICLES WERE RETRIEVED IN DETAIL BASED ON TITLES AND ABSTRACTS
- WE REVIEWED 57 ARTICLES EVALUATING THE EFFECTS OF VARIOUS PHARMACOLOGICAL, NUTRACEUTICAL, AND PHYTOPHARMACEUTICAL FOR THE TREATMENT OF CANCER RELATED FATIGUE.
Total number of manuscripts identified from databases based on search terms from 1947 to May 15, 2019
N = 953

- Systematic review, or quality/literature review excluded
  N = 98

Titles and abstracts of the manuscripts reviewed
N = 855

- Manuscripts excluded at the title and abstract review stage
  N = 677

Full-text of the manuscripts reviewed
N = 178

- Not a randomized controlled trial: n = 58
- Not measuring fatigue as primary or secondary outcomes: n = 15
- Anemia as eligibility criterion: n = 21
- Multi-modal therapy: n = 5
- Cancer specific therapy as an agent: n = 6
- Not a pharmacological/nutraceutical/phytopharmaceutical intervention: n = 1
- Fatigue prevention treatment: n = 1
- Included patients without cancer diagnosis: n = 2
- Retrospective/secondary data analysis: n = 4
- Study protocol, cases study: n = 3
- Duplicate manuscripts: n = 5

Eligible manuscripts included in the review
N = 57
RESULTS

- TO THE BEST OF KNOWLEDGE WE STILL DO NOT HAVE ANY PHARMACOLOGICAL, NUTRACEUTICAL, AND PHYTOPHARMACEUTICAL AGENTS TO MANAGE CRF APPROVED BY THE US FOOD AND DRUG ADMINISTRATION.
- THE LAST DECADE HAS SEEN AN INCREASE IN THE NUMBER OF WELL-DESIGNED CLINICAL TRIALS BASED ON SET CRITERIA BY NIH, AND VARIOUS CANCER RELATED FATIGUE GROUPS.
METHYLPHENIDATE (SHORT ACTING)

- MECHANISM: BLOCKS DOPAMINE TRANSPORTERS AND NOREPINEPHRINE TRANSPORTERS
- STARTING DOSE: 5-20MG
- SIDE-EFFECTS: INSOMNIA, NAUSEA, HEADACHE, DIZZINESS, NERVOUSNESS, IRRITABILITY
METHYLPHENIDATE AND FORMULATIONS

SHORT ACTING METHYLPHENIDATE

- NUMBER STUDIES INCLUDED = 7
- AVERAGE PEDRO SCORE = 9.14; LEVEL OF EVIDENCE = 1
- RECOMMENDATION = NOT TO USE FOR TREATMENT OF CANCER RELATED FATIGUE IN ADVANCE CANCER AT THIS TIME

Bruera JCO 2006  
Bruera JCO 2013
METHYLPHENIDATE AND FORMULATIONS

D-METHYLPHENIDATE

NUMBER STUDIES INCLUDED = 2

AVERAGE PEDRO SCORE = 9.5

LEVEL OF EVIDENCE = 3

RECOMMENDATION = NO GUIDELINE POSSIBLE

Butler JM 2007
Roth AJ 2010
METHYLPHENIDATE AND FORMULATIONS

DEXAMPHETAMINE

✓ NUMBER OF STUDIES INCLUDED = 1
✓ AVERAGE PEDRO SCORE = 9.5
✓ LEVEL OF EVIDENCE = 1
✓ RECOMMENDATION = NO GUIDELINE POSSIBLE

Lower EE et al. JPSM 2009
Auret KA JPSM 2009
METHYLPHENIDATE AND FORMULATIONS

LONG ACTING METHYLPHENIDATE

• NUMBER STUDIES INCLUDED= 2
• AVERAGE PEDRO SCORE= 8.5
• LEVEL OF EVIDENCE =3
✓ RECOMMENDATION = NO GUIDELINE POSSIBLE

Mosarka AR et al. 2010
Escalante CP et al. 2014
MODAFINIL / ARMODAFINIL

- PSYCHO-STIMULANT WITH WAKE PROMOTING AGENT
- MECHANISM UNKNOWN
- HYPOCRETIN SYSTEM THROUGH DOPAMINE- AND/OR NOREPINEPHRINE-RELATED PATHWAYS, OR BY INCREASING ELECTRICAL COUPLING AT GAP JUNCTIONS.
- ARMODAFINIL – R-ISOMER OF MODAFINIL- LONGER LASTING
- SIDE-EFFECTS: RASH, HEADACHES, NAUSEA, INSOMNIA, DIZZINESS, MOOD CHANGES
- STARTING DOSE: MODAFINIL- 200MG/DAY; ARMODAFINIL 150MG DAILY

MODAFINIL

NUMBER STUDIES INCLUDED = 4
AVERAGE PEDRO SCORE = 9.5
LEVEL OF EVIDENCE = 1
RECOMMENDATION = NOT TO USE FOR TREATMENT OF CANCER RELATED FATIGUE.

Spathis A et al. JCO 2014
Jean-Pierre P et al. Cancer 2010
ARMODAFINIL

- NUMBER STUDIES INCLUDED = 3
- AVERAGE PEDRO SCORE = 9
- LEVEL OF EVIDENCE = 1
- RECOMMENDATION = NOT TO USE FOR TREATMENT OF CANCER RELATED FATIGUE.

Page BR et al. Neuro-onc 2005
Lee EQ et al. Neuro-onc 2015
DEXAMETHASONE AND METHYLPREDNISOLONE

• MECHANISM: INFLAMMATION; HYPO-THALMOPITUITARY MODULATION
• NUMBER STUDIES INCLUDED= 3
• AVERAGE PEDRO SCORE= 9.66
• LEVEL OF EVIDENCE =1;
• RECOMMENDATION = REASONABLE TO SUGGEST TO USE FOR TREATMENT OF CANCER RELATED FATIGUE IN ADVANCED CANCER.
• DOSE 8MG OF DEXAMETHASONE EQUIVALENT PER DAY FOR 1-2 WEEKS
• SIDE EFFECTS: GLUCOSE INTOLERANCE, MYOPATHY, INSOMNIA, ORAL CANDIDIASIS, GASTRIC IRRITATION

Yennurajalingam 2013
Paulsen 2014
PAROXETINE (3) & SERTALINE (1)

- SELECTIVE SEROTONIN REUPTAKE INHIBITOR
- NUMBER STUDIES INCLUDED = 4
- AVERAGE PEDRO SCORE = 8.5
- LEVEL OF EVIDENCE = 1
- RECOMMENDATION = NOT TO USE PAROXETINE FOR TREATMENT OF CANCER RELATED FATIGUE.

Roscoe JA 2005
Morrow 2003
Other Pharmaceuticals**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Number of studies</th>
<th>Average Pedro Score</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megestrol***</td>
<td>1</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Donepezil</td>
<td>1</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Thyrotropic Hormone</td>
<td>1</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>1</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>1</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

**No guideline possible**
NUTRACEUTICALS AND PHYTOPHARMACEUTICALS*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Number of studies</th>
<th>Average Pedro Score</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wisconsin Ginseng</td>
<td>2</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Asian Ginseng</td>
<td>1</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Guarana</td>
<td>2</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Mistletoe</td>
<td>6</td>
<td>6.5</td>
<td>2</td>
</tr>
<tr>
<td>ATP infusions</td>
<td>1</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>L-carnitine</td>
<td>2</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Melatonin</td>
<td>2</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Astragalus</td>
<td>1</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Taurine</td>
<td>1</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

✓*No guideline possible
PROMISING TREATMENTS

- PSYCHOSTIMULANTS (METHYLPHENIDATE) IN SUBGROUP OF FATIGUE PATIENTS WITH ANXIETY AND/OR DEPRESSION

- GINSENG (AMERICAN AS WELL AS ASIAN)

- GUARANA?

- FISH OIL/ SOY OIL (O6)?

- GHRELIN AGONISTS?

- OPEN LABELED PLACEBO?

- BUPROPION
Comparison of Pharmaceutical, Psychological, and Exercise Treatments for Cancer-Related Fatigue: A Meta-analysis

Karen M. Mustian, PhD, MPH; Catherine M. Alfano, PhD; Charles Heckler, PhD, MS; Amber S. Kleckner, PhD; Ian R. Kleckner, PhD; Corinne R. Leach, PhD; David Mohr, PhD; Oxana G. Palesh, PhD, MPH; Luke J. Peppone, PhD, MPH; Barbara F. Piper, PhD; John Scarpato, MA; Tenbroeck Smith, MA; Lisa K. Sprod, PhD, MPH; Suzanne M. Miller, PhD
Figure 2. Forest Plot of Weighted Effect Sizes (WESs)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>No. of Effect Sizes</th>
<th>WES</th>
<th>SE</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>127</td>
<td>0.33</td>
<td>0.05</td>
<td>(0.24-0.43)</td>
</tr>
<tr>
<td>Pharmaceutical</td>
<td>14</td>
<td>0.09</td>
<td>0.05</td>
<td>(0.00-0.19)</td>
</tr>
<tr>
<td>Exercise plus psychological</td>
<td>10</td>
<td>0.26</td>
<td>0.07</td>
<td>(0.13-0.38)</td>
</tr>
<tr>
<td>Psychological</td>
<td>34</td>
<td>0.27</td>
<td>0.05</td>
<td>(0.21-0.33)</td>
</tr>
<tr>
<td>Exercise</td>
<td>69</td>
<td>0.30</td>
<td>0.03</td>
<td>(0.25-0.36)</td>
</tr>
</tbody>
</table>
WHEN IS THE RIGHT TIME TO USE A
PHARMACOLOGICAL, NUTRACEUTICAL, AND
PHYTO-PHARMACEUTICAL INTERVENTION
TO MANAGE CANCER RELATED FATIGUE?

- PHYSICAL VS MENTAL FATIGUE
- FRIAL OR OLDER OR ADVANCED CANCER PATIENTS
- TIME OR LOGISTIC CONSTRAINTS
- MEDICATION COST
- COEXISTING SYMPTOMS (INSOMNIA, DEPRESSION, ANXIETY, DYSPNEA, NO DELIRIUM)
- METASTATIC/ PRIMARY BRAIN TUMORS
- MULTIORGAN FAILURE
EFFICACY OF PLACEBO (METANALYSIS)
CARMELIA MARIA NOIA BARRETO ET AL. J CLIN ONCOL 37, 2019 (SUPPL; ABSTR E23157)

- 29 STUDIES WITH 3,758 PATIENTS WITH ANY PRIMARY SITE OF NEOPLASIA AND ANY STAGE OF CANCER WERE INCLUDED IN THE META-ANALYSIS.

- PLACEBO HAD A MEAN EFFECT OF +4.88 (95%CI +2.45 TO +7.29) USING THE FACIT-F SCALE, ALTHOUGH IT WAS STATISTICALLY WORSE THAN THE INTERVENTIONS STUDIED (P = 0.005).

- USING THE BFI SCALE, PLACEBO HAD AN AVERAGE EFFECT OF +0.64 (95%CI +0.02 TO +1.30), ALTHOUGH IT WAS ALSO WORSE THAN THE OTHER INTERVENTIONS STUDIED (P = 0.002).

- IN TERMS OF THE RESPONSE RATE, 29% (95%CI 25%–32%) OF PATIENTS TAKING A PLACEBO REPORTED A SIGNIFICANT IMPROVEMENT IN CRF COMPARED TO 36% OF PATIENTS TREATED WITH OTHER INTERVENTIONS (P = 0.030).
EFFICACY OF PLACEBO (ADHOC ANALYSIS)
S YENNU ET AL. FREQUENCY AND FACTORS ASSOCIATED WITH PLACEBO RESPONSE IN CANCER-RELATED FATIGUE TREATMENT TRIALS

POOLED ANALYSIS OF THE PLACEBO ARM IN SIX RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIALS FOR CANCER RELATED FATIGUE.

BASELINE PATIENT CHARACTERISTICS, SYMPTOMS (FACIT-F, AND ESAS), GLOBAL SYMPTOM EVALUATION (GSE, RATED AS BETTER, SAME AND WORSE).

RESPONSE WAS DEFINED AS AN INCREASE (D FACIT-F SCORE) ≥ 3.5 POINTS FROM BASELINE OR CHANGE IN ESAS OF ≤ 1.

PLACEBO RESPONSE WAS 176/306 (58%) WITH FACIT-F SUBSCALE ≥ 3.5 POINTS AND 185 (60%) WITH ESAS FATIGUE ≤ 1. MEAN CHANGE IN FATIGUE USING FACIT- F SUBSCALE SCORE WAS 7.18 (11.68) AND ESAS WAS -2.21 (2.82).
OPEN LABELED PLACEBO (OLP) TREATMENT FOR CANCER RELATED FATIGUE
HOENEMEYER TW, KAPTCHUK TJ ET AL.

• 21 DAY ASSESSOR BLINDED RCT (38 OLP VS 35 TREATMENT AS USUAL)
• CANCER SURVIVORS WITH CRF
• 2 PILLS TWICE A DAY FOR 21 DAYS
• 29% IMPROVEMENT IN OLP COMPARED TO TAU (P =0.008, D= 0.63)
• 39% FATIGUE DISTURBED QOL (P=0.002, D=0.76)
REFERENCES


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