Pharmaceutical, Psychological, and Exercise Interventions for Cancer-Related Fatigue: Findings From A Comparative Meta-Analysis

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Purpose

- The purpose of this study was to perform a meta-analysis to validate and compare the mean weighted effect sizes (WES) for cancer-related fatigue (CRF) interventions:
  - Exercise
  - Psychological
  - Combination of exercise & psychological
  - Pharmaceutical
Selection Criteria

- **P** = adults (18+) with cancer
- **I** = exercise, psychological, pharmaceutical
  - No erythropoietin drugs
  - No complementary and alternative interventions (except: yoga and tai chi)
- **C** = RCT design
- **O** = CRF severity
  - NOT a treatment toxicity
  - Not energy, vitality, or vigor
Search Strategy

- Published in English
- Database’s inception and April, 2009
- Controlled-vocabulary search terms
  - cancer-related fatigue, neoplasms, questionnaires, intervention strategies, and study design
- Databases
  - MEDLINE, PsycINFO, CINAHL, EMBASE, and the Cochrane Library
13,710 potentially relevant studies identified and screened for retrieval by title and abstract

13,571 studies excluded based on title and abstract

139 studies retrieved for full article review

73 studies excluded based on inclusion criteria

66 articles met inclusion criteria

24 articles provided insufficient data for effect size calculations

42 articles provided sufficient data for effect size calculations

48 comparisons were included in analyses

6 articles two intervention conditions compared to a control condition

12 effect sizes calculated

36 articles have one intervention condition compared to a control condition

36 effect sizes were calculated

18 exercise interventions
17 psychological interventions
3 exercise plus psychological interventions
4 pharmaceutical interventions

73 studies excluded based on inclusion criteria
Methods

- Independently reviewed
  - 10 raters in 3 groups
  - systematic and blinded

- Meta-Analyzer System

- Modified 12-item PEDro scale
  - Physiotherapy Evidence-Based Database
  - Delphi expert consensus

- Exercise interventions
  - aerobic, non-aerobic and both

- Psychological interventions
  - cognitive behavioral, psycho-educational and eclectic
Data Analyses

- **Weighted effect-sizes**
  - Within and between arms

- **Moderators**
  - identified a priori

- **Sensitivity Analyses**
  - 3 arms = no significant influence

- **Publication Bias Analyses**
  - Funnel Plot and Duval and Tweetie’s
    - Possible bias?
    - Fail Safe N = 1242

- **Random and Fixed Effects Models & Method of Moments Estimation**
Participants

- **Participants**
  - 5,016 participants
  - 57% (N=24) women with breast cancer
  - 26% (N=11) cancer patients and survivors of mixed diagnoses
  - 17% (N=7) men with prostate cancer (N=3), leukemia (N=1), brain cancer (N=1), head and neck cancer (N=1) and lymphoma (N=1)

- **Sex**
  - 82% were female

- **Mean age** = 57 years

- **Race, education and partnered status could not be accurately summarized**
Participants

- **Stage**
  - 40% (N=17) all stages
  - 24% (N=10) early-stage
  - 2% (N=1) metastatic disease
  - 34% (N=14) no staging information

- **Treatments**
  - 45% (N=19) primary treatment
  - 38% (N=16) completed primary treatment
  - 17% (N=7) mixed treatment status

- **Retention**
  - 75% post-intervention
    - baseline N=5,016 to post-intervention N=3,752
  - Could not be evaluated during follow-up periods
Design & Intervention

- RCT design
  - 37 = traditional 2-arm RCT design
  - 6 = 3-arm RCT designs
- Sample sizes average = 55 (SD=48.7) at baseline
  - 52 (SD=47.5) in control groups
  - 57 (SD=50.2) in the intervention conditions
- Interventions
  - Average = 13 weeks, 23 sessions, and 58 minutes per session
  - Pharmaceutical = 50% methylphenidate & 50% paroxetine
  - Exercise = 67% = aerobic, 11% = non-aerobic, 22% = combination
  - Psychological = 50% psychoeducational, 44% cognitive behavioral, 6% eclectic
- Controls
  - 74% = usual cancer care, standard cancer care, no intervention, or waitlist
  - 26% = placebo, time, attention, or education control
Study Quality

- 10.4 = average PEDro score
  - 0-12 = range
  - 12 = highest quality

- All studies
  - Specified inclusion/exclusion criteria
  - Employed random allocation
  - Reported between-group comparisons

- 69% used intent-to-treat

- 36% concealed allocation from participants or blinded outcome assessors

- 48% monitored treatment quality, drift, and fidelity
Results: Main Effects on CRF

- **Within Group**
  - All Studies both during and post-treatment
    - Across all 4 interventions
      - WES=0.30; CI=0.23-0.38; p<0.05
    - By treatment modality:
      - Exercise WES=0.35; CI=0.23-0.48, p<0.05
      - Psychological WES=0.29; CI=0.18-0.41; p<0.05
      - Combinations WES=0.25; CI=-0.07-0.56; p>0.05
      - Pharmaceutical WES=0.19; CI=-0.05-0.44; p>0.05
  - Patterns held for study subgroups (all p<0.05)
    - primary treatment
    - post-treatment only

- **Between Groups**
  - All studies both during and post-treatment
    - significant differences between exercise and pharmaceutical interventions favoring exercise interventions (p<0.05)
  - No significant differences by study subgroups
Control Comparisons

- **Within Group**
  - All studies using usual or standard care, no intervention, or a waitlist
    - Across all 3 interventions
      - WES = 0.26; CI = 0.17-0.35; p < 0.05
    - By treatment modality
      - Exercise WES = 0.39; CI = 0.23-0.56
      - Psychological WES = 0.20; CI = 0.08-0.31; all p < 0.05
      - Combination WES = 0.19; CI = -0.23-0.61; p > 0.05
      - Pharmaceutical = NA
  - All studies using time, attention, education or placebo
    - Across all 3 interventions
      - WES = 0.29; CI = 0.15-0.44; p < 0.05
    - By treatment modality
      - Exercise WES = 0.35; CI = 0.11-0.58
      - Psychological WES = 0.30; CI = 0.06-0.54; both p < 0.05
      - Pharmaceuticals WES = 0.21; CI = -0.06-0.48; p > 0.05
      - Combination = NA

- **Between Group**
  - No significant differences between modalities within study subgroups
Moderators

- **Stage**
  - WES=0.30; CI=0.22-0.38; p<0.05
  - non-metastatic WES=0.38; CI=0.26-0.50
  - mixed WES=0.24; CI=0.12-0.36; p<0.05

- No other potential moderators were found (age, gender, cancer type, treatment status, experimental treatment format and mode, research design, and PEDro quality indexes and total score).
Strengths

- **Strengths**
  - First meta-analysis to compare exercise, psychological and pharmaceutical
  - Rigorous literature search by experienced librarian
  - Abstracting and consensus-building of the data by highly qualified, experienced, and independent raters
  - Adherence to stringent inclusion/exclusion criteria and analytic methods
  - Use of standard and valid measures of CRF severity
  - Initial analyses examining potential moderators
  - QUOROM – Quality of Reporting of Meta-Analyses (Moher et al. Lancet 1999)
Limitations

- < 50% provided detailed information on race, education, socioeconomic status, and other demographic factors
- Most studies did not screen for/require a specific level of fatigue for inclusion
- Most studies did not designate a priori the fatigue severity outcome as primary
- Trials were not registered (e.g., Clinical Trials)
- Moderator analyses cannot be considered definitive due to the lack of random assignment for subgroup comparison
- Small number of published RCTs examining the combination of exercise plus psychological interventions and pharmaceutical interventions
- Very few studies utilize appropriate control conditions for specific effects
- Many published reports did not include the basic statistics needed for inclusion in this meta-analysis
- Long-term follow-up lacking
Summary

- Both exercise and psychological interventions improve CRF during and after primary treatment
  - **BUT**, effects are small to moderate at best

- Exercise interventions are significantly better than methylphenidate and paroxetine for reducing CRF
  - **BUT**, only four pharmaceutical studies

- **Hypothesis generating**
  - Positive benefits of exercise and psychological interventions on CRF may be due to something other than simple time, attention and education
  - Stage of disease may moderate intervention effectiveness and warrants additional investigation
  - The combination of exercise plus psychological interventions, as studied to date, are not effective for reducing CRF
Recommendations

- **INTERVENTIONS**
  - Greater improvements in CRF from exercise and psychological interventions are desirable
    1. Standardization and improved quality
    2. Dose
    3. Tailoring
    4. Portability
    5. Accessibility
  - **Personalized medicine approach** to prescribe exercise and psychological therapy accounting for patient preference, whether and when exercise or psychological interventions are contraindicated, availability, and accessibility
  - More research is needed on the **combination of exercise and psychological** interventions
  - More research is needed on promising **pharmaceutical agents**

- **RCT DESIGN AND REPORTING**
  - **CRF needs to be identified a priori as a primary outcome** and RCTs designed accordingly
  - **CRF severity inclusion/exclusion criteria need to be part of screening and study design**
  - Appropriate identification and use of appropriate specific-component control conditions to test for specific mechanisms of action
  - **Register clinical trials**
  - **Detailed assessment and reporting of demographics**
  - **Adherence to CONSORT criteria**
Acknowledgements

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- FCCC Behavioral Research Core
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QUESTIONS ???
Sensitivity Analyses

- Conducted due to studies with multiple treatment conditions that resulted in two or more intervention comparisons with the same control groups
- To detect an artificial reduction of heterogeneity and a bias in the overall mean effect size
- Series of analyses
  - included only one comparison per study
  - Included the comparison with the larger effect size
  - Included the comparison with the smaller effect size.
Publication Bias Analyses

- **Funnel plots**
  - The funnel plot is a plot of standard error on the vertical axis as a function of effect size on the horizontal axis. In the absence of publication bias we would expect studies to be distributed symmetrically about the combined effect size.

- **Duval and Tweedie’s Trim and Fill**
  - To examine the influence of large studies with positive effects on the results.
  - Looks for missing studies to the left side of the mean effect and estimates an adjusted mean effect size.
  - To examine stability of the overall effect, fail-safe N was calculated to determine the number of studies with a null effect size needed to reduce the overall effect to non-significance.
Publication and Sensitivity

- Funnel plot examination indicated a possible publication bias where smaller studies with non-significant findings were not reported.

![Funnel Plot of Standard Error by Std diff in means](image)

**Standard Difference in Weighted Effect Size = d**
Publication and Sensitivity

- Duval and Tweedie’s trim and fill methods also suggested possible publication bias.
  - Overall random effects model WES=0.30 (CI=0.23-0.38; p<0.05)
  - Duval and Tweedie’s imputed WES=0.18 (CI=0.09-0.27; p<0.05).

- The Fail Safe N for CRF was N = 1242 null studies

- Sensitivity analyses suggested no artificial reduction of heterogeneity or bias when multiple intervention comparisons from the same study were included in the analyses
### Forest Plot

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