

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

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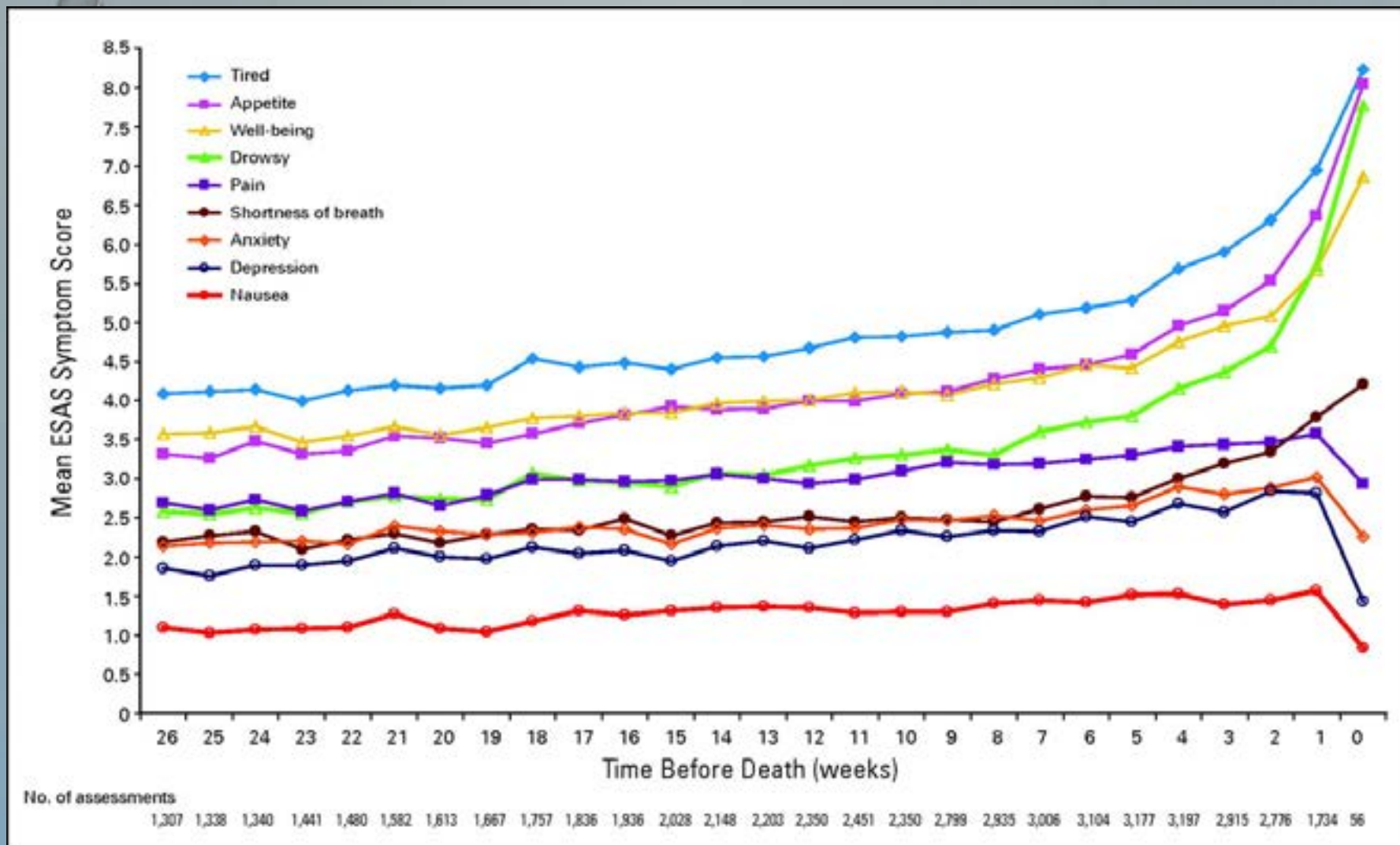
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Symptom Prevalence, Summarized from the Palliative Symptom Grid

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

Minimum-maximum range of prevalence (%) is shown

- [Joao Paulo Solano](#), et al
[Journal of Pain and Symptom Management](#), 2006



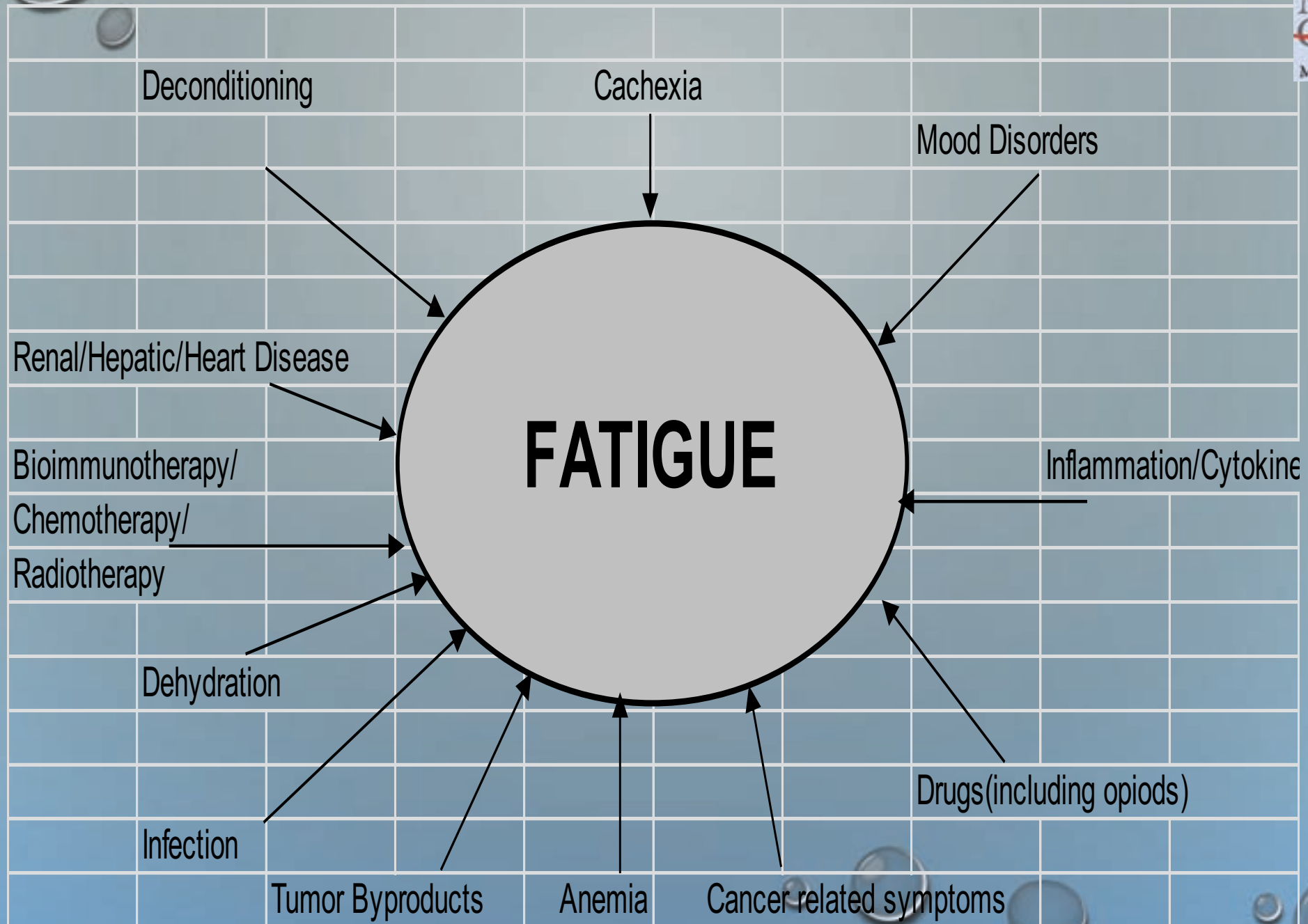
Ontario's cancer system Data: trajectory of Edmonton Symptom Assessment System (ESAS) symptom scores for Patients With Cancer During the Last Six Months of Life

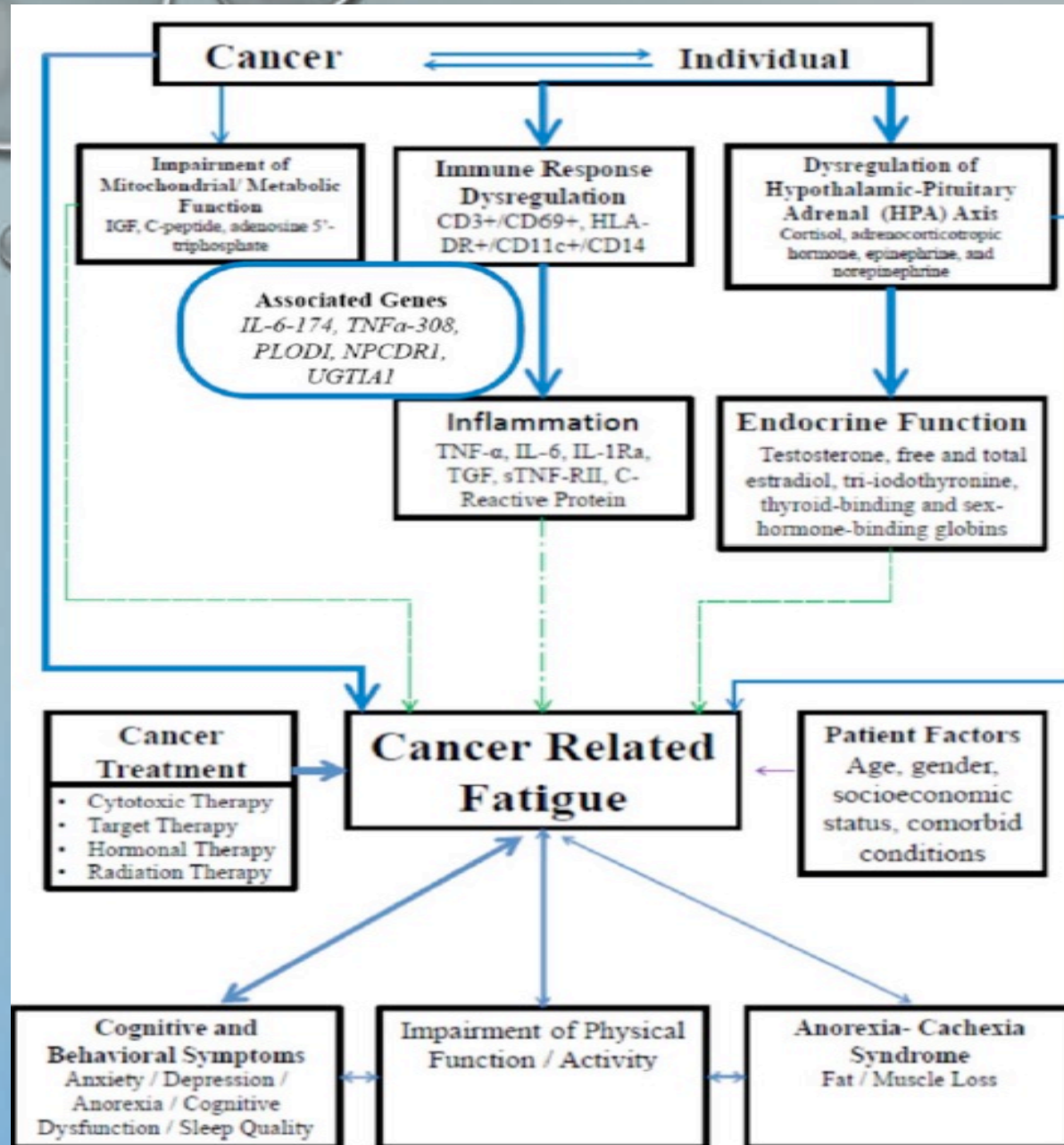
Hsien Seow et al. *Clinical Oncology* 29, no. 9 (March 2011) 1151-1158.

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.





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**

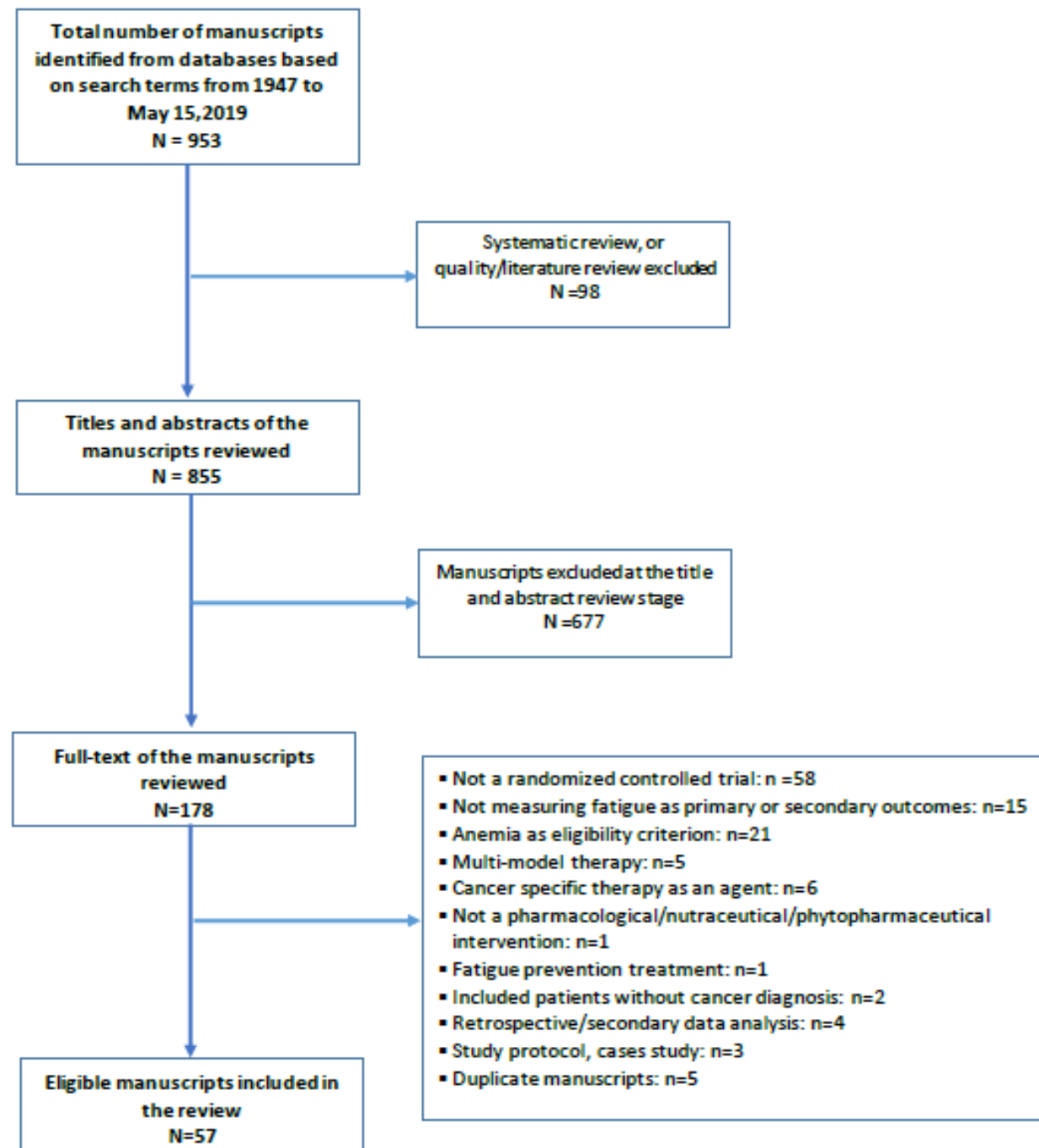
- ASSESSMENT OF FATIGUE USING TREATMENT TOXICITY ONLY USING THE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) OR EQUIVALENT WAS NOT ACCEPTABLE
- COMBINATIONS TREATMENTS, (E.G COMBINATION TREATMENT OF COENZYME-Q, N ACETYL CARNITINE)
- HEMOPOIETIN GROWTH FACTORS
- WE USED **PEDRO QUALITY SCORING 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 DEXMETHYPHENIDATE; 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 METHYLPREDINSONE, 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 ANTINEOPLASTIC AGENTS, FATIGUE AND PLACEBO, FATIGUE AND CANCER AND ANTICYTOKINE 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.



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.

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**

Agent	Number of studies	Average Pedro Score	Level of Evidence
Megestrol***	1	9	2
Donepezil	1	10	3
Thyrotropic Hormone	1	9	3
Eszopiclone	1	8	3
Abiraterone	1	9	3

****No guideline possible**

NUTRACEUTICALS AND PHYTO- PHARMACETICALS*

Agent	Number of studies	Average Pedro Score	Level of Evidence
Wisconsin Ginseng	2	9	2
Asian Ginseng	1	5	3
Guarana	2	8	2
Mistletoe	6	6.5	2
ATP infusions	1	5	3
L-carnitine	2	7	2
Melatonin	2	9	2
Astragalus	1	9	2
Taurine	1	10	3

✓*No guideline possible

PROMISING TREATMENTS

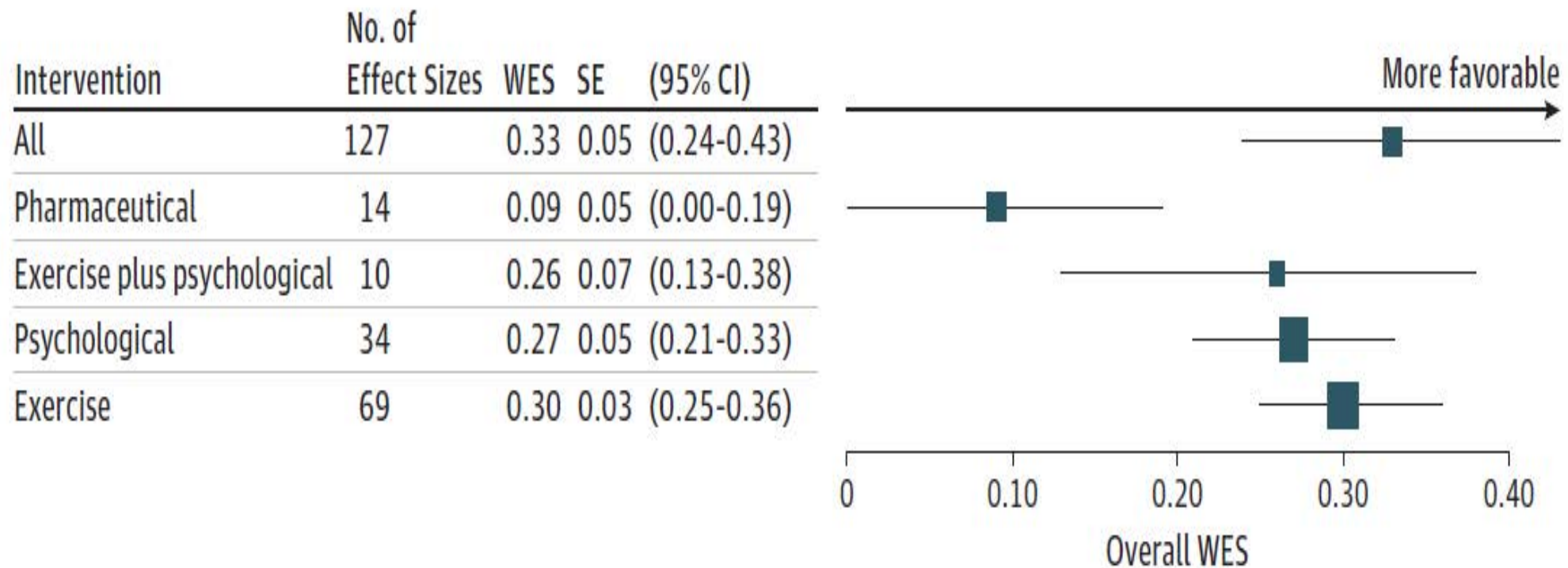
- PSYCHOSTIMULANTS (METHYLPHENIDATE) IN SUBGROUP OF FATIGUE PATIENTS WITH ANXIETY AND/OR DEPRESSION
- GINSENG (AMERICAN AS WELL AS ASIAN)
- GUARANA?
- FISH OIL/ SOY OIL (O6)?
- GHRELIN AGONISTS?
- OPEN LABELED PLACEBO?
- BUPROPION

JAMA Oncology | **Original Investigation**

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)



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

DOI: 10.1200/JCO.2016.34.26_SUPPL.210 JOURNAL OF CLINICAL ONCOLOGY 34, NO. 26_SUPPL (OCTOBER 9 2016) 210-210.

- 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% IMPROVEMNET IN OLP COMPARED TO TAU (P =0.008, D= 0.63)
- 39% FATIGUE DISTRUPTED QOL (P=0.002, D=0.76)

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