Personalized Therapy In Cancer Related Fatigue: Targeting Mechanisms, Role Of Corticosteroids, And Combination Therapy

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

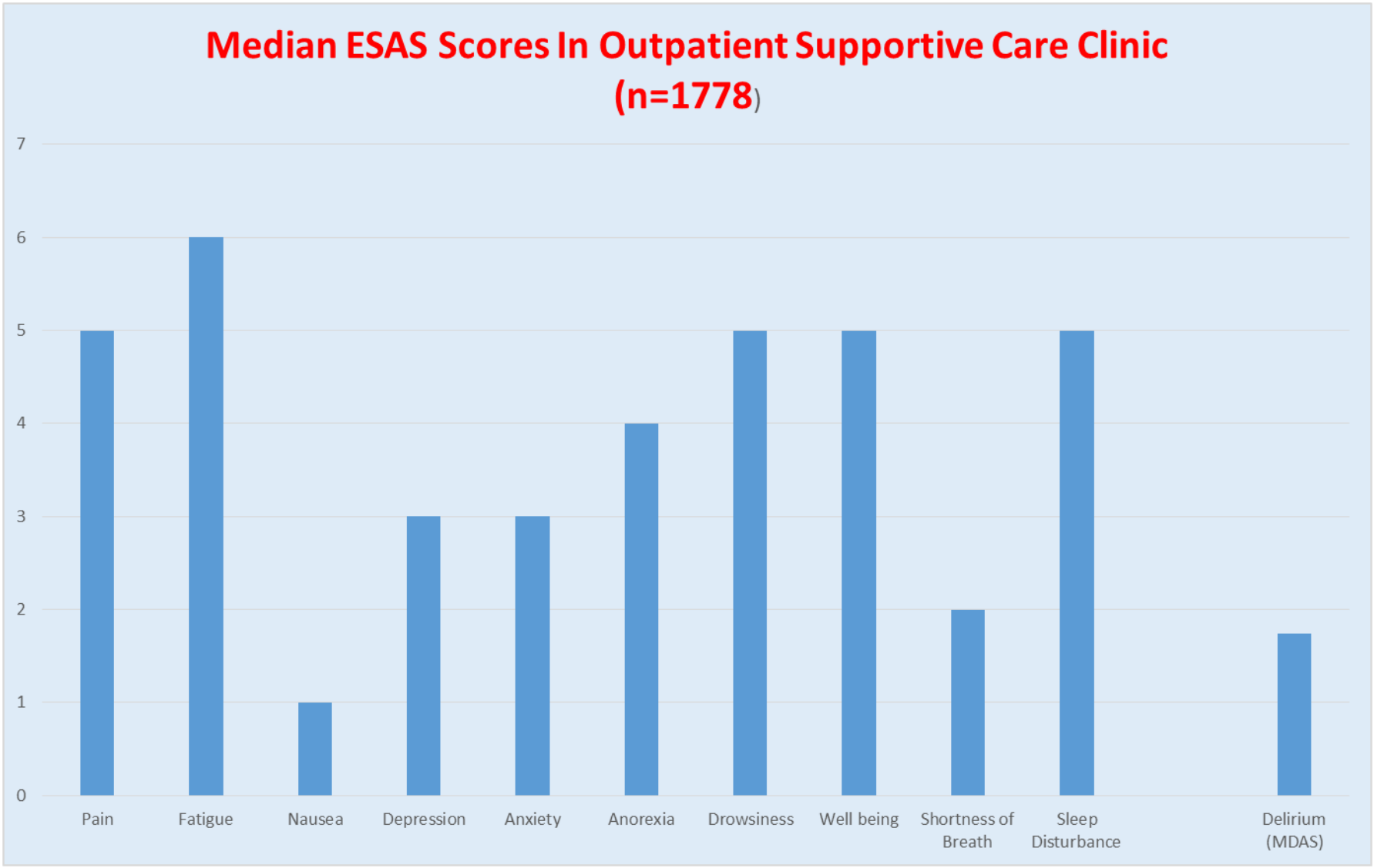
Sriram Yennu, M.D., M.S. (syennu@mdanderson.org)

Objectives

- Frequency of fatigue
- New Definition of CRF
- Etiology of Cancer related fatigue
- Assessment
- Management of CRF
- Personalized Therapy In Cancer Related Fatigue

MD Anderson Cancer Center

Median ESAS Scores In Outpatient Supportive Care Clinic (n=1778)



Yennu 2013

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

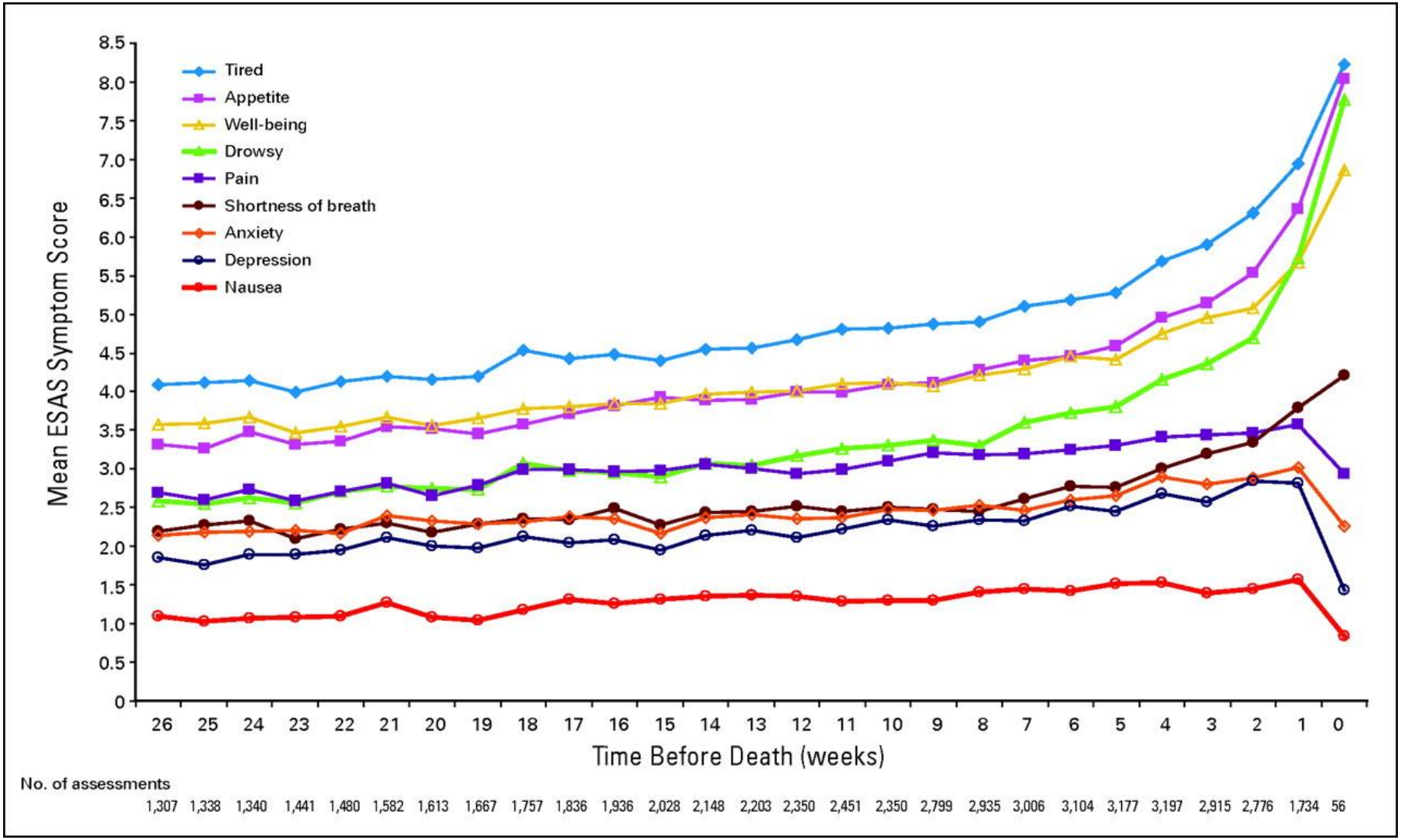
Frequency of Symptoms in Terminal Cancer Patients*†

Symptom	TPCU	Referral hospitals	Hospices	"p" value
Pain	116/156 74 percent	300/639 47 percent	231/407 57 percent	<0.0001**
Activity	138/154 90 percent	561/624 90 percent	356/431 83 percent	0.0014**
Nausea	55/152 36 percent	125/636 20 percent	93/368 25 percent	0.0001**
Depression	87/148 59 percent	250/573 44 percent	179/391 46 percent	0.0042**
Anxiety	102/152 67 percent	288/583 49 percent	202/403 50 percent	0.0003**
Drowsiness	111/154 72 percent	394/621 63 percent	310/417 74 percent	0.0006**
Appetite	116/152 76 percent	502/617 81 percent	314/428 73 percent	0.0082
Well being	118/147 80 percent	390/540 72 percent	262/404 65 percent	0.001**
Shortness of breath	76/153 50 percent	206/630 33 percent	151/393 38 percent	0.0004**

* Symptoms were considered present when the visual analogue score upon admission was (30/100)

** P value significant after boferroni correction

† Reproduced with from Bruera, E, Neumann, CM. Respective limits in palliative care and oncology in the supportive care of cancer patients. Support Care Cancer 1999; 7:321.



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.

Prevalence

Frequency of CRF ranges from 60% to 90%

- Chemotherapy – 30% to 91%
- Radiotherapy – 25% to 93%
- Combined modality – 59% to 83%
- Palliative Care Setting – 48% to 75%

Lawrence DP, 2004

Significance

- Significant Impact on Quality of Life
- more than 91% reported that they could not lead normal lives because of it.
- fatigued patients were absent an average of 4.2 days per month during and immediately after treatment, due to fatigue

Vogelzang, Cella 1997
Curt, 2000

Definition

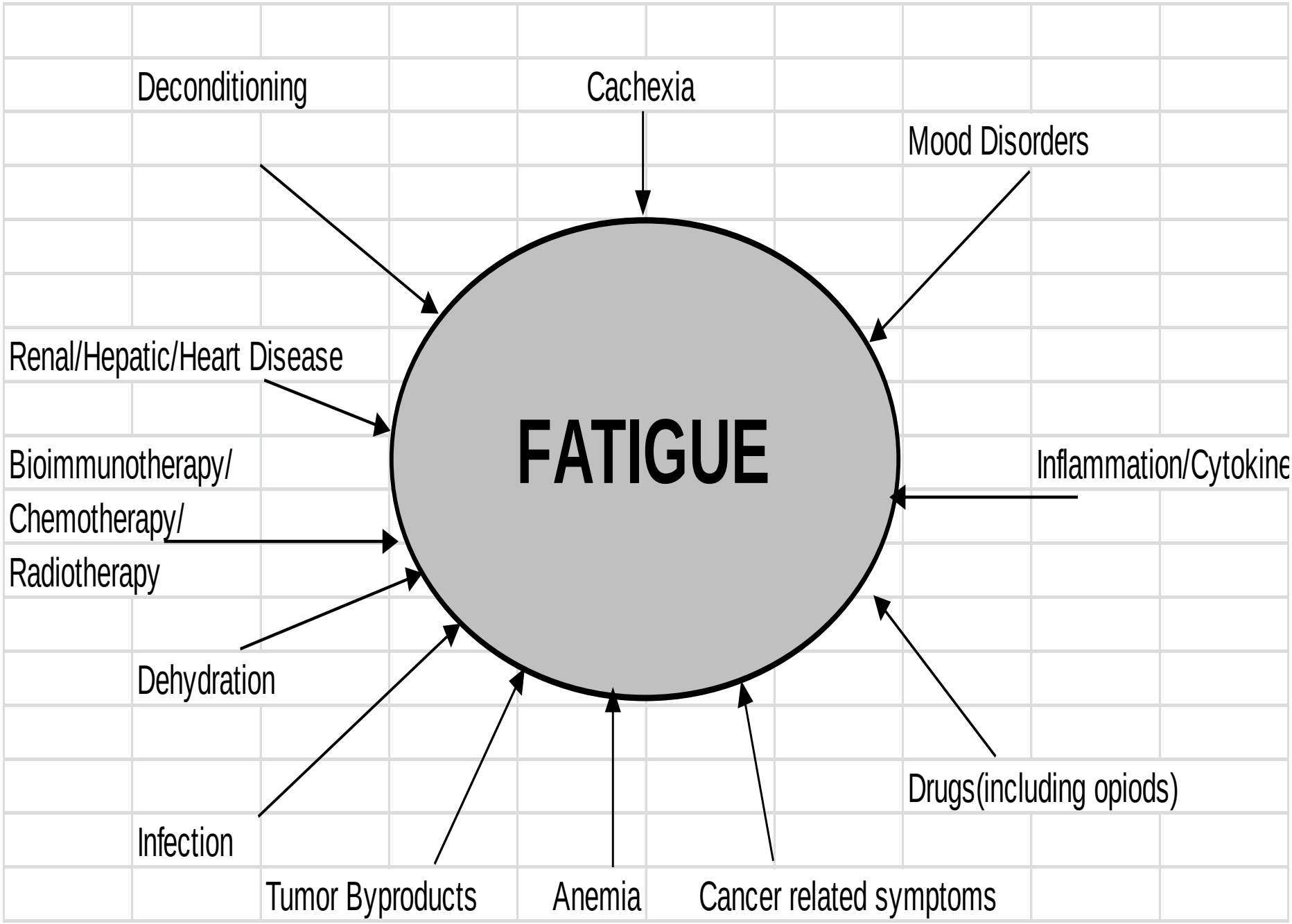
MD Anderson Cancer Center

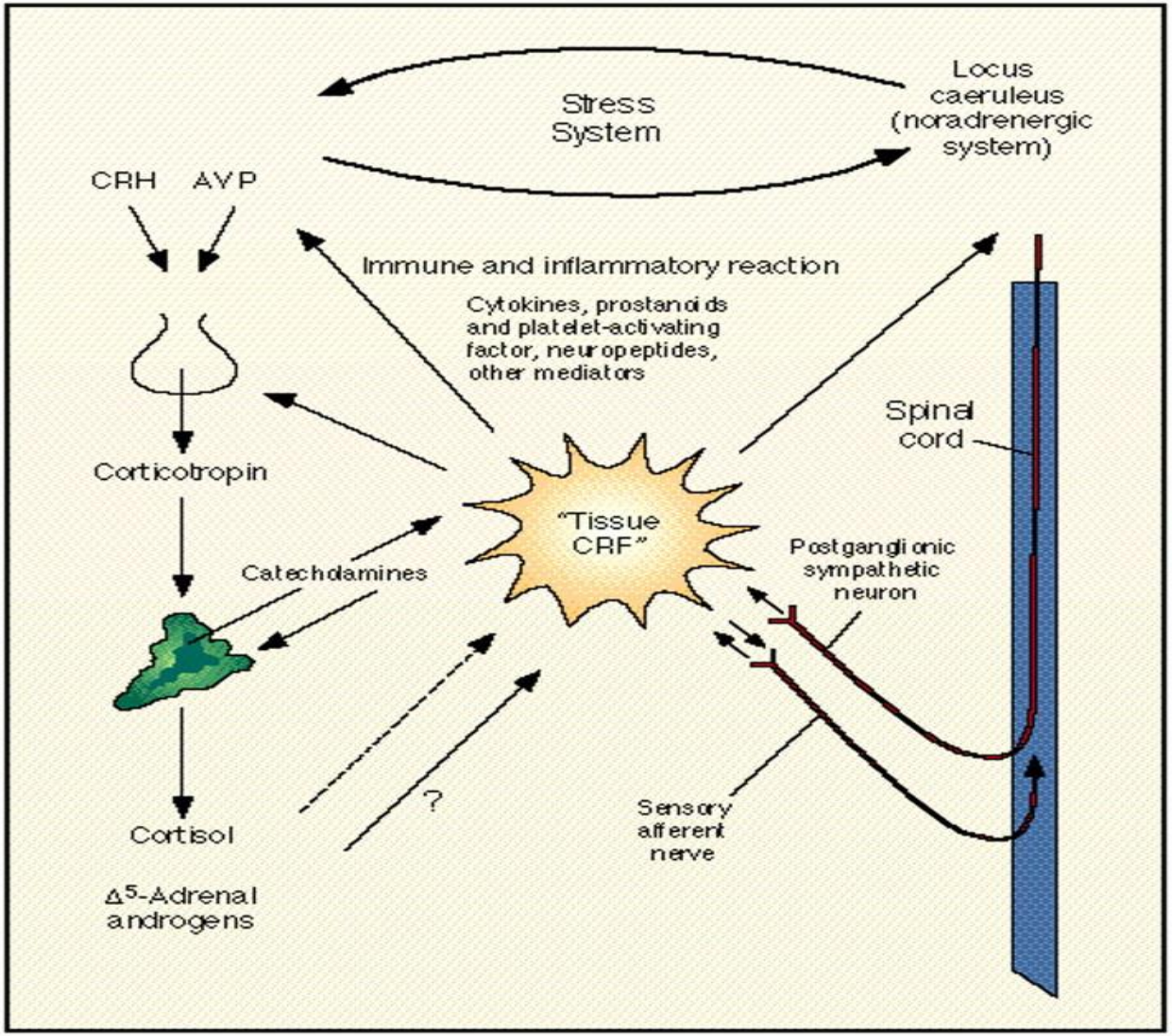
- Distinguish fatigue from depression, delirium, drowsiness, psychomotor retardation and weakness.
- Psychomotor retardation involves a slowing–down of thought and a reduction of physical movements in an individual
- Weakness is a term commonly used to describe a state of lack of physical or muscle or motor strength

DEFINITION
[Version 1:2010]

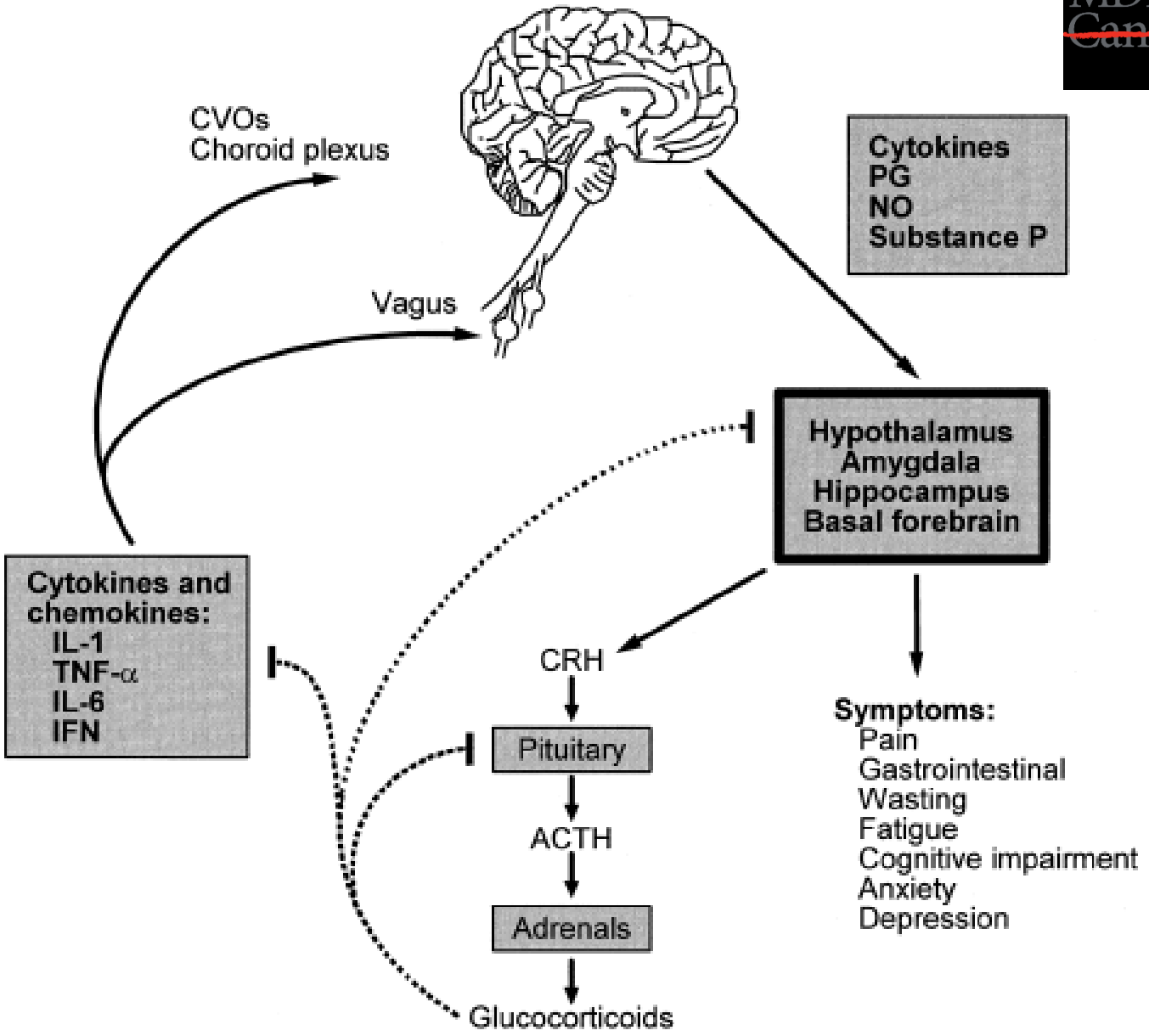
- Cancer–related fatigue is a distressing persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.

Piper BF, Cella D JCCN 2010 +

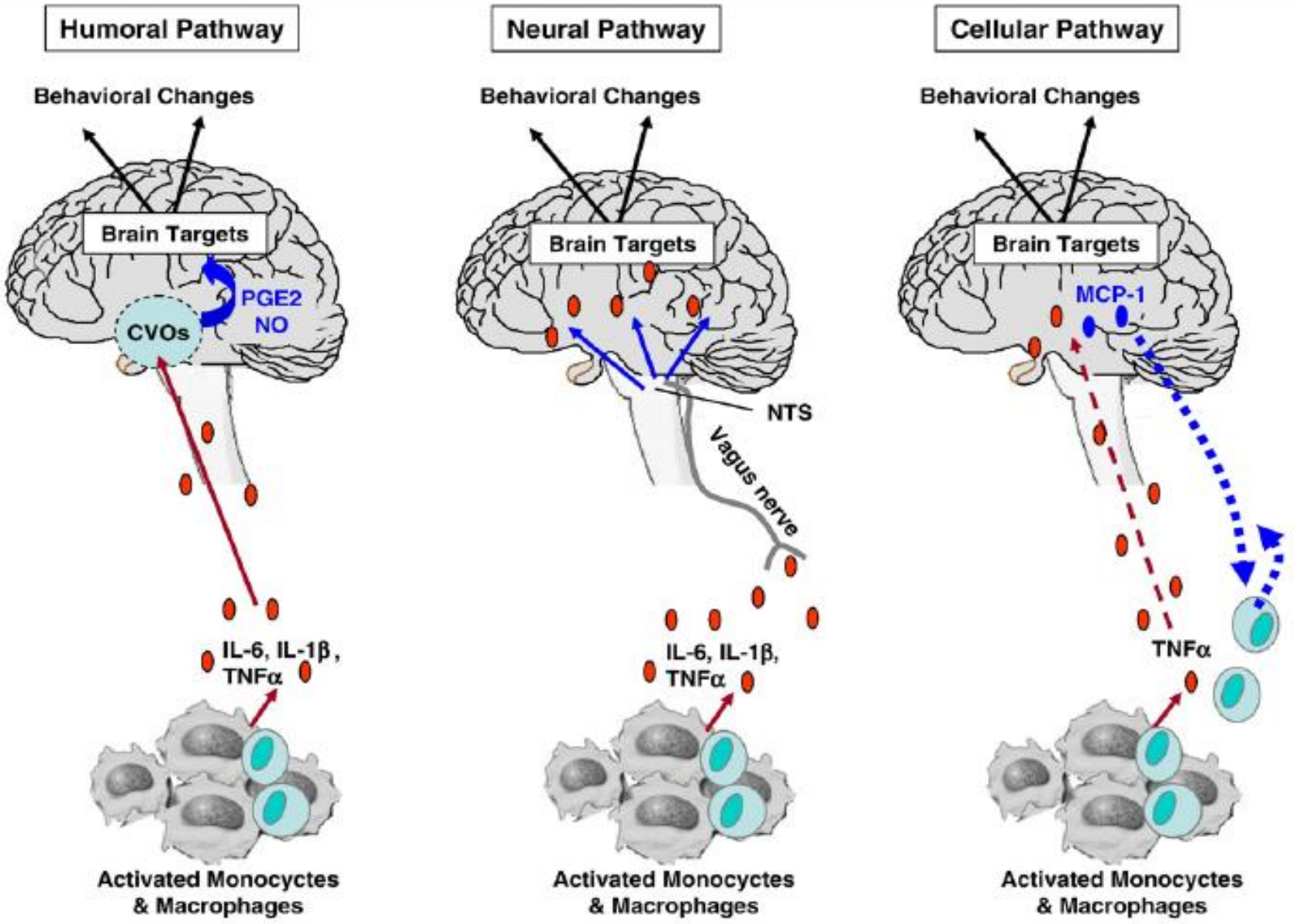

Deconditioning
Cachexia
Mood Disorders
Renal/Hepatic/Heart Disease
FATIGUE
Bioimmunotherapy/
Chemotherapy/
Radiotherapy
Inflammation/Cytokine
Dehydration
Drugs(including opiods)
Infection
Tumor Byproducts
Anemia
Cancer related symptoms



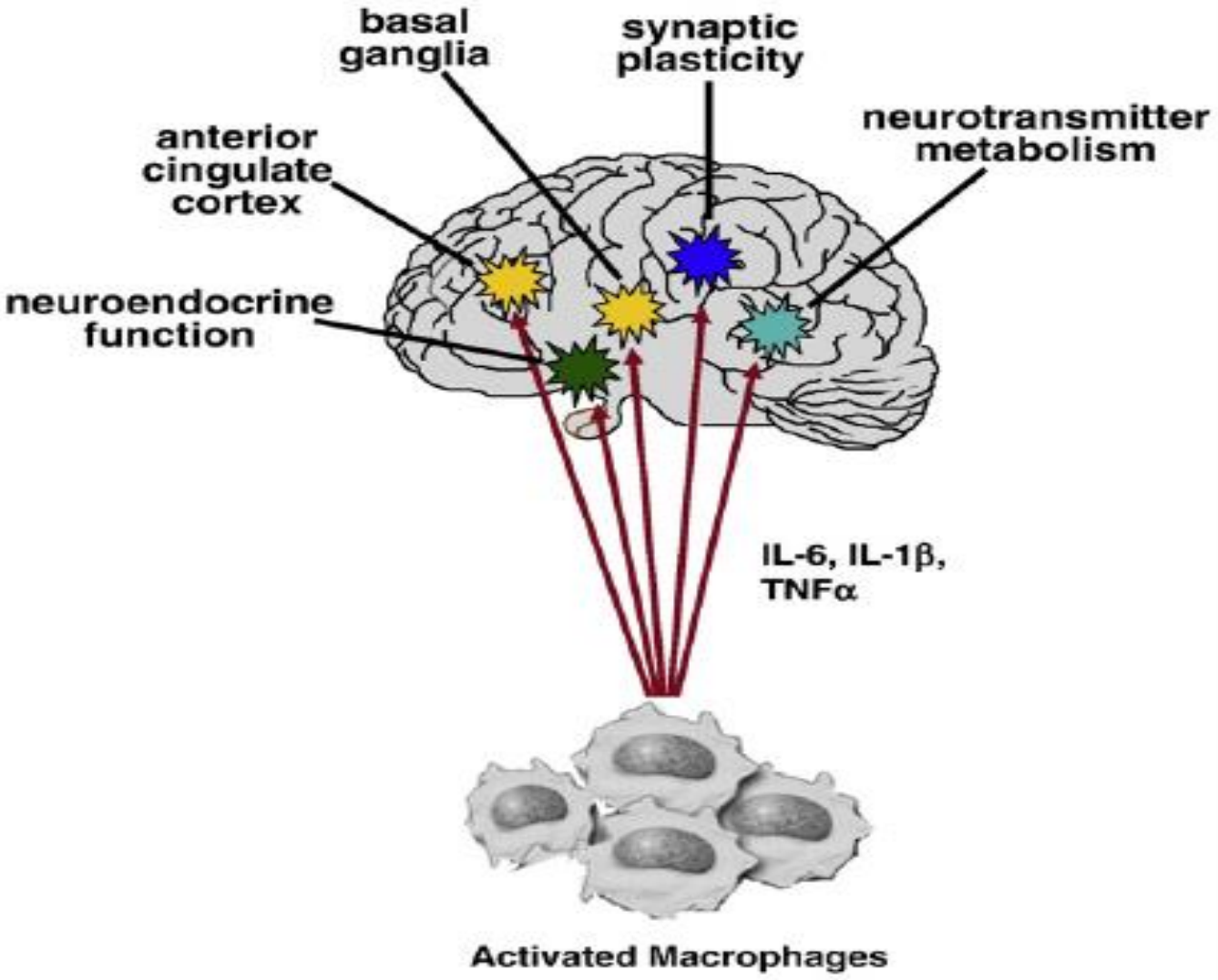
Chrussos 1995



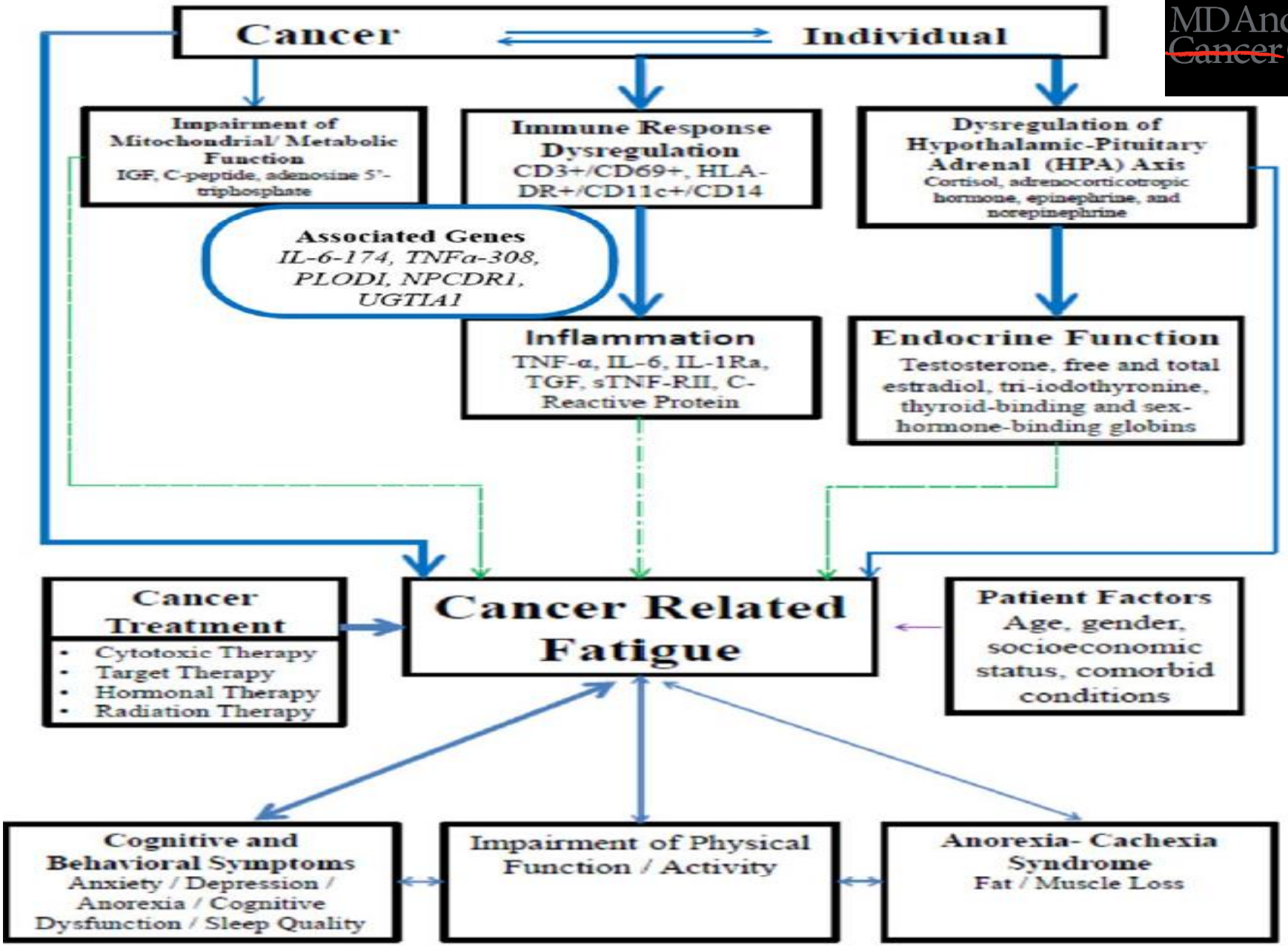
Dantzer, et al., 2004



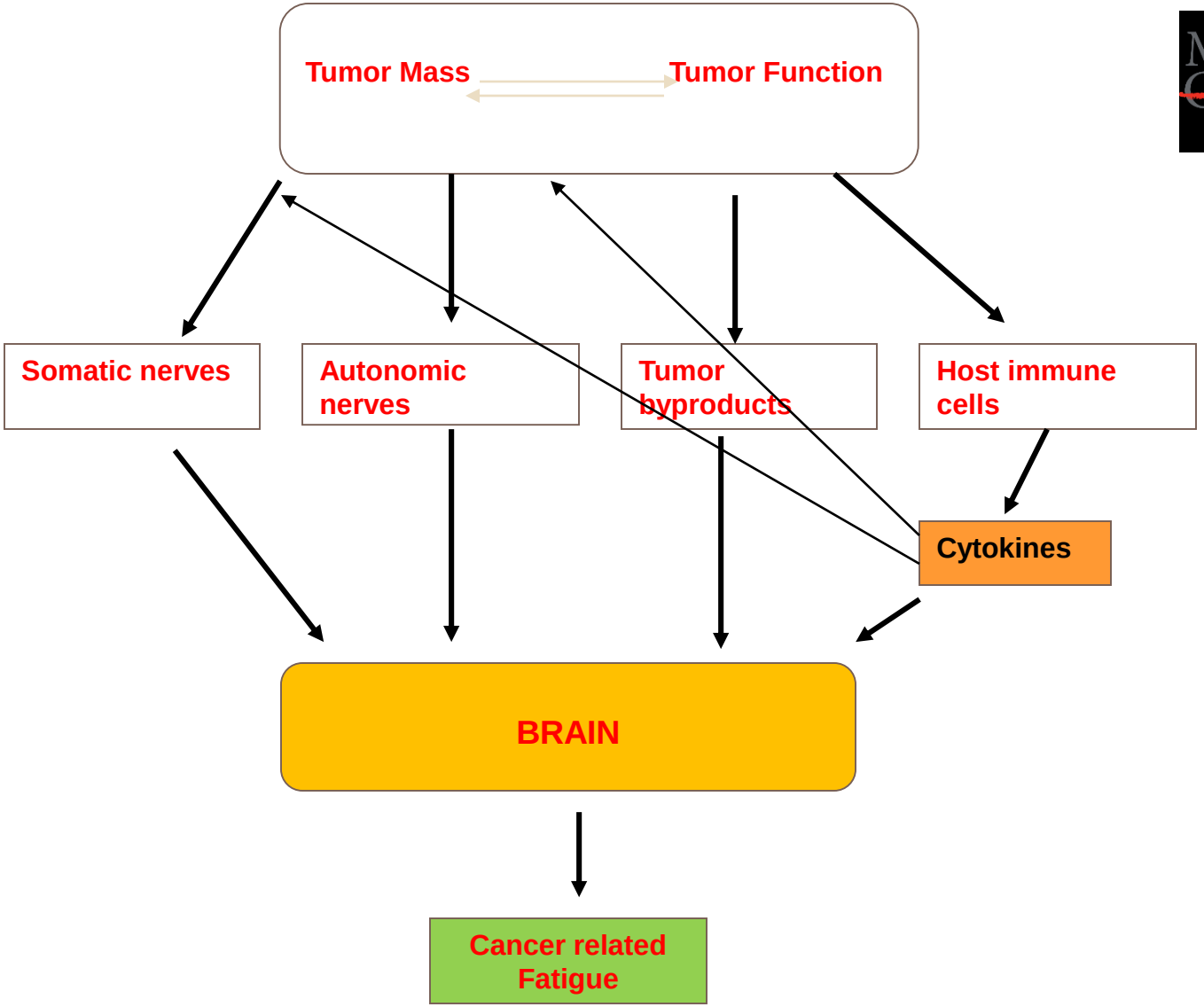
Capuron & Miller 2011



Capuron & Miller 2011



MASCC Biomarker Group
Saligan et al JSCC 2015


Tumor Mass
Tumor Function
Somatic nerves
Autonomic nerves
Tumor byproducts
Host immune cells
Cytokines
BRAIN
Cancer related Fatigue

Predictors of Severity of Fatigue in Advanced cancer (N=1778;Yennu 2013)

	Full model		Reduced model	
Variable	**B (SE)**	**p-value**	**B (SE)**	**p-value**
ESAS items				
Pain	0.09 (0.02)	< 0.0001	0.09 (0.02)	< 0.0001
Nausea	0.09 (0.02)	0.0001	0.09 (0.02)	0.0001
Depression	0.09 (0.03)	0.0017	0.1 (0.02)	< 0.0001
Anxiety	0.03 (0.03)	0.3118		
Appetite	0.17 (0.02)	< 0.0001	0.17 (0.02)	< 0.0001
Drowsiness	0.08 (0.02)	< 0.0001	0.08 (0.02)	< 0.0001
Feeling of well-being	0.12 (0.03)	< 0.0001	0.12 (0.03)	< 0.0001
Shortness of breath	0.14 (0.02)	< 0.0001	0.14 (0.02)	< 0.0001
Sleep disturbance	0.00 (0.02)	0.9689		
Low Albumin	0.64 (0.16)	< 0.0001	0.66 (0.16)	< 0.0001
Male	-0.10 (0.12)	0.3775		
Anemia	0.10 (0.15)	0.5258		

ESAS- Edmonton symptom assessment scale; B- Beta; SE- standard error

Causes of CRF in Advanced Cancer

Multifactorial

- Cancer related symptoms

  Physical symptoms:1) pain, 2) dyspnea, 3)nausea 4) insomnia, 5)anorexia, 6)drowsiness

  Psychological distress: 1) anxiety and 2)depression
- Low Albumin
- ? Inflammatory cytokines(IL-6, TNF-A, IL-1b)
- Hemoglobin levels, sleep disturbance not contributory in Advanced Cancer

Yennurajalingam 2008
Yennurajalingam 2010
Oh, 2011
Minton, 2011

Objectives

- Characterize patients with fatigue
  - New Definition of CRF
  - Etiology of Cancer related fatigue
- **Assessment**
- Management of CRF

Assessment

- Screening for clinically significant fatigue

  Use of 0-10 scale e.g., ESAS Tool
- Multidimensional tool

  Use of multidimensional fatigue tool e.g., MFI(multidimensional fatigue inventory)
- Ideally tools should capture the various dimensions, contributors of CRF & impact on function based on the proposed model

Yennu & Bruera JAMA 2007

Assessment of Fatigue

- Multidimensional Fatigue Inventory
- Multidimensional Fatigue Symptom Inventory
- Revised Piper Fatigue Scale
- Brief Fatigue Inventory
- Patient Reported Outcome (PROMISE)
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

Investigations

Medical Condition	Assessment Modality
Anemia	Complete blood count, serum vitamin B_{12} , folate, iron, transferring saturation, ferritin levels, fecal occult blood tests, and, if positive, further evaluation for blood loss
Medication side effects and polypharmacy	Anticholinergics, antihistamines, anticonvulsants, neuroleptics, opioids, central α antagonists, beta-blockers, diuretics, SSRI and tricyclic antidepressants, muscle relaxants and benzodiazepines
Cognitive or functional impairment	Assessments such as ADL, IADL, MMSE, and "get up and go" test
Mood disorders	Assessment of depression and anxiety following the DSM IV criteria
Side effects of primary disease treatment	Recent radiation therapy, chemotherapy, surgery
Malnutrition	Serum albumin, pre-albumin, cholesterol
Infections	Blood cultures, urine culture, chest radiography, HIV antibody, RPR, PPD skin test
Other contributing medical conditions	Directed based on clinical finding

Yennu & Bruera JAMA 2007

Objectives

- Characterize patients with fatigue
  - New Definition of CRF
  - Etiology of Cancer related fatigue
- Assessment
- **Management of CRF**

CRF Management

Specific treatment of underlying causes

- Cachexia
- Autonomic failure
- Anemia
- Infection
- Hypoxia
- Hypogonadism
- Depression
- Others

Symptomatic Treatment

Pharmacological & Complementary

- Corticosteroids
- Psychostimulants(?)
- New agents
  - –Ginseng?

Non-pharmacological

- Energy conservation
- Physical Activity (Aerobic or Resistance)*; Yoga*
- Psychosocial:
  - Cognitive Behavioral therapy* (CBT-BT-CBT-I)
  - Mindfulness based stress reduction
  - Psycho-educational
  - Supportive Expressive Therapy
- Massage?
- Acupuncture?
- Qigong?

* Level 1 evidence

Physical Activity and Cancer

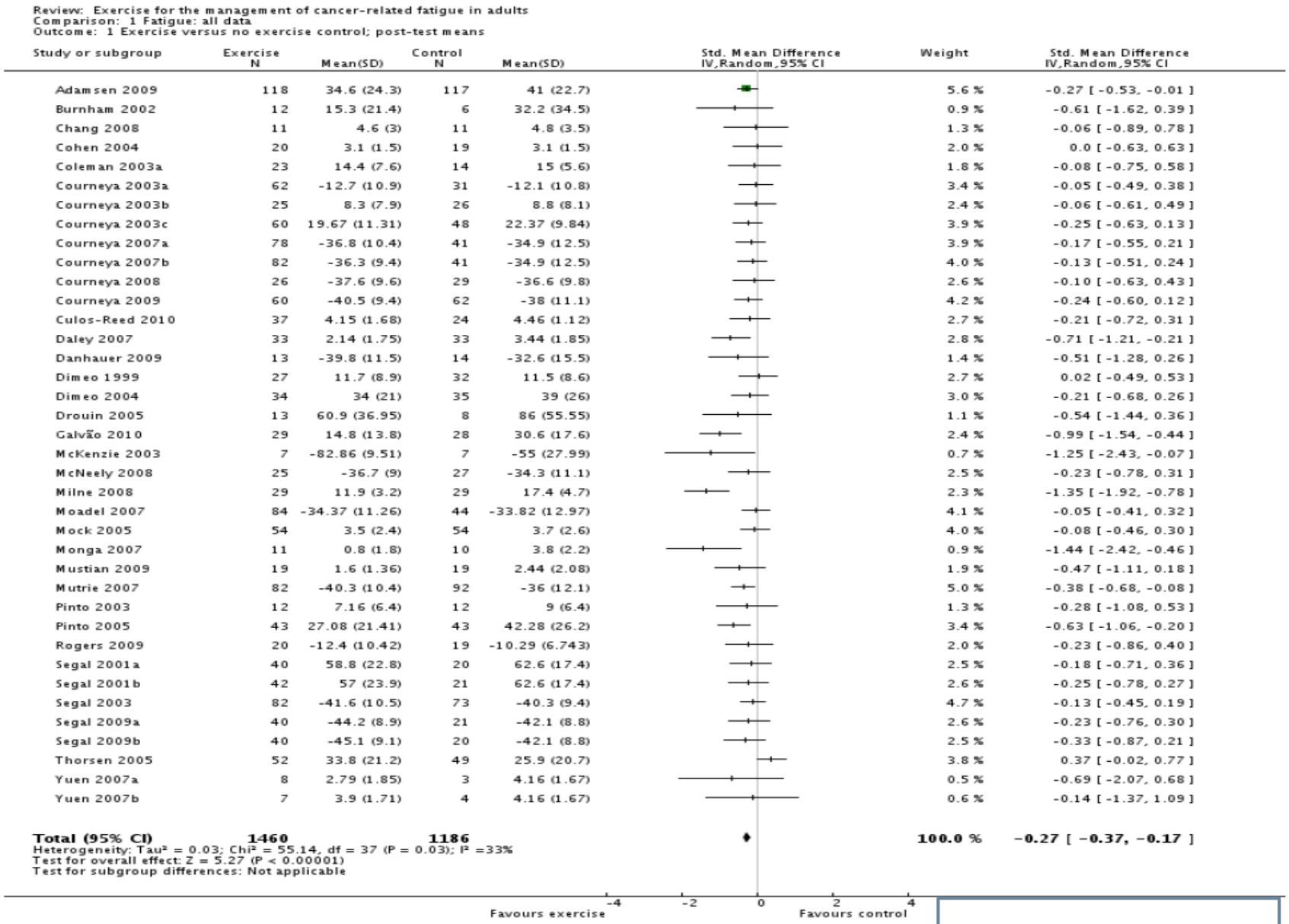
MD Anderson Cancer Center

Exercise results in significant increases in:

- Cardiovascular capacity
- Improved QOL
- Less fatigue
- Fewer sleeping problems and
- Increased self-reported physical functioning, well-being, self esteem, and energy.

Randomized Controlled Trials and Physical Activity

- Segal et al.(2009) both resistance and aerobic exercise – improvement of fatigue, QOL, strength, triglyceride levels, and body fat
- Cochrane meta-analysis (28 clinical trials-2000pts) – PA improved fatigue, both during and after treatment for cancer (SMD −0.27)



Cramp F, 2012

1 Exercise versus no exercise control; post-test means

Physical Activity

- Exercise program: both endurance and resistance exercise[Kangas M et al. 2008; Cramp F 2008]
- **150min/week**

  30 min of moderate activity most days of the week
- May require a referral to Physical therapy if:

  h/o CAD, recent surgery, bony metastasis, immuno-suppression/fever, thrombocytopenia, risk of falls, anemia
- **Advanced cancer- optimal type, intensity, timing of exercise intervention needed (Cramp F, 2012)**

Oldervoll LM, 2011

MD Anderson Cancer Center

- RCT, N= 231 patients with incurable cancer and a life expectancy of three months to two years
- Exercise (60 minutes twice a week for eight weeks)
- Significant improvement in physical performance as assessed by a hand grip strength test and the shuttle walk test
- No significant improvement in Fatigue after 8 weeks of treatment

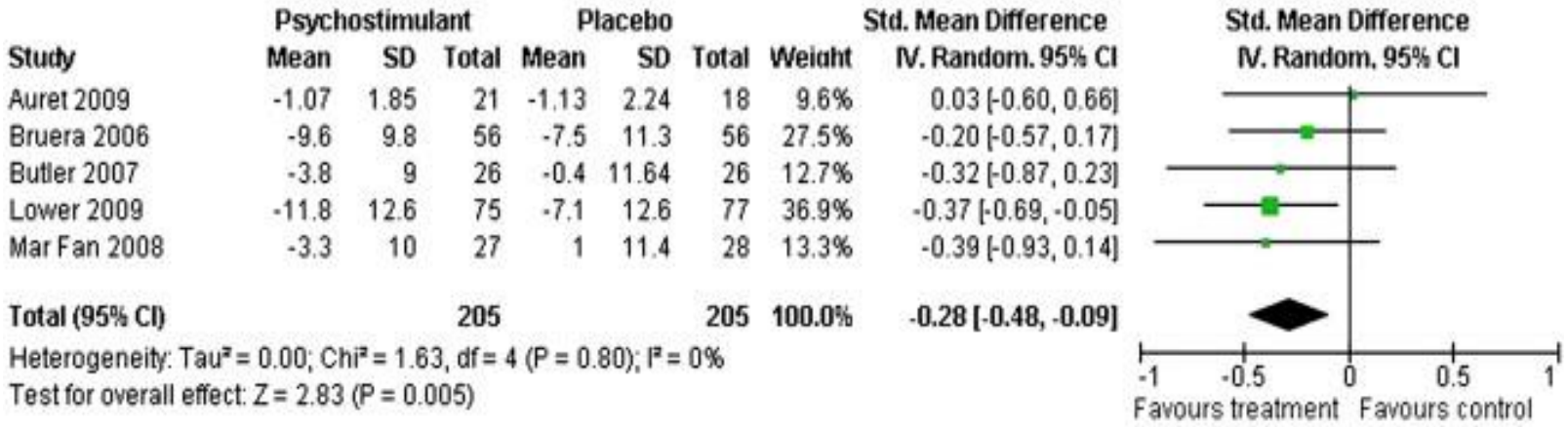
Ligibel 2016

- *Cancer* 2016;122:1169-77
- RCT, N= 101 patients with metastatic breast cancer
- Moderate intensity exercise (150 min a week for 16 weeks)
- Improvement in physical performance as assessed by a minutes of weekly exercise, Bruce Ramp Treadmill test, and physical functioning (EORTC QLQ 30)
- No significant improvement in Fatigue (FACIT-F subscale) after 16 weeks of treatment

Psychostimulants

- Fatigue
- Opioid induced sedation*
- Depression
- Hypoactive delirium

* Level 1



Ollie Minton , Alison Richardson , Michael Sharpe , Matthew Hotopf , Patrick C. Stone

Psychostimulants for the Management of?Cancer-Related Fatigue: A Systematic Review and Meta-Analysis

Journal of Pain and Symptom Management Volume 41, Issue 4 2011 761 - 767

http://dx.doi.org/10.1016/j.jpainsymman.2010.06.020

METHYLPHENIDATE AND/OR A NURSING TELEPHONE INTERVENTION FOR FATIGUE IN PATIENTS WITH ADVANCED CANCER: A RANDOMIZED PLACEBO-CONTROLLED PHASE II TRIAL

Eduardo Bruera, Sriram Yennurajalingam*, J. Lynn Palmer, Pedro E Perez-Cruz, Susan Frisbee-Hume, Julio Allo, Janet Williams, and Marlene Z. Cohen

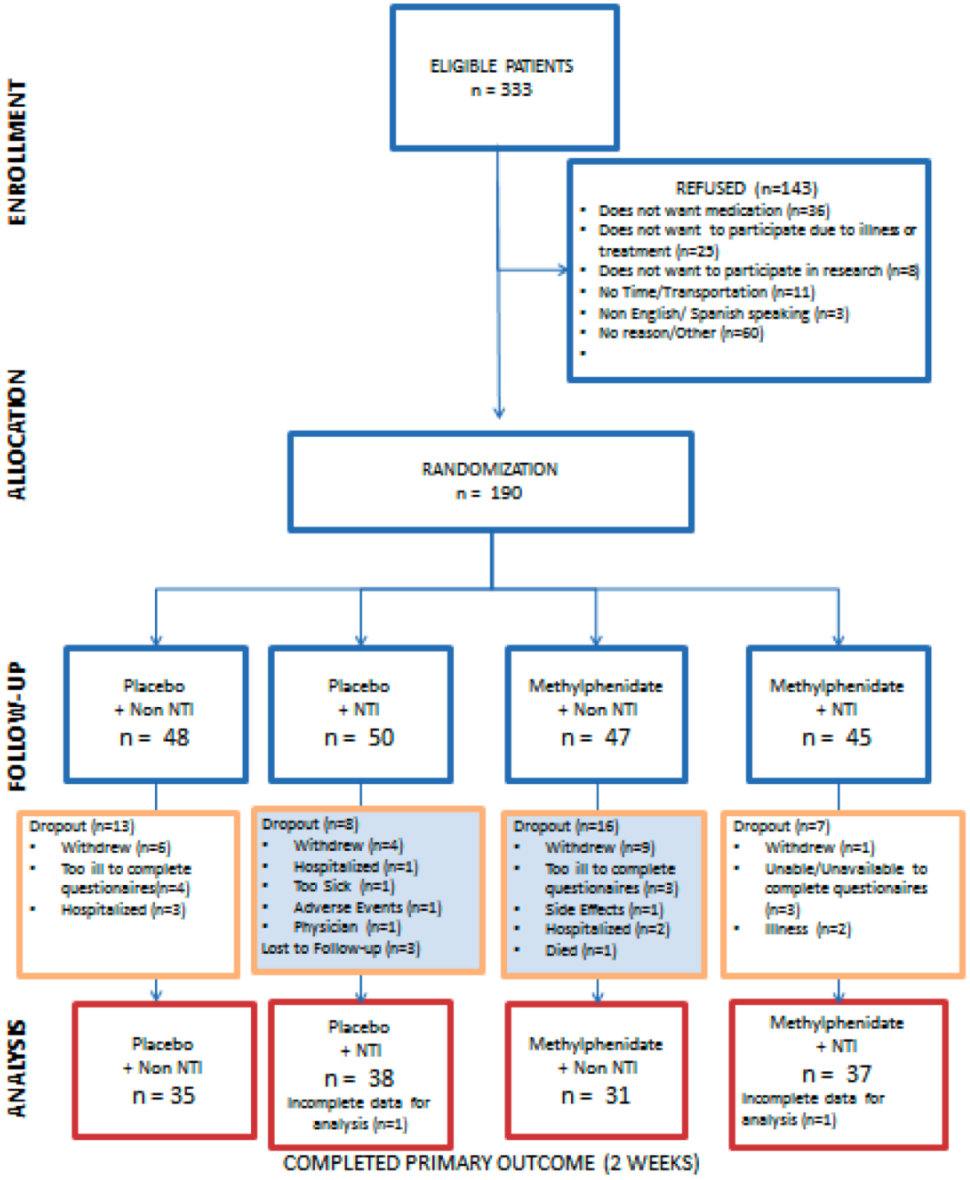
Objectives

- Primary: To determine the affect of methylphenidate on advanced cancer patients with CRF as compared to placebo.
- Secondary: Investigate role of nursing telephone intervention (NTI) in the improvement of CRF.
- Rationale: Prior research by our group suggests that methylphenidate and a NTI are both capable of significantly reducing fatigue (Bruera et. al., JCO 2006).

Methods

Patients:

- Advanced cancer patients with fatigue ≥ 4/10 on the Edmonton Symptom Assessment Scale (ESAS),
- Normal cognition evidenced by the Mini Mental State Examination (MMSE),
- No evidence of major depression and hemoglobin ≥ 8 are eligible.
- The primary endpoint was fatigue as measured by the change in Functional Assessment of Chronic Illness–Fatigue (FACIT–F) subscale scores, administered at baseline and day 15.


ENROLLMENT
ELIGIBLE PATIENTS
n = 333
REFUSED (n=143)
Does not want medication (n=36)
Does not want to participate due to illness or treatment (n=25)
Does not want to participate in research (n=8)
No Time/Transportation (n=11)
Non English/ Spanish speaking (n=3)
No reason/Other (n=60)
ALLOCATION
RANDOMIZATION
n = 190
FOLLOW-UP
Placebo + Non NTI n = 48
Placebo + NTI n = 50
Methylphenidate + Non NTI n = 47
Methylphenidate + NTI n = 45
Dropout (n=13)
Withdrew (n=6)
Too ill to complete questionaires(n=4)
Hospitalized (n=3)
Dropout (n=8)
Withdrew (n=4)
Hospitalized (n=1)
Too Sick (n=1)
Adverse Events (n=1)
Physician (n=1)
Lost to Follow-up (n=3)
Dropout (n=16)
Withdrew (n=9)
Too ill to complete questionaires (n=3)
Side Effects (n=1)
Hospitalized (n=2)
Died (n=1)
Dropout (n=7)
Withdrew (n=1)
Unable/Unavailable to complete questionaires (n=3)
Illness (n=2)
ANALYSIS
Placebo + Non NTI n = 35
Placebo + NTI n = 38 Incomplete data for analysis (n=1)
Methylphenidate + Non NTI n = 31
Methylphenidate + NTI n = 37 Incomplete data for analysis (n=1)
COMPLETED PRIMARY OUTCOME (2 WEEKS)

MD Anderson Cancer Center

Table 3. Change in the Fatigue Scores at Day 8 and Day 15 by Treatment/Intervention

	FACIT-F (Fatigue Subscale)						ESAS Fatigue					
	Day 8-Baseline			Day 15-Baseline			Day 8-Baseline			Day 15-Baseline		
	N	Median (IQR)	P	N	Median (IQR)	P*	N	Median (IQR)	P	N	Median (IQR)	P*
Treatment			0.87			0.69			0.98			0.86
Methylphenidate	71	6.00 (0,16.00)		68	5.50 (-1.00, 11.00)		71	-2.00 (-3.00, 0)		66	-2.00 (-4.00, 0)	
Placebo	76	7.00 (0.50, 12.00)		73	6.00 (2.00, 11.00)		76	-2.00 (-3.00, 0		71	-2.00 (-5.00, 0)	
Nursing Intervention			0.22			0.27			0.00			0.14
NTI	78	6.50 (1.00, 15.58)		75	6.00 (0, 14.00)		79	-2.00 (-4.00, -1.00)		74	-2.50 (-5.00, 0)	
CTI	69	6.00 (-1.00,12.00)		66	5.50 (1.00, 10.00)		68	-1.00 (-2.50, 1.00)		63	-2.00 (-4.00, 0)	
ALL Groups			0.19			0.16			0.02			0.45
MP+ NTI	39	4.00 (0, 16.00)		37	4.00 (-2.00, 11.00)		40	-2.00(-3.00, -1.00)		37	-3.00 (-4.00, -1.00)	
MP+ CTI	32	6.50 (0.50, 16.00)		31	7.00 (2.00, 11.00)		31	-1.00 (-2.00, 0)		29	-1.00 (-3.00, 0)	
PL+ NTI	39	10.00 (4.00, 15.00)		38	8.50 (3.00, 17.00)		39	-2.00 (-4.00, -1.00)		37	-2.00 (-5.00, 0)	
PL +CTI	37	6.00 (-3.00, 10.00)		35	5.00 (0,6.00)		37	-1.00 (-3.00, 1.00)		34	-2.00 (-4.00, 0)	

*Wilcoxon two sample test and Kruskal-Wallis test

Abbreviations: MPI+NTI - methylphenidate plus Nursing Telephone Intervention, PL+NTI - placebo plus NTI, MP + CTI methylphenidate plus Control Telephone Intervention, and PL+CTI - placebo plus CTI. FACIT-F-Functional Assessment of Chronic Illness Therapy-Fatigue; ESAS-Edmonton Symptom Assessment Scale.

MD Anderson Cancer Center

Table 5. Summary of Types of Adverse Events (Grade ≥3) Experienced by Patients in the Methylphenidate and Placebo Groups*†

Event	No. of Events	Methylphenidate (N=11)	Placebo (N=12)
Pain	6	3	3
Insomnia	6	2	4
Mood alteration (depression or anxiety)	3	2	1
Nausea	1	0	1
Hypertension	1	1	0
Anorexia	1	1	0
Syncope	1	0	1
Flu-like symptom	2	1	1
Tachycardia	1	0	1
Slurred speech	1	1	0

* Only Grade ≥3 adverse events (AE's) related to the study treatment were summarized.

† No significant differences were found in the incidence of grade ≥3 toxicities between patients who received methylphenidate and those who received placebo (p=0.06).

Conclusions

- Neither MP or an NTI alone nor the two combined was superior to PL for improving CRF.
- Future research on MP in the advanced cancer setting should focus on subgroups of patients with higher levels of anxiety or depression.

MD Anderson Cancer Center

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Modafinil for the Treatment of Fatigue in Lung Cancer: Results of a Placebo-Controlled, Double-Blind, Randomized Trial

Anna Spathis, Kate Fife, Fiona Blackhall, Susan Dutton, Ronja Bahadori, Rose Wharton, Mary O'Brien, Patrick Stone, Tim Benepal, Nick Bates, and Bee Wee

Modafinil vs Placebo

Placebo controlled; Double blind RCT, 1:1—100mg D1-14; 200mg D15-28

- Eligibility
  - NSC Lung Ca, stg >3
  - PS<3
  - Fatigue NRS >/=5
  - No chemo or Rtx in last 4 weeks

Table 1. Baseline Patient Demographic and Clinical Characteristics

Characteristic	Modafinil Arm (n = 104) No.	%	Placebo Arm (n = 103) No.	%
Age at random assignment, years				
Mean	68.60		69.18	
SD	9.10		9.46	
Sex				
Female	53	51.0	51	49.5
Male	51	49.0	52	50.5
WHO performance status				
0	10	9.6	10	9.6
1	56	53.9	57	54.8
2	38	36.5	37	35.6
Disease stage				
3a	8	7.7	12	11.6
3b	24	23.1	22	21.4
4	68	65.4	62	60.2
Recurrent	4	3.8	7	6.8
NRS screening fatigue score				
5-6	47	45.2	51	49.5
7-10	57	54.8	52	50.5
Haemoglobin at random assignment, g/dL				
Mean	12.35		12.64	
SD	1.69		1.84	
Corrected calcium at random assignment, mmol/L				
Mean	2.37		2.39	
SD	0.16		0.22	

Abbreviations: NRS, numeric rating scale; SD, standard deviation.

Table 2. Outcomes at Baseline, Day 14, and Day 28

Scale	Modafinil Arm				Placebo Arm			
	Mean	SD	No.	Range	Mean	SD	No.	Range
FACIT-Fatigue score								
Baseline	24.64	10.58	104	1-45	24.98	10.83	103	3-47
Day 14	30.58	12.17	88	1-52	29.43	11.57	90	3-49
Day 28	31.28	13.66	75	1-52	30.66	13.85	85	3-51
ESS score								
Baseline	8.61	5.18	103	0-21	9.31	5.17	100	1-21
Day 14	6.51	5.25	86	0-21	7.51	5.10	87	0-24
Day 28	6.45	5.15	74	0-22	7.27	5.45	84	0-24
HADS-Depression score								
Baseline	7.09	4.40	104	1-19	7.27	4.27	103	0-18
Day 14	5.94	4.14	88	0-16	6.11	4.10	90	0-18
Day 28	5.71	4.21	75	0-18	5.94	4.76	85	0-18
QOL-LAS score								
Baseline	6.00	1.84	104	0-10	5.83	1.72	103	2-10
Day 14	6.14	1.89	88	0-10	6.02	1.90	90	0-10
Day 28	6.15	1.93	75	1-10	6.02	2.27	84	0-10

NOTE. Higher FACIT-Fatigue score indicates less severe fatigue. Higher ESS and HADS scores indicate more severe symptoms. Higher QOL-LAS score indicates better quality of life. Score ranges: FACIT-Fatigue, 0-52; ESS, 0-24; HADS-Depression, 0-21; QOL-LAS, 0-10.

Abbreviations: ESS, Epworth Sleepiness Scale; FACIT, Functional Assessment of Chronic Illness Therapy; HADS, Hospital Anxiety and Depression Scale; QOL-LAS, quality of life linear analog scale; SD, standard deviation.

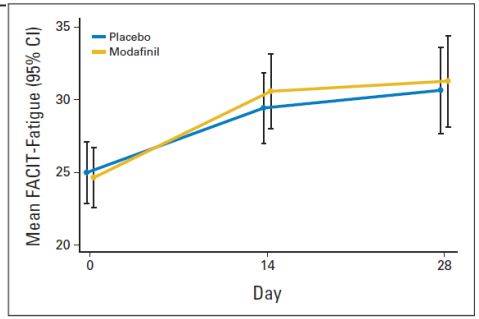


Fig 2. Change in fatigue over time in intervention and control arms. FACIT, Functional Assessment of Chronic Illness Therapy.

Who responds to Methylphenidate?

Aims

- To identify the specific patient characteristics associated with response to methylphenidate
- To compare day 1 response with day 8 response.

Methods

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

- Pooled analysis of patients in two prospective controlled clinical trials who had received methylphenidate for cancer–related fatigue.
- Baseline patient characteristics, symptoms (as assessed by ESAS and FACIT–F), and response (change in fatigue) at the end of Day 1 treatment were analyzed

Results: Patient Characteristics (N = 82)

Patient Characteristic	Frequency (%)
Gender	
Female	54 (66)
Male	28 (34)
Ethnicity	
White	61 (74)
Hispanic	11 (13)
African-American	7 (9)
Asian	3 (4)
Primary Cancer Diagnosis	
Lung	5 (6)
Breast	30 (36)
Gastrointestinal	4 (5)
GU	5 (6)
Melanoma	1 (1)
Hematologic	10 (12)
Gynecologic	5 (6)
Head and Neck Cancer	12 (16)
Other*	10 (12)

*Sarcoma, brain, skin, unknown primary cancer

Associations between Change in FACIT-F Fatigue Subscale and ESAS Baseline Symptoms, N=82

ESAS Symptom*	*Spearman correlation coefficient, significance*
Pain	r = 0.12, *P* = 0.25
Fatigue	**r = 0.36, *P* = 0.0009**
Nausea	r = -0.05, *P* = 0.67
Depression	r = 0.08, *P* = 0.45
Anxiety	r = 0.07, *P* < 0.51
Drowsiness	r = -0.03, *P* = 0.79
Dyspnea	r = -0.07, *P* = 0.5
Anorexia	r = -0.007, *P* = 0.94
Insomnia	r = 0.001, *P* = 0.98
Feeling of well-being	r = -0.13, *p* = 0.24

*Edmonton symptom assessment scale**Functional assessment of chronic illness therapy - fatigue subscale

Associations between Change in FACIT-F Fatigue Subscale and Baseline FACT-G subscales, Daily opioid use, Day 1 Response

FACT- Physical	r = -0.12, p = 0.28
FACT- Social	r = -0.07, p = 0.24
FACT- Emotional	r = -0.07, p = 0.54
FACT- Function	r = -0.065, p = 0.56
FACIT-F subscale	r = -0.475, p<0.0001
Daily opioid use [MEDD*]	r = 0.13, p = 0.24
Day 1 ESAS response**	r = -0.39, p = 0.0004

*Morphine equivalent daily dose

** Similar findings (opposite direction) were found for change in day 1 ESAS(F) response and change in Day 8 ESAS(F) response (r=0.47, p<0.0001)

Hematopoetic Growth Factors and PRBC Transfusion

- Most Studies (open labeled) showed benefit in improving fatigue
- Erythropoetin and Darbepoetin improves fatigue in patients receiving chemotherapy(12gm/dl) (Minton 2008)
- Safety concerns – Thrombovascular events, tumor growth (June 2008)
- RBC transfusions – immediate correction of the hemoglobin level

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Reduction of Cancer-Related Fatigue With Dexamethasone: A Double-Blind, Randomized, Placebo-Controlled Trial in Patients With Advanced Cancer

Sriram Yennurajalingam, Susan Frisbee-Hume, J. Lynn Palmer, Marvin O. Delgado-Guay, Janet Bull, Alexandria T. Phan, Nizar M. Tannir, Jennifer Keating Litton, Akhila Reddy, David Hui, Shalini Dalal, Lisa Massie, Suresh K. Reddy, and Eduardo Bruera

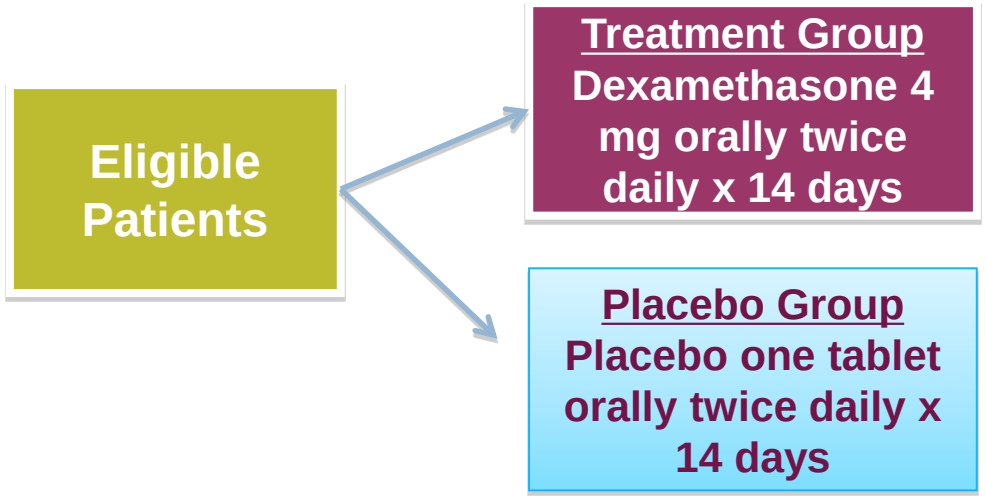
Funded by American Cancer Society Career Development award Grant

Rationale

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

- CRF associated with inflammation (Miller,2008; Seruga, 2008)
- Preliminary steroid studies show benefit!
- No steroid study to date with CRF as a primary outcome
- No steroid study to date which assessed CRF using a validated outcome measure

Treatment Schema



Trial Registration clinicaltrials.gov Identifier: NCT00489307

Objectives

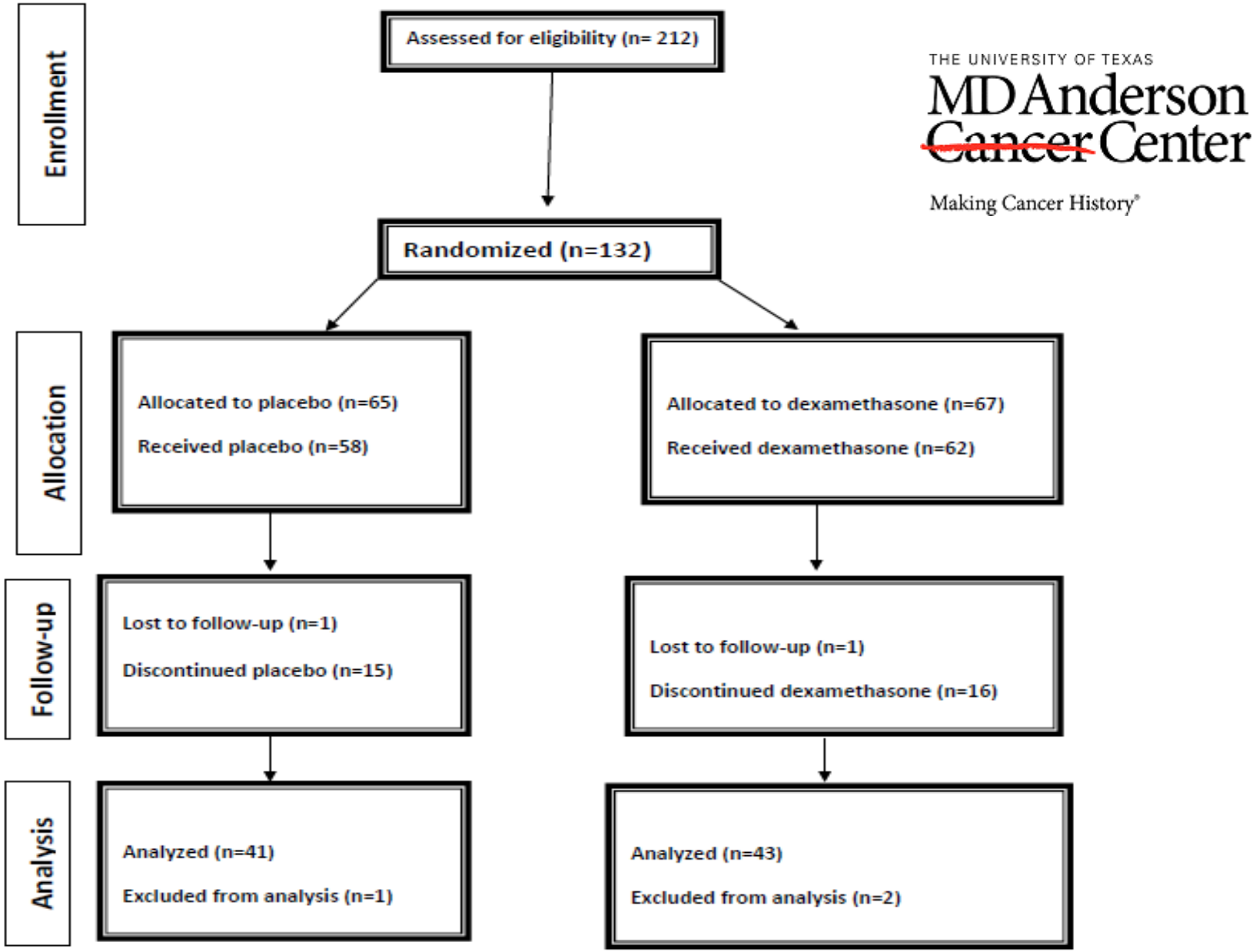
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

- To compare the effects of dexamethasone and placebo on CRF
- To determine the role of dexamethasone on anorexia, anxiety, depression, and overall symptom distress

Eligibility Criteria: Inclusion

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

- History of Advanced Cancer
- Fatigue ≥ 4 on the Edmonton Symptom Assessment Scale (ESAS; a 0–10 scale)
- Two other fatigue related symptoms (pain, nausea, loss of appetite, depression, anxiety, or sleep disturbance) at a score of ≥ 4/10 (ESAS)
- Normal cognition
- Hgb ≥ 9g/dl
- Life expectancy 4 weeks or more

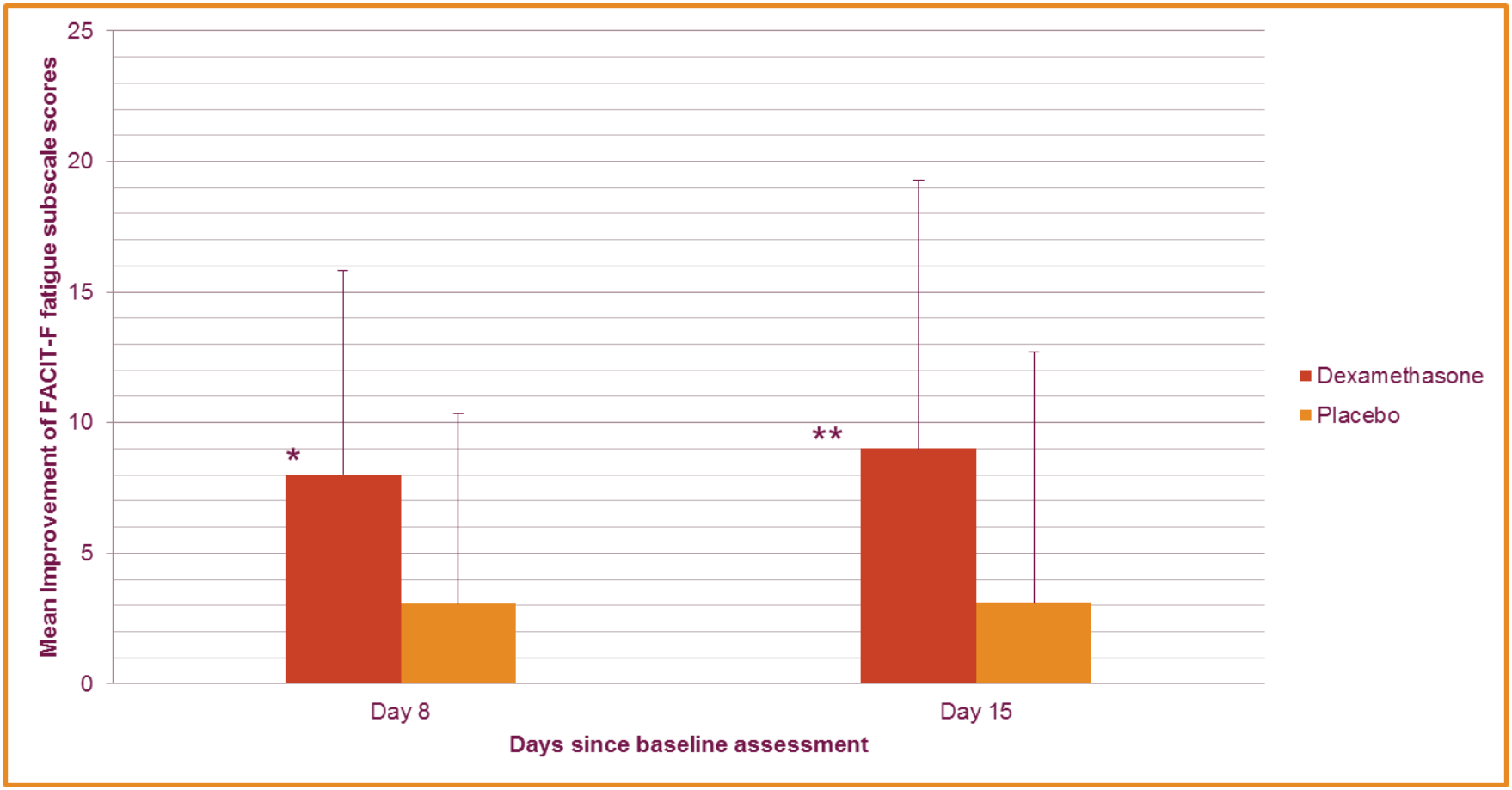


THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Patient Characteristics

Characteristics	No. of Patients			
	Dexamethasone (n=67)	Placebo (n=65)	Total (n=132)	p
Age, years				
Median	60.5	60	60	0.438
Sex, n				
Male	25	37	62	**0.024**
Female	42	28	70	
Race, n				
White	42	39	81	0.252
Hispanic	11	10	21	
Black	13	10	23	
Asian/Other	1	6	7	
Diagnosis, n				
Breast cancer	7	6	13	0.528
Head&Neck, Lung cancer	24	21	45	
Gastrointestinal cancer	15	24	39	
Genitourinary cancer	6	4	10	
Sarcoma cancer	6	3	9	
Gynecological cancer	4	5	9	
Other	5	2	7	
FACIT-Fatigue subscale score				
Mean	18.40	21.57	19.64	0.069

Mean improvement in the FACIT -F fatigue subscale in the dexamethasone and placebo arms



*p=0.005; **p=0.008

Results

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Instrument*	Dexamethasone (N=43)		Placebo (N=41)			Dexamethasone (N=43)		Placebo (N=41)		
	Day 15 - Baseline		Day 15 - Baseline			Day 8 - Baseline		Day 8 - Baseline		
	Mean	SD	Mean	SD	P†	Mean	SD	Mean	SD	P†
FACIT Fatigue Subscale	**9.0**	**10.30**	**3.1**	**9.59**	**0.008**	8.01	7.81	3.06	7.28	**0.005**
FACIT Physical	5.25	6.01	1.32	5.52	**0.002**	4.37	5.14	1.34	4.50	**0.007**
FACIT Social/family	-0.05	5.50	0.2	4.77	0.820	-0.22	4.06	0.52	3.58	0.40
FACIT Emotional	1.85	4.93	1.18	4.49	0.490	0.59	3.57	1.44	4.07	0.33
FACIT-Functional	1.3	6.21	1.51	5.17	0.820	0.55	5.20	1.11	4.80	0.56
FACIT-F total Score	18.16	22.88	7.87	19.93	**0.030**	13.37	13.22	7.5	14.04	0.06

*As values were normally distributed, data are presented as means and standard deviation (SD); **ł** Paired t-test; the ESAS psychological scores were not normally distributed, so Wilcoxon two-sample tests were used in those analyses. **FACIT-F** - Functional Assessment of Chronic Illness Therapy –Fatigue

Results

Instrument*	Dexamethasone (N=43)		Placebo (N=41)			Dexamethasone (N=43)		Placebo (N=41)		
	Day 15 – Baseline		Day 15 – Baseline			Day 8 – Baseline		Day 8 – Baseline		
	Mean	SD	Mean	SD	P‡	Mean	SD	Mean	SD	P‡
ESAS Physical	−10.15	9.8	−5.39	10.56	**0.046**	−7.52	8.2	−3.95	10.85	0.08
ESAS Psychological	−1.48	4.67	−2.08	4.73	0.76	−1.26	4.68	−1.81	5.01	0.91
ESAS Symptom distress	−12.2	13.49	−8.86	15.91	0.22	−10	12.28	−6.95	16.38	0.23
HADS Anxiety	−0.66	3.45	−1.00	3.54	0.75	−0.85	3.16	−1.09	2.32	0.59
HADS Depression	−1.39	3.59	−0.31	3.90	0.29	−1.23	4.02	−0.43	3.12	0.65
FAACT	15.22	19.7	6.46	19.52	**0.04**	9.12	14.21	5.53	16.06	0.31

*As values were normally distributed, data are presented as means and standard deviation (SD); ǂ Paired t-test; the ESAS psychological scores were not normally distributed, so Wilcoxon two-sample tests were used in those analyses. **FAACT**- Functional Assessment of Anorexia/Cachexia Therapy; **ESAS** - Edmonton Symptom Assessment Scale **HADS** – Hospital Anxiety Depression Scale.

Adverse Events

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

- No significant difference in the number of grade ≥3 adverse events(CTC V.3.0) between dexamethasone vs. placebo group (17/62 vs. 11/58, P=0.27)

Conclusions

- Dexamethasone is more effective than placebo in reducing CRF in patients with advanced cancer.
- There was a significant improvement in quality of life, physical well-being, and physical distress.
- Larger long-term efficacy and safety studies are needed.

The Oncologist®

Symptom Management and Supportive Care

Effects of Dexamethasone and Placebo on Symptom Clusters in Advanced Cancer Patients: A Preliminary Report

SRIRAM YENNURAJALINGAM,[a] JANET L. WILLIAMS,[a] GARY CHISHOLM,[b] EDUARDO BRUERA[a]

Departments of [a]Palliative Care and Rehabilitation Medicine and [b]Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Symptom clusters • Interventions • Dexamethasone • Principal component analysis • Cytokines

Table 2. Association between cluster scores at baseline, day 8, and day 15[§].

Fatigue-Anorexia/Cachexia-Depression Cluster	Baseline Median (IQR) 1.42(1.10,1.71)	Day 8 Median (IQR) 1.71(1.28,2.08)	Day 15 Median (IQR) 1.78(1.38,2.20)
Baseline	___	.755*	.549*
Day 8	___	___	.788*

Sleep-Anxiety-Drowsiness Cluster	Baseline Median (IQR) 1.58(1.35,2.33)	Day 8 Median (IQR) 1.96(1.30,2.42)	Day 15 Median (IQR) 1.86(1.43,2.26)
Baseline	___	.25	-.13
Day 8	___	___	0.23

Pain-Dyspnea Cluster	Baseline Median (IQR) 1.10(0.81,1.43)	Day 8 Median (IQR) 1.38(0.04,1.56)	Day 15 Median (IQR) 1.43(1.25,1.68)
Baseline	___	.360*	.081
Day 8	___	___	.446*

[§]Correlation measured using Spearman rho correlation coefficients

* Significant at $P < 0.001$

Abbreviations: IQR- Interquartile range; *FACIT-F- Functional Assessment of Chronic* Illness Therapy-Fatigue subscale (Fatigue); FAACT- Functional Assessment of Anorexia/Cachexia Therapy-Anorexia-Cachexia Subscale (Anorexia-Cachexia); BPI- Brief Pain Inventory(Pain); HADS- Hospital Anxiety and Depression Scale (Anxiety-Depression); ESAS- Edmonton Symptom Assessment Scale(Sleep-Drowsiness-Dyspnea)

Table 3. Median changes in Cluster scores at day 8 and day 15

	Dexamethasone		Placebo			Dexamethasone		Placebo		
	Day 15 - Baseline		Day 15 - Baseline			Day 8 - Baseline		Day 8 - Baseline		
	N	Median (IQR)	N	Median (IQR)	P	N	Median (IQR)	N	Median (IQR)	P
Fatigue-Anorexia-Drowsiness	41	.22 (-.04, .45)	33	.06 (-.30, .20)	0.016	40	.15 (-.84, .35)	35	-.095 (-.35, .16)	0.017
Pain-Sleep-Dyspnea	35	.05 (-.54, .68)	31	-0.14 (-.54,.55)	0.79	35	-.19(-.58, .55)	29	.15 (-.65,.50)	0.42
Anorexia-Depression	39	0.25 (-.05, .60)	34	.16 (-.14, .42)	0.35	40	.21 (-.21, .49)	36	.18 (-.33, .49)	0.82

Abbreviations: IQR- Interquartile range; FACIT-F- Functional Assessment of Chronic Illness Therapy-Fatigue subscale (Fatigue); FAACT- Functional Assessment of Anorexia/Cachexia Therapy- Anorexia-Cachexia Subscale (Anorexia-Cachexia); BPI- Brief Pain Inventory(Pain); HADS- Hospital Anxiety and Depression Scale (Anxiety-Depression); ESAS- Edmonton Symptom Assessment Scale(Sleep-Drowsiness-Dyspnea)

Conclusions

- FAD cluster showed significant improvement with dexamethasone
- These findings suggest that fatigue–anorexia/cachexia– and depression share a common pathophysiologic basis.
- Further studies are needed to investigate this cluster and target with anti-inflammatory therapies.

Psychosocial Interventions

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

- Cognitive behavioral therapy
- Energy conservation
- Yoga/meditation, acupuncture, massage

INTEGRATIVE MEDICINE AND CANCER RELATED FATIGUE:

ROLE OF GINSENG

“ginseng”

- *ginseng* has been used medicinally in the Far East for several millennia.
- Is currently one of the most widely used botanical dietary supplements in the U.S.
- Standardized extracts and other commercial products are prepared from dried root,
- Preparation by either drying or bleaching with sulfur dioxide, or by steaming and then air drying, create the white and red types, respectively.
- Other plant species also go by the common name “ginseng”, are American ginseng, *Panax quinquefolius* L., and Siberian ginseng, *Eleutherococcus senticosus* (Rupr. & Maxim).

Dharmananda S, 2002

"ginseng"

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

- "standardized" – consistent amounts of labeled total ginsenosides, Rb1/Rg1 ratios demonstrated greater variation.
- This variability – different pharmacologic effects.
- P. ginseng and P. quinquefolium (American ginseng), where the ratio of Rg1 to Rb1 is higher in P. ginseng.

Dharmananda S, 2002

Mechanism of Action on Fatigue

ginseng reduces fatigue by action on:

a) CNS, including cognition/memory, sleep disturbance, anxiety/ depression,

b) Pain, and

c) Inflammatory cytokines

Phase III evaluation of American ginseng (panax quinquefolius) to improve cancer-related fatigue: NCCTG trial N07C2.

Patients:

Inclusion

- Patients with cancer undergoing or having completed curative intent treatment and experiencing fatigue
- Rated at least 4 on a numeric analogue fatigue scale (1–10) for ≥1 month, were eligible.

Exclusion

- CNS lymphoma,
- Brain malignancies, or prior use of ginseng or chronic systemic steroids.
- Other etiologies for fatigue, such as pain and sleep, were also excluded.

Research Design

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Design &Treatment

- Patients were randomized to receive, in a double blind manner, 2,000 mg/d of American Ginseng or placebo in BID dosing for 8 weeks.

The primary endpoint

change from baseline in the general subscale of the Multidimensional Fatigue Symptom Inventory (MFSI) at 4 & 8 weeks.

Other MFSI subscales, the fatigue-inertia subscale of the Profile of Mood States (POMS) and Brief Fatigue Inventory were also analyzed.

Results

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

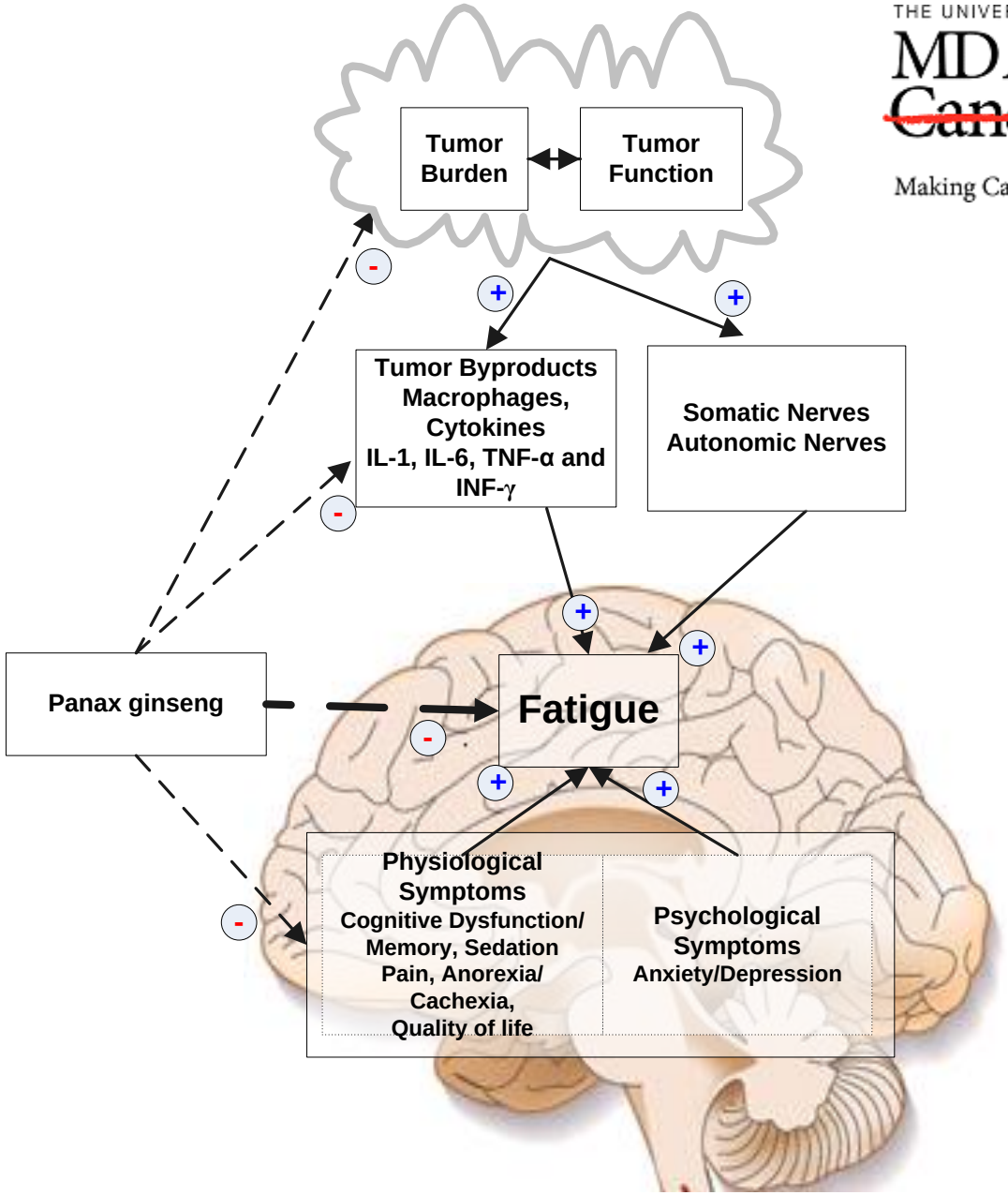
Fatigue measure	Weeks	Change scores (SD)		
		Ginseng n=147	Placebo n=152	p value
MFSI – general	4	14.4 (27.1)	8.2 (24.8)	0.0737
	8	20.0 (27.0)	10.3 (26.1)	0.0029
MFSI – physical	4	1.6 (15.9)	−0.4 (14.7)	0.3942
	8	3.0 (17.9)	−1.7 (18.2)	0.0043
MFSI – total	4	4.1 (13.4)	2.1 (12.9)	0.2061
	8	6.7 (14.0)	3.7 (14.6)	0.0193
POMS – fatigue/inertia	4	14.5 (25.0)	7.7 (23.6)	0.0795
	8	18.6 (24.8)	10.2 (26.1)	0.0083

Results

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

- Subgroups – Patients receiving cancer treatment improved at Week 4 and Week 8(p=0.02)
- There were no statistically significant differences in any grade of toxicity or self reported side effects between ginseng and placebo.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®



Original Article

High-Dose Asian Ginseng (Panax Ginseng) for Cancer-Related Fatigue: A Preliminary Report

Integrative Cancer Therapies
1–9

DOI: 10.1177/1534735415580676
ict.sagepub.com
SAGE

Sriram Yennurajalingam, MD, MS[1], Akhila Reddy, MD[1], Nizar M. Tannir, MD[2], Gary B. Chisholm[3], Richard Tsong Lee, MD[4], Gabriel Lopez, MD[4], Carmen P. Escalante, MD[5], Ellen F. Manzullo, MD[5], Susan Frisbee Hume, RN, MS, CCRC[1], Janet L. Williams, MPH, CCRP[1], Lorenzo Cohen, PhD[4], and Eduardo Bruera, MD[1]

Objectives

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

- Primary* To evaluate the safety and tolerability of high-dose, standardized PG extract for the management of CRF.
- Secondary*To examine the effects PG on QOL measures including cancer related fatigue

Patient Eligibility

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

- Patients must have been diagnosed with cancer and currently undergoing outpatient chemotherapy at the cancer center
- Experiencing CRF with an average intensity of ≥ 4 on the Edmonton Symptom Assessment Scale (ESAS; a 0–10 scale) during the 24 hours
- CRF was described as being present every day for most of the day for a minimum of 2 weeks.
- Other important eligibility criteria were as follows:
  - Normal cognition; no infections;
  - Hemoglobin ≥ 8 g/L within 2 weeks of enrollment
  - Zubrod performance status of ≤2
  - No current uncontrolled pain or depressive symptoms
  - No uncontrolled diabetes or treatment with anticoagulants or systemic steroids

Intervention

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

- Eligible patients were given a 29-day supply of 400-mg PG capsules.
- They were directed to take one capsule orally twice a day for 4 weeks.
- The patients were instructed to take one capsule of the study medication in morning and one capsule prior to 3 pm daily so as to avoid interference with sleep.

Table 2. Patient Characteristics at Baseline (N = 30).

Characteristic	
Age, years	
Median	58
Range	48-68
Sex, n	
Male	16
Female	16
Education, years	
Median	14
Range	12-16
Diagnosis, n	
Breast cancer	7
Lung cancer	3
Gastrointestinal cancer	2
Genitourinary cancer	10
Lymphoma	3
Melanoma	1
Hematologic	6
Currently receiving treatment, n (%)	26/30 (87)
Currently on combination chemotherapy, n (%)	10/30 (33)
Carboplatin, paclitaxel	3 (10)
Cisplatin	1 (3)
Carboplatin, docetaxel, 5 florouracil (FU)	1 (3)
Oxaliplatin, 5 FU	1 (3)
Rituxan, cyclo, etoposide, vincristine, prednisone	1 (3)
Cepecitabine	1 (3)
Gemcitabine, docetaxel	1 (3)
Lenolidamide	1 (3)
Currently on targeted therapy, n (%)	10/30 (33)
Pazopanib	3 (10)
Sunitinib	1 (3)
Dasatinib	1(3)
Sorafenib	1 (3)
Sirolimus	1 (3)
Everolimus	1 (3)
Temsirolimus	1 (3)
Trastuzamab	1 (3)
Currently on endocrine therapy, tamoxifen, n (%)	1 (3)
Recently on radiation therapy (in the past 30 days), n (%)	4/30 (13)

Patient Characteristics at Baseline (N=30)		
Characteristic	Mean	SD
FACIT-Fatigue subscale score	23.08	9.29
FACT-G	70.7	16.66
HADS – Anxiety score	6.17	3.44
HADS – Depression score	6.80	3.47
ESAS Pain	3.10	2.69
ESAS Fatigue	6.20	1.73
ESAS Nausea	1.33	2.04
ESAS Depression	1.34	2.06
ESAS Anxiety	2.13	2.06
ESAS Drowsiness	3.33	2.35
ESAS Shortness of Breath	1.67	2.42
ESAS Appetite	4.10	2.92
ESAS Sleep	4.97	2.46
ESAS Feeling of Well-being	4.53	2.09
ESAS Physical distress score	19.73	8.32
ESAS Psychological distress score	3.50	3.83
ESAS Symptom distress score	23.67	10.61

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Abbreviations: FACIT-F- Functional Assessment of Chronic Illness Therapy-Fatigue; HADS- Hospital Anxiety Depression Scale; ESAS- Edmonton Symptom Assessment Scale; SD –Standard Deviation

Table 4. Changes From Baseline in Symptom Scores at Day 29 and Day 15.

	Day 29 − Baseline (n = 24)			Day 15 − Baseline (n = 28)		
Instrument	Mean	SD	P^a	Mean	SD	P^a
FACIT Fatigue Subscale	14.21	17.54	**.0006**	10.21	17.18	**.004**
FACIT Physical	2.74	3.89	**.002**	1.32	4.58	.14
FACIT Social/family	0.19	3.07	0.76	0.32	4.01	.67
FACIT Emotional	1.21	3.56	0.11	0.93	2.98	.11
FACIT-Functional	1.75	4.83	0.08	0.61	4.23	.45
FACT-G	5.88	10.32	**.01**	3.14	10.92	.14
ESAS Pain	–0.88	1.70	**.01**	–0.21	2.48	.65
ESAS Fatigue	–2.46	2.15	**.0001**	–2.07	2.05	**.001**
ESAS Nausea	–0.04	2.31	0.93	–0.32	2.40	.48
ESAS Depression	0.00	1.67	1.00	–0.43	1.10	.05
ESAS Anxiety	–0.63	2.00	0.14	–1.11	1.66	**.002**
ESAS Drowsiness	–0.79	2.23	**.09**	–1.11	2.13	**.01**
ESAS Shortness of breath	0.13	2.42	0.80	–0.32	2.74	.53
ESAS Appetite	–1.33	2.32	**.0097**	–0.61	2.96	.28
ESAS Sleep	–1.13	2.74	.056	–1.61	2.67	**.004**
ESAS Feeling of well-being	–0.04	2.44	.93	–0.83	2.67	.15
HADS Anxiety	–0.63	2.00	.19	–0.61	2.92	.28
HADS Depression	–1.00	3.55	.60	–0.89	3.21	.15

Abbreviations: FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; ESAS, Edmonton Symptom Assessment Scale; HADS, Hospital Anxiety and Depression Scale. Bold faced entries suggest statistical significance.

[a]Paired *t* test.

Table 3. Summary of Types of and Severity of Adverse Events Experienced by Patients Who Received *Panax ginseng* (N = 18).

Adverse Event	Grade ≤3 (N = 16), n	Grade >3 (N =2), n
Death not otherwise specified		1
White blood cell decreased		1
Pain	3	
Nausea	3	
Constipation	1	
Cognitive disturbance	1	
Diarrhea	1	
Enterocolotis infection	1	
Gastrointestinal pain	1	
Hypertension	1	
Infections and infestations	1	
Laryngeal inflammation	1	
Rash maculopapular	1	
Seizure	1	

Comments

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

- High-dose PG was safe and tolerable, and no adverse events related to the study drug were reported.
- CRF and other symptoms including pain, appetite, and overall QOL improved with PG treatment for 4 weeks.
- Unclear the effects are due to psycho-stimulation and/ or immuno-modulatory

Study Objectives and Design

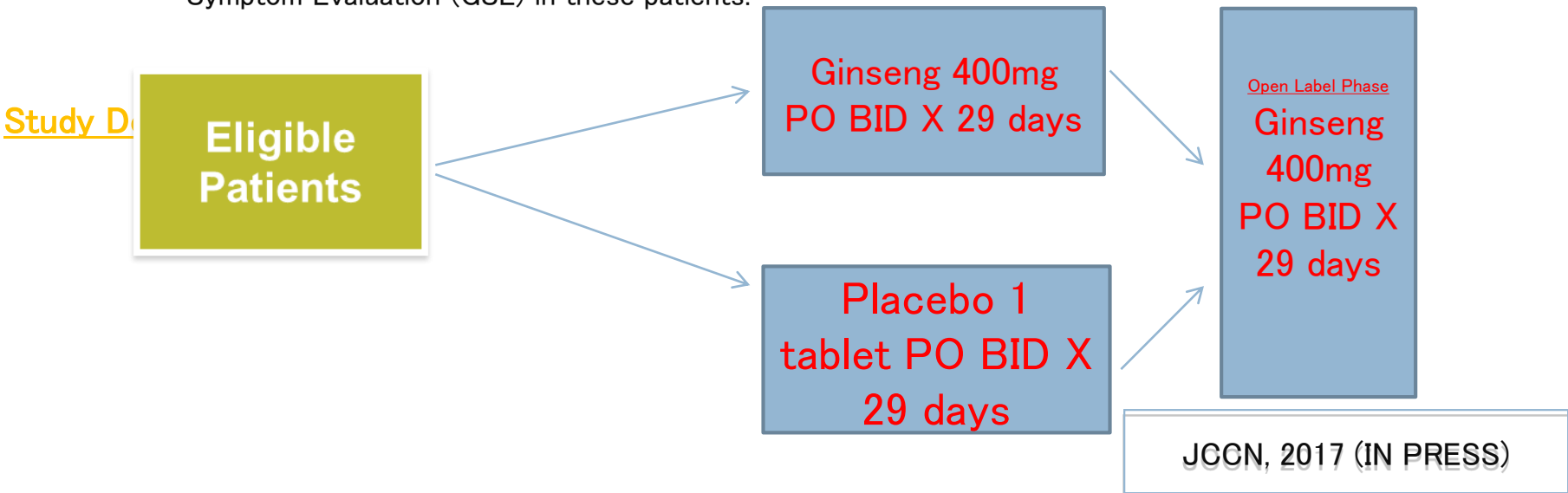
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Objectives

A.1. To explore effects of 800mg of *P. ginseng* as compared to placebo on cancer-related fatigue as determined by FACIT-F (Functional Assessment of Chronic Illness Therapy-Fatigue) at the end of 29 days.

A.2. Exploratory Objectives

- To explore its effect on physical activity as measured by Six minute walk test.
- To explore its impact on quality of life-related variables, mood (HADS -- Hospital Anxiety and Depression Inventory), quality of life domains ((FACT-G)), neurocognitive function (SDMT), and Global Symptom Evaluation (GSE) in these patients.



Eligibility Criteria

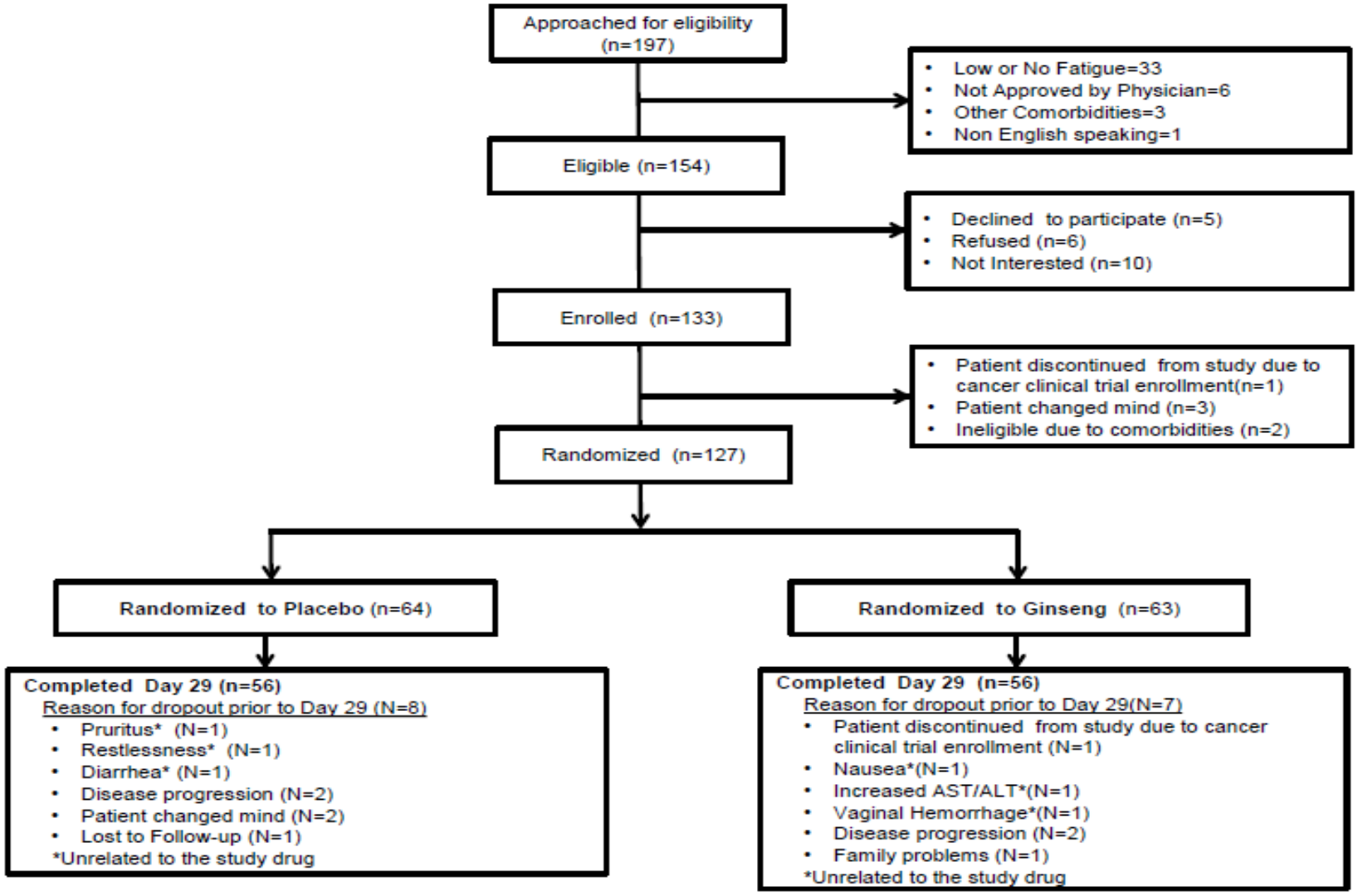
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Inclusion:

- All patients with a histological diagnosis of cancer.
- Rate fatigue on a numerical scale during the previous 24 hours as >/=4.
- Fatigue present for most of the day for the past 2 weeks.
- MDAS </=13 ---Zubrod < / = 2
- 18 years of age or older
- Hemoglobin level of >/= 8 g/dl within 2 weeks of enrollment.
- No concurrent use of chronic systemic steroids. Controlled pain and depression symptoms if present.

Exclusion:

- Major contraindication to Ginseng.
- Currently taking Ginseng, Methylphenidate, or modafinil.
- Current diagnosis of major depression, manic depressive disorder, OCD, or schizophrenic.
- Symptomatic tachycardia or uncontrolled hypertension (defined as >/= 140/90 mm/hg).
- Currently receiving Phenobarbital, diphenylhydantione, primidone, phenylbutazone, MAOI's, clonidine and tricyclic antidepressant.
- Uncontrolled diabetes (random glucose > 200 mg/dl)
- No concurrent full dose of anticoagulant therapy
- History of Hepatitis A, B & C.
- Women who are pregnant or nursing.

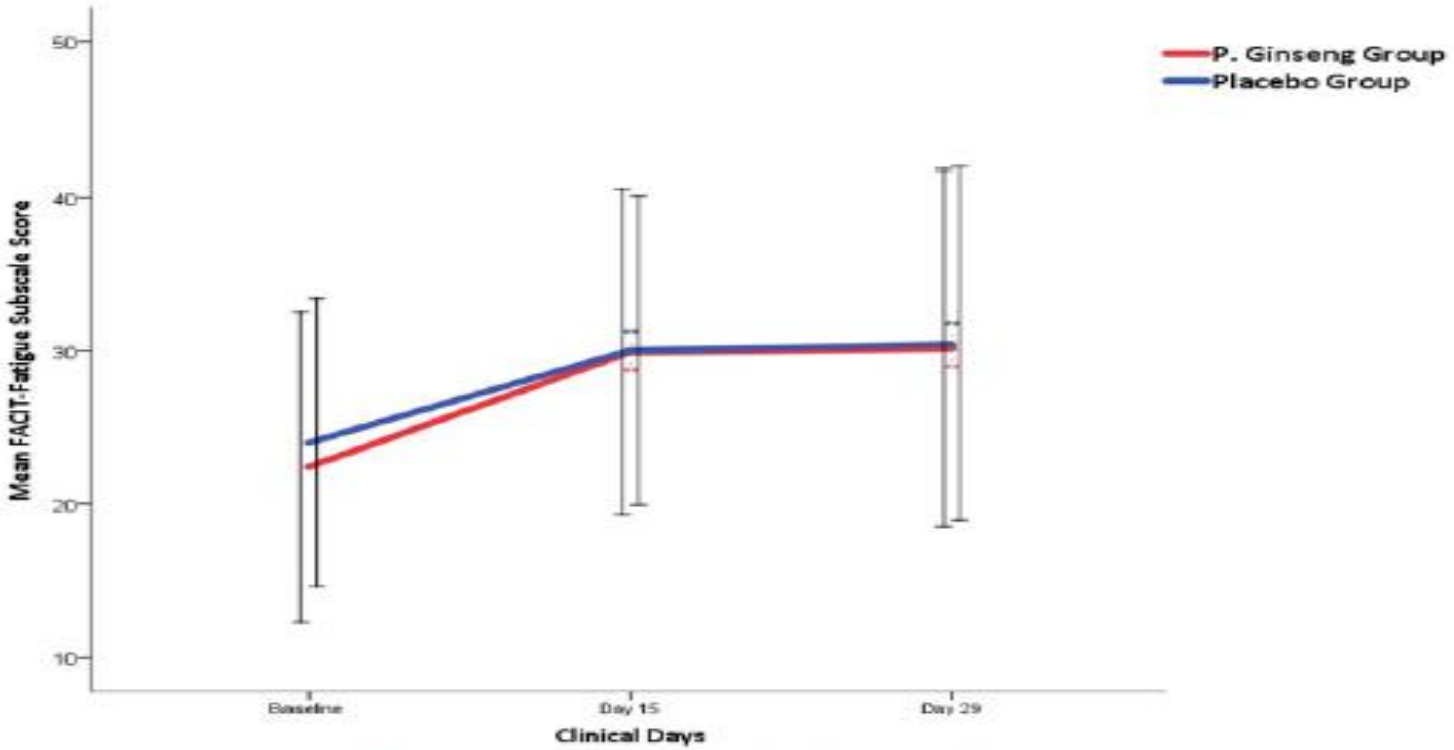


Consort Diagram

Patient Demographics and Clinical Characteristics at Baseline				
Characteristic	Placebo (%, N =64)	Ginseng (%, N =62)	Total (N =126)	P*
Median age (IQR), years	61.0 (53.25–66.75)	61.5 (55.50–67.25)	61.0 (54.0–67.0)	.66
Women, %(N)	37.5% (24)	46.8% (29)	42.1% (53)	.29
Race/Ethnicity, %(N)				.30
White	84.4% (54)	77% (47)	80.8%(101)	
African American	4.7% (3)	6.5% (4)	5.6% (7)	
Asian/other	9.4% (6)	0 (0)	4.8% (6)	
Hispanic	1.6% (1)	16.1% (10)	8.7% (11)	
Median education (IQR), years	14.0 (12.0–16.0)	15.0 (13.0–16.0)	14.5 (12.0–16.0)	.57
Diagnosis				.007
Breast Cancer	6.3% (4)	14.5% (9)	10.3% (13)	
GI Cancer	0% (0)	9.7% (6)	4.8% (6)	
GU Cancer	76.6% (49)	54.8 (34)	65.9%(83)	
Gynecologic Cancer	1.6% (1)	0 (0)	0.8% (1)	
Hematological Cancer	0% (0)	3.2 (2)	1.6% (2)	
Sarcoma	1.6% (1)	0 (0)	0.8% (1)	
Thoracic Cancer	7.8% (5)	12.9 (8)	10.3% (13)	
Other	6.3% (4)	4.8 (3)	5.6% (7)	
Zubrod Performance Status Score				.27
0	7.9 (5)	15.0 (9)	11.4 (14)	
1	74.6 (47)	61.7 (37)	68.3 (84)	
2	17.5 (11)	23.3 (14)	20.3 (25)	

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Figure 1: Change in Mean(SD) Fatigue Score (FACIT-F) for P. Ginseng and Placebo Groups



* *P. Ginseng group: Baseline - 22.4 (10.1) vs. Day 15 29.9 (10.6), P<0.001
Baseline - 22.4 (10.1) vs. Day 29 30.1 (11.6), P<0.001
* *Placebo group: Baseline - 24 (9.4) vs. Day 15 30 (10.1), P<0.001
Baseline - 24 (9.4) vs. Day 29 30.4 (11.5), P<0.001

JCCN, 2017 (IN PRESS)

Table 2: Change in Symptom Scores at Day 15 and Day 29										
Instrument	Day 29 From Baseline					Day 15 From Baseline				
	Ginseng (N=56)		Placebo (N=56)		P	Ginseng (N=52)		Placebo (N=54)		P
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
FACIT-Fatigue Subscale	7.5	12.7	6.5	9.9	.67	7.1	10.4	6.1	10.1	.62
FACIT Physical Well-Being	[illegible]	[illegible]	2.1	5.1	.44	2.3	4.7	2.2	4.7	.98
FACIT Social/Family Well-Being	0.3	4.1	-0.5	3.6	.29	-0.1	4.9	-0.3	3.5	.77
FACIT Emotional Well-Being	1.0	3.9	0.1	3.2	.17	1.0	4.0	1.3	2.9	.73
FACIT Functional Well-Being	1.4	3.9	-0.1	4.2	.07	0.7	3.4	0.9	4.2	.75
FACIT-F total Score	13.0	20.6	8.2	19.0	.20	11.2	18.4	10.1	17.8	.76
ESAS Pain	-0.6	2.0	-0.1	3.0	.34	-0.1	2.7	0.0	2.2	.93
ESAS Fatigue	-1.9	2.6	-2.1	2.6	.71	-1.5	2.4	-1.6	2.4	.72
ESAS Nausea	-0.8	2.4	-0.3	2.1	.29	-0.6	2.6	-0.4	2.0	.67
ESAS Depression	-0.3	2.2	0.1	2.2	.36	-0.3	1.6	-0.4	1.8	.90
ESAS Anxiety	1.3	3.2	1.3	3.7	.90	1.3	2.5	1.6	3.3	.61
ESAS Drowsiness	-0.9	3.1	-0.6	3.2	.56	-0.4	2.6	-0.7	2.5	.57
ESAS Shortness of Breath	-0.7	2.0	0.0	2.5	.11	-0.5	2.3	-0.1	2.0	.27
ESAS Appetite	-0.4	3.2	-0.8	3.6	.52	-0.6	2.9	-0.6	2.9	.99
ESAS Sleep	-0.7	2.8	0.2	3.2	.10	-0.7	2.1	-0.5	2.3	.59
ESAS Feeling of Well Being	-1.5	2.9	-0.6	3.3	.16	-1.3	2.5	-1.2	2.7	.84
ESAS Symptom Distress	-7.6	15.3	-4.7	14.7	.32	-6.1	11.0	-5.8	10.9	.88
HADS Anxiety	-1.3	4.3	-0.8	2.8	.45	-1.2	3.7	-1.0	3.1	.77
HADS Depression	-0.7	3.0	-0.9	2.6	.66	-0.6	2.4	-1.0	2.1	.43

* Abbreviations: **FACIT-F** - Functional Assessment of Chronic Illness Therapy –Fatigue; **ESAS** – Edmonton Symptom Assessment Scale; **HADS** – Hospital Anxiety Depression Scale.

JCCN, 2017 (IN PRESS)

Conclusions

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

- Both PG at a dose of 800mg orally and placebo daily resulted in significant improvement in CRF with minimal side-effects.
- PG was not significantly superior to placebo after 4 weeks of treatment

JCCN, 2017 (IN PRESS)

Multimodal Therapy for CRF

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

- Most individual treatments (pharmacological &non-pharmacological) have mixed results
- Physical Activity (PA); erythropoetin (EP) have positive effect but have low clinical relevance such as a) compliance (PA), b) low effect size (PA), c) toxicity(EP)
- ? COMBINED THERAPIES TARGET MULTIDIMENSIONAL CRF RATHER THAN INDIVIDUAL THERAPIES

Multimodal Therapy and CRF

- P.J. de Raaf, JCO, 2013
- 152 fatigued patients with advanced cancer
- RCT–protocolized patient–tailored treatment (PPT) of symptoms or care as usual
- Fatigue dimensions, fatigue NRS score, interference of fatigue with daily life, symptom burden, quality of life, anxiety, and depression were measured at baseline and after 1, 2, and 3 months.

Multimodal Therapy and CRF

- P.J. de Raaf, JCO, 2013 (condt.)
- PPT significantly improved general fatigue

($P = .01$)

- Significant group differences in favor of PPT at month 1 (effect size, 0.26; $P = .007$) and month 2 (effect size, 0.35; $P = .005$).
- PPT also resulted in improvement of "reduced activity" and "reduced motivation," fatigue NRS, symptom burden, interference of fatigue with daily life, and anxiety (all $P \leq .03$).

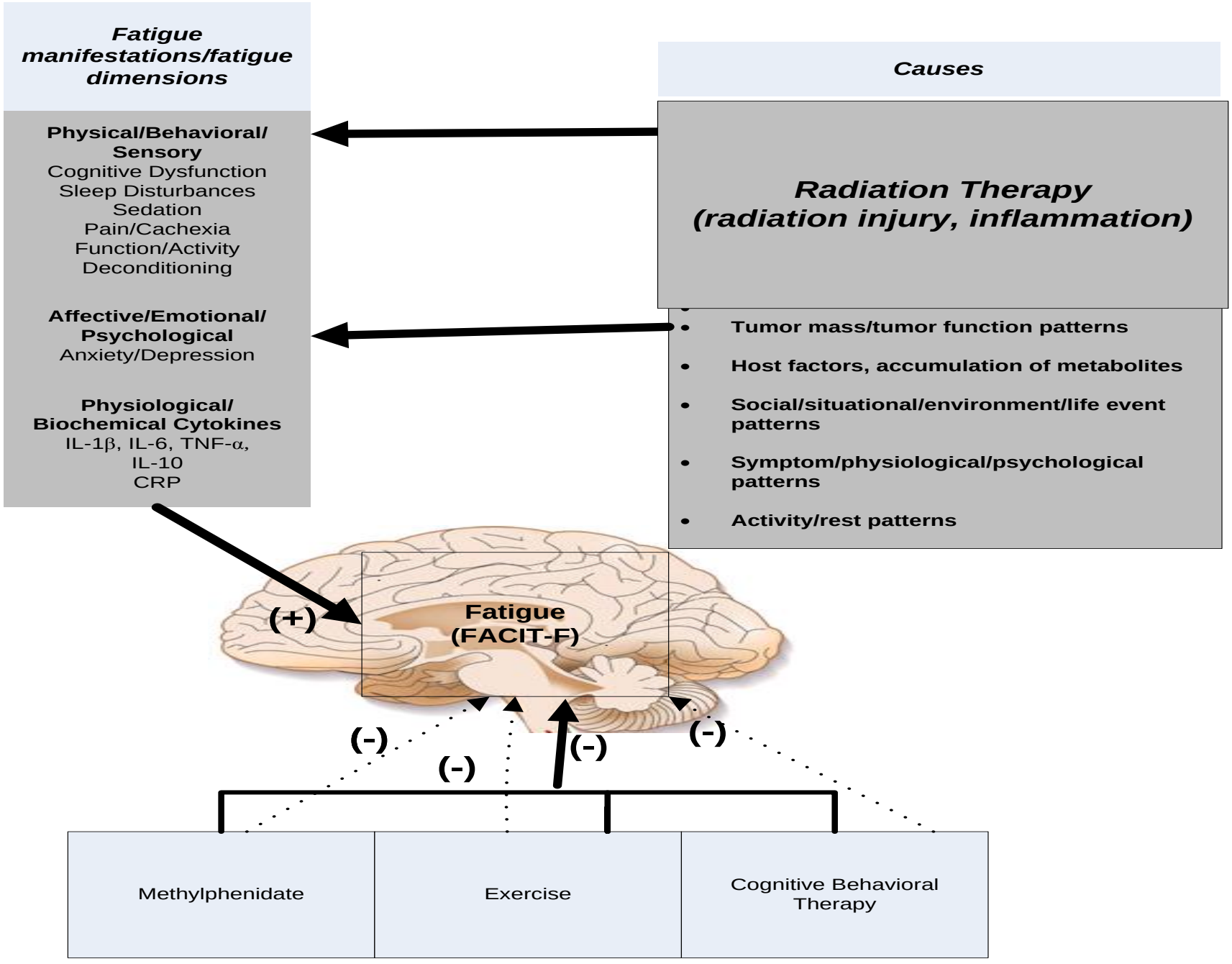
Multimodal Therapy for the Treatment of Cancer Related Fatigue in Patients with Prostate Cancer receiving Androgen Deprivation Therapy and Radiation.

Sriram Yennu, Karen Basen-Engquist, Valerie Klairisa Reed, Cindy L. Carmack, Andrew Lee, Usama Mahmood, Seungtaek Choi, Kenneth R. Hess, Jimin Wu, Janet L. Williams, Zhanni Lu, David Cella*, Deborah A. Kuban, Eduardo Bruera

The University of Texas MD Anderson Cancer Center, Houston, TX; *Feinberg School of Medicine: Northwestern University, Chicago, IL

ASCO 2017

J Clin Oncol 35, 2017


Fatigue manifestations/fatigue dimensions
Causes
Physical/Behavioral/ Sensory
Cognitive Dysfunction
Sleep Disturbances
Sedation
Pain/Cachexia
Function/Activity
Deconditioning
Affective/Emotional/ Psychological
Anxiety/Depression
Physiological/ Biochemical Cytokines
IL-1β, IL-6, TNF-α,
IL-10
CRP
Radiation Therapy
(radiation injury, inflammation)
Tumor mass/tumor function patterns
Host factors, accumulation of metabolites
Social/situational/environment/life event patterns
Symptom/physiological/psychological patterns
Activity/rest patterns
(+)
Fatigue
(FACIT-F)
(-)
(-)
(-)
(-)
Methylphenidate
Exercise
Cognitive Behavioral Therapy

Objectives

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Primary objective:

Aim 1. To obtain preliminary estimates of the effects of various treatments[exercise, CBT, Methylphenidate] and combinations of treatments in MMT in reducing CRF in patients with prostate cancer receiving RT, as measured by change in FACIT-F subscale scores taken at baseline and on Day 57.

Secondary objectives:

Aim 2. To explore the effect of MMT on anxiety (Hospital Anxiety

Depression Scale [HADS]), depressed mood (HADS), physical activity (accelerometer), and function (handgrip dynamometer), before and after treatment with various fatigue treatment combinations of MMT;

Aim 3. To determine the safety of MMT (type, frequency, and severity of the adverse events).

Multimodal therapy for CRF

Inclusion Criteria

(1) Have a diagnosis of prostate cancer and are scheduled to receive radiotherapy with androgen deprivation therapy.

(2) Rate fatigue 1 or higher on a scale of 0–10.

(3) Describe fatigue as being present every day for most of day for a minimum of 2 weeks

(4) Have no clinical evidence of cognitive failure as evidenced by Memorial Delirium Assessment Scale (MDAS) score of </=13 at baseline.

(5) Have a hemoglobin level of >/=10 g/dL within 2 weeks of enrollment.

(6) Have a Zubrod performance status of 0 to 2.

Exclusion Criteria

(1) Have a major contraindication to MP (e.g., allergy/hypersensitivity to study medications or their constituents), exercise (e.g., cardiac disease), cognitive behavioral therapy (e.g., schizophrenia), or conditions making adherence difficult as determined by the attending physician.

(2) Be currently taking MP or have taken it within the previous 10 days.

(3) Are regularly engaged in moderate- or vigorous-intensity exercise for at least 150 minutes per week.

(4) Regularly used cognitive behavioral therapy in the last 6 weeks.

(5) Need monoamine oxidase inhibitors, tricyclic antidepressants, or clonidine.

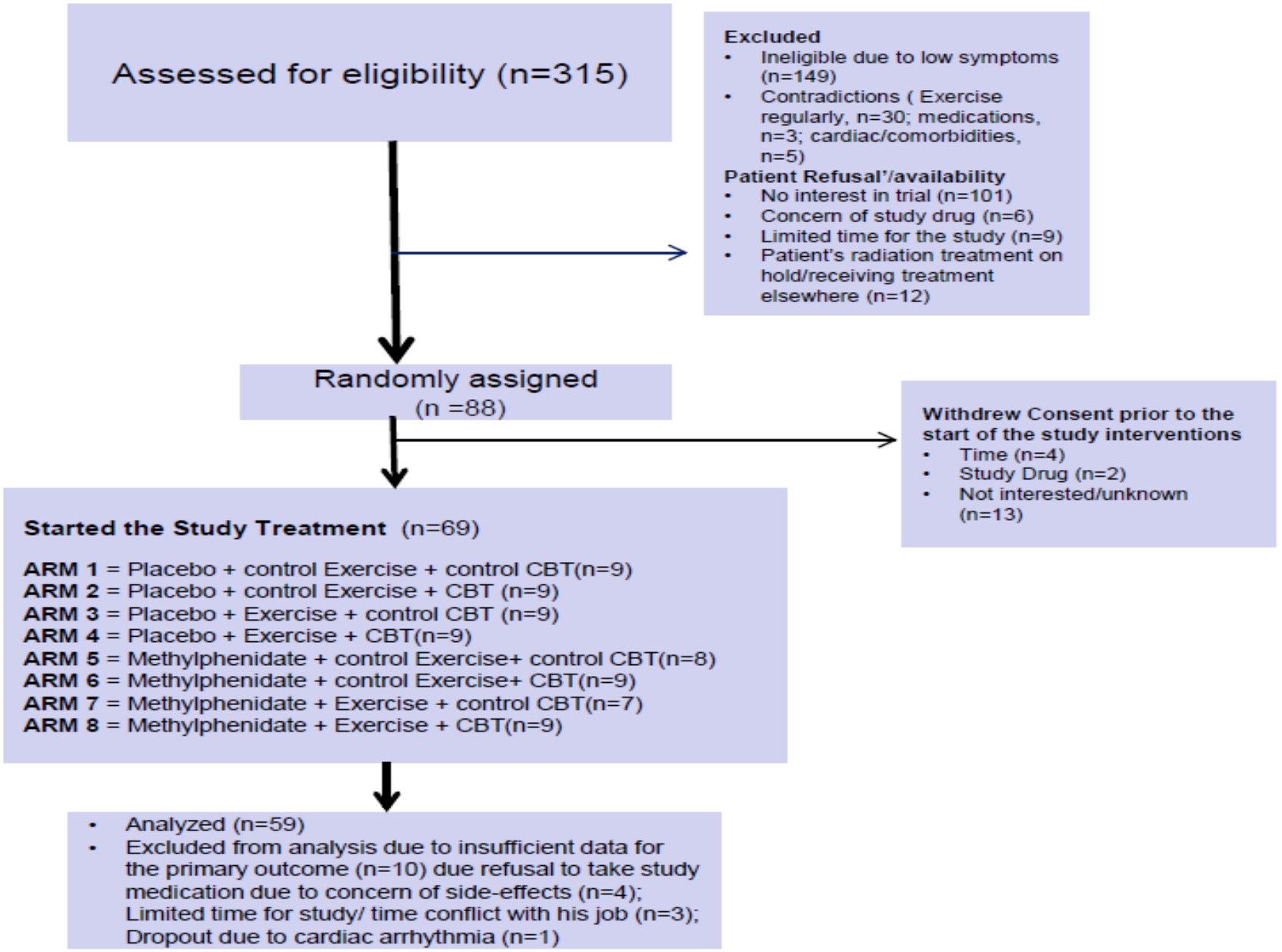
(6) Have glaucoma.

(7) Have with history of severe cardiac disease (New York Heart Association functional class III or IV).

(8) Have tachycardia and/or uncontrolled hypertension

(9) Be currently receiving anticoagulants, anticonvulsants (phenobarbital, diphenylhydantoin, primidone), phenylbutazone, and/or tricyclic drugs (imipramine, clomipramine, or desipramine).

(10) History of uncontrolled hypothryoidism as evidenced by thyroid test (TSH) within the last month, hypercalcemia or hyperglycemia (within the last 15 days).



Consort Diagram

Table 1 Patient Characteristics (N=69)

Age; (median, IQR)	66. (60,71)	.25*
Race; %(N)		
African American	4.3 (3)	
Asian	0 (0)	.68*
Caucasian	95.7 (66)	
Other	0 (0)	
Marital; %(N)		
Divorced	7.2 (5)	
Married	88.4 (61)	
Single/Lives with a partner	0 (0)	.44*
Single/Never Married		
Widowed	0 (0)	
Not Reported	0 (0)	
	4.3 (3)	
Education; %(N)		
Less than High School	0 (0)	
High School/Tech School	10.1 (7)	
Associate Degree/some college	31.9 (22)	.68*
Bachelors' Degree	31.9 (22)	
Advanced Degree	24.6 (17)	
Not Reported	1.4 (1)	
Employment; %(N)		
Full-time	37.3 (26)	
Homemaker	0 (0)	
Part-time	2.9 (2)	.66*
Retired	46.4 (32)	
Unemployed	0 (0)	
Other	13.0 (9)	

***P-value: The median differences across 8 groups. The significance level is .05.**

Table 2
Symptom Severity at Baseline

(Median, IQR)	Total (N=69)	P*
‡ESAS Pain	0 (0,1)	.70
ESAS Fatigue	4 (2,5)	.19
ESAS Nausea	0 (0,0)	.66
ESAS Depression	0 (0,1)	.51
ESAS Anxiety	0 (0,2)	.53
ESAS Drowsiness	1 (0,2)	.91
ESAS Shortness of Breath	0 (0,1)	.18
ESAS Appetite	0 (0,2)	.40
ESAS Sleep	3 (2,5)	.46
ESAS Feeling of Well Being	1 (0,3)	.86
‡ESAS Symptom Distress	8 (3,14)	.72
HADS Anxiety	3 (1,6)	.47
HADS Depression	2 (1,4)	.36

*P-value: The median differences across 8 groups, Kruska Wallis test. The significance level is .05.
‡ESAS (Edmonton Symptom Assessment System): pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, anorexia, sleep disturbance, and feelings of well- experienced by patients during last 24 hours, rated on a numerical scale of 0-10 (0 = no symptom, 10 = worst possible severity).
‡ ESAS Symptom Distress: Sum of the scores for pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, lack of appetite, and lack of well-being.

Results

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

- 62/69 (89%) randomized patients were evaluable
- There were no differences in the demographics and baseline fatigue between groups
- The adherence rates for pills, exercise and CBT were 96.5%, 67%, and 90% respectively
- No significant difference in adverse events by groups ($p = .29$)

Table 3
Comparison AUC by Treatment

Interventions	AUC FACIT-F median scores and p-value	AUC FACT-G (median scores and p-value)
Methylphenidate vs Placebo	2328 vs. 2095 (p=0.0536)	4923 vs. 4532 (p=0.042)
Exercise vs control exercise	2143 vs 2285 (p=0.59)	4667 vs 4813 (p=0.37)
CBT vs control CBT	2247 vs 2197 (p=0.4)	4710 vs 4722 (p=0.84)

Results

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

- No significant difference between the 8 randomized groups AUC FACIT-F subscale (p = 0.25), and FACT-G (p = 0.06) scores [due to small sample]

- For Patients receiving drug compared to placebo, the median AUC was 2328 vs 2095 (p = 0.053)

- The drug effect (estimate, 95% CI) in Patients who received:
  - Exercise was 596 (68.3, 1125), p = 0.029
  - CBT was 354 (−121, 830), p = 0.12
  - Combined Exercise and CBT was −187 (−802,427), p = 0.52
  - Control Exercise, control CBT was 294 (−192,781), p = 0.21

Conclusion

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

- Methylphenidate containing combinations were superior to no drug combinations.
- Methylphenidate + Exercise provided the best signal and should proceed to large randomized control trials.

Table 1. Summary of Intervention Studies Including Patients With Advanced Cancer With Fatigue As Primary End Point

Study	Year	No. of Patients	Fatigue Severity	Duration of Follow-Up	Intervention	Results (effect size)*		
						Fatigue	Symptom Burden	QoL
Nonpharmacologic intervention								
Headley et al[17]	2004	38	—	120 days	Seated exercise	?†	—	—
Adamsen et al[18]	2009	269	—	6 weeks	High-intensity exercise	0.33†	—	NS
Oldervoll et al[19]	2011	231	—	8 weeks	Physical exercise	NS	—	—
Ream et al[20]‡	2006	103	—	4 months	Nurse-led education, coaching, emotional support	0.25†	—	—
Armes et al[21]§	2007	60	Significant	9 months	Behavior-oriented intervention	NS	—	—
de Raaf et al[22]	2013	152	NRS ≥ 4	3 months	Systematic monitoring, protocolized treatment of physical symptoms	0.35†	0.41‖	NS
Drug therapy								
Morrow et al[23]¶	2003	479	NRS > 1	3 months	Paroxetin 20 mg	NS	—	—
Bruera et al[24]	2007	142	NRS ≥ 4	15 days	Donezepil 5 mg	NS	NS	—
Beijer et al[25]	2010	99	—	8 weeks	Adenosine triphosphate	NS	—	NS
Cruciani et al[26]	2012	176	Moderate to severe	4 weeks	L-carnitine 1 g	NS	NS	—
Bruera et al[27]	2006	112	NRS ≥ 4	8 days	Methylphenidate 5 to 20 mg	NS	NS	—
Butler et al[28]	2007	68	—	12 weeks	Methylphenidate 5 to 15 mg twice per day	NS	—	—
Kerr et al[29]	2012	34	NRS ≥ 4	14 days	Methylphenidate 10 to 40 mg	2.12†	NS	—
Moraska et al[30]	2012	148	NRS ≥ 4	4 weeks	Methylphenidate 18 to 54 mg	NS	NS	—
Auret et al[31]	2009	50	NRS ≥ 4	8 days	Dexamphetamine 10 mg twice per day	NS	—	NS
Yennurajalingam et al[32]	2013	84	≥ three symptoms; NRS ≥ 4	15 days	Dexamethason 4 mg twice per day	0.59‖	0.60†#	0.48†

De Raaf, 2013

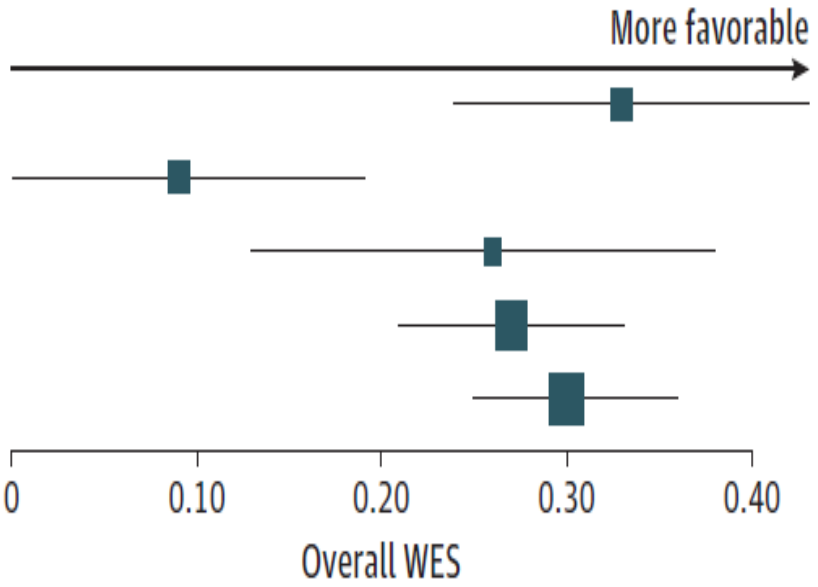
JAMA Oncology | Original Investigation

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)

Intervention	No. of Effect Sizes	WES	SE	(95% CI)
All	127	0.33	0.05	(0.24-0.43)
Pharmaceutical	14	0.09	0.05	(0.00-0.19)
Exercise plus psychological	10	0.26	0.07	(0.13-0.38)
Psychological	34	0.27	0.05	(0.21-0.33)
Exercise	69	0.30	0.03	(0.25-0.36)



Personalized Therapy In Cancer Related Fatigue

Fatigue 8/10

	Patient 1(%)	Patient 2(%)
Depression	60	10
Pain	10	50
Cachexia	10	10
Anemia	20	0
Opioids	0	30

Definition– ASCPRO

Assessing the Symptoms of Cancer Using Patient-Reported Outcomes (ASCPRO): searching for standards

J Pain Symptom Manage. 2010 Jun;39(6):1077-85.

- Subjective (self report)
- Physical sensation (tiredness)
- Impact on functioning (difficulty completing tasks)
- Unpleasant emotions (distress)
- Decreased cognitive ability (decreased attention)
- Temporal variability (pervasive)

Descriptors Applied to Fatigue

Related to a Sense of Energy or Vitality	Related to Cognitive Change	Related to Sleep	Related to Strength	Related to Mood
Fatigue	Clouded or Confused	Somnolent or Sleepy	Weakness	Irritability
Lack of Energy	Apathetic	Non-restorative Sleep	Fatigability of Muscles	Lability
Lethargic	Inattentive		Post-exertional breathlessness or exhaustion	Depressed
Tiredness	Poor Concentration			
Exhaustion	Poor Memory			

Portenoy, et al. Pain consortium.nih.gov Interactive textbook of symptom research

Subtypes

MD Anderson Cancer Center

	Adjuvant Chemo/RT	Survivor	Advanced Chemo
Chemo/Targeted -	+++	+?	++
Radiation -	+++	0	++
Deconditioning -	+	++	++
Depression/Anxiety -	++	++	++
Cachexia -	0	0	+++
Opioids -	0	0	++
Anemia -	+	0	++
Metabolic -	+	0	+
Cytokines -	++	+	++
Tumor Products -	0	0	++

Future Trials for Treatment of CRF

Role of combined therapy

Brain– methylphenidate, donepezil

Mood– mirtazapine– or other SNRI?

Inflammation– thalidomide, dexamethasone, melatonin

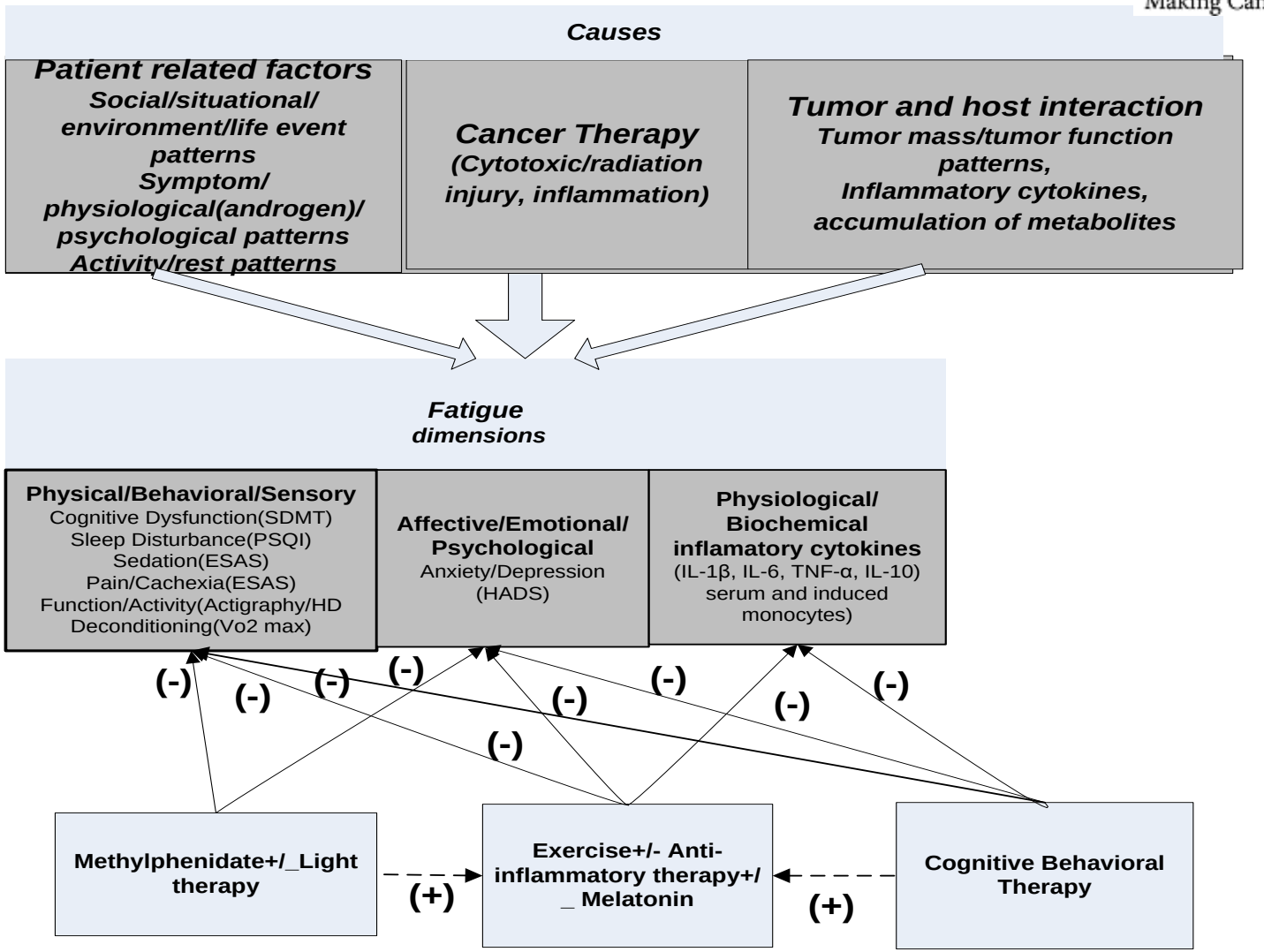
Anemia– blood transfusions, EPO

Anaerobic– 02

Muscle– testosterone, Myostatin receptor agonists?, Ghrelin Agonists?

Deconditioning– exercise

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®



Progress towards Personalized Therapy In Cancer Related Fatigue

- Physical – Advanced Cancer– Short Course Dexamethasone (Yennu et al J Clin Oncol 2013) +/– Exercise
- Clusters: Fatigue + Anorexia + Depression – Dexamethasone (Yennu et al. Oncologist 2016)
- Fatigue + Insomnia – Yoga [Mustian et al. J Clin Oncol 35, 2017 (suppl; abstr 10007)]
- Fatigue+ RTX+Androgen Deprivation – ? Methylphenidate + Exercise (Yennu et al. ASCO 2017;J Clin Oncol 35, 2017)

Summary

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

- Identify cancer related fatigue, subtype
- Investigate for correctable causes (lytes, sx's)
- Co-manage with patients on a daily basis !
- What helps? Combined Approach based on the predominant dimension
  - Physical Activity enhancement –Sleep hygiene
  - Psychosocial interventions e.g., behavioral therapy
  - Nutrition –Acupuncture– Massage therapy–Yoga
  - Refractory cases– Trial of steroids/ psychostimulants