ESMO PRECEPTORSHIP SUPPORTIVE & PALLIATIVE CARE

SESSION 3

“CANCER DISEASE AND CANCER-TREATMENT RELATED FATIGUE: MECHANISM AND MANAGEMENT”

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Friday February 1, 2019 / 14:20-14:55
Novotel Lugano

Incidence of fatigue & types

CtRF, physical, emotional, cognitive, mixed

Symptomatic management

Principles
Exercise and nutrition
Drugs: Methylpenidate, C-steroids, others

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DISCLOSURE information Florian Strasser

Institutional financial interests (KSSG): Unrestricted industry grants for clinical research: Helsinn, Celgene, Fresenius Participation in company-lead clinical trial: Novartis

Leadership roles: Society on Sarcopenia, Cachexia and Wasting Disorders (SCWD): Board member – Swiss Society Medical Oncology: National representative oncological rehabilitation - European Society for Medical Oncology, Palliative and Supportive Care / Designated Centers Working Group: past Chair (2014-2017) - Swiss Group Clinical Cancer Research (SAKK), Working Group Supportive and Palliative Cancer Care: past Chair (2002-2016) - Multinational Association of Supportive Care in Cancer (MASCC), Working Group Nutrition and Cachexia: past Co-Chair (until 2016)

PUNCTUAL advisorship (advisory boards, expert meetings) that have been paid to my institution - not to me directly: Danone, Grünenthal, Helsinn, ISIS Global, Mundipharma, Novartis, Novelpharm, Obexia, Ono Pharmaceutical, Psioxus Therapeutics, PrIME Oncology, Sunstone Captial, Vifor

„a subjective feeling of tiredness, weakness, or lack of energy“

physical

cognitive

psychological

Slide adapted from Jann Arends 2018

Incidence of fatigue

Authors	Setting	Incidence
Walsh D et al. Support Care Cancer 2000	Palliative medicine program, n=971	69%
Romito F et al. Support Care Cancer 2008	Palliative cancer patients n=80	Moderate 57% Severe 7%
Wallengren O et al. Support Care Cancer 2013	Palliative care program n=405	63%
Zhou T et al. J Pain Symptom Manage 2017	Advanced cancer patients n=306 non-CX pre-CX CX refractory CX	 35% 62% 55% 77%
Di Marco M et al. Acta Biomed 2018	CHT in pancreatic cancer n=48	94%

Slide adapted from Jann Arends 2018

Symptomdistress (ESAS) last 6 months of >10‘000 cancer patients

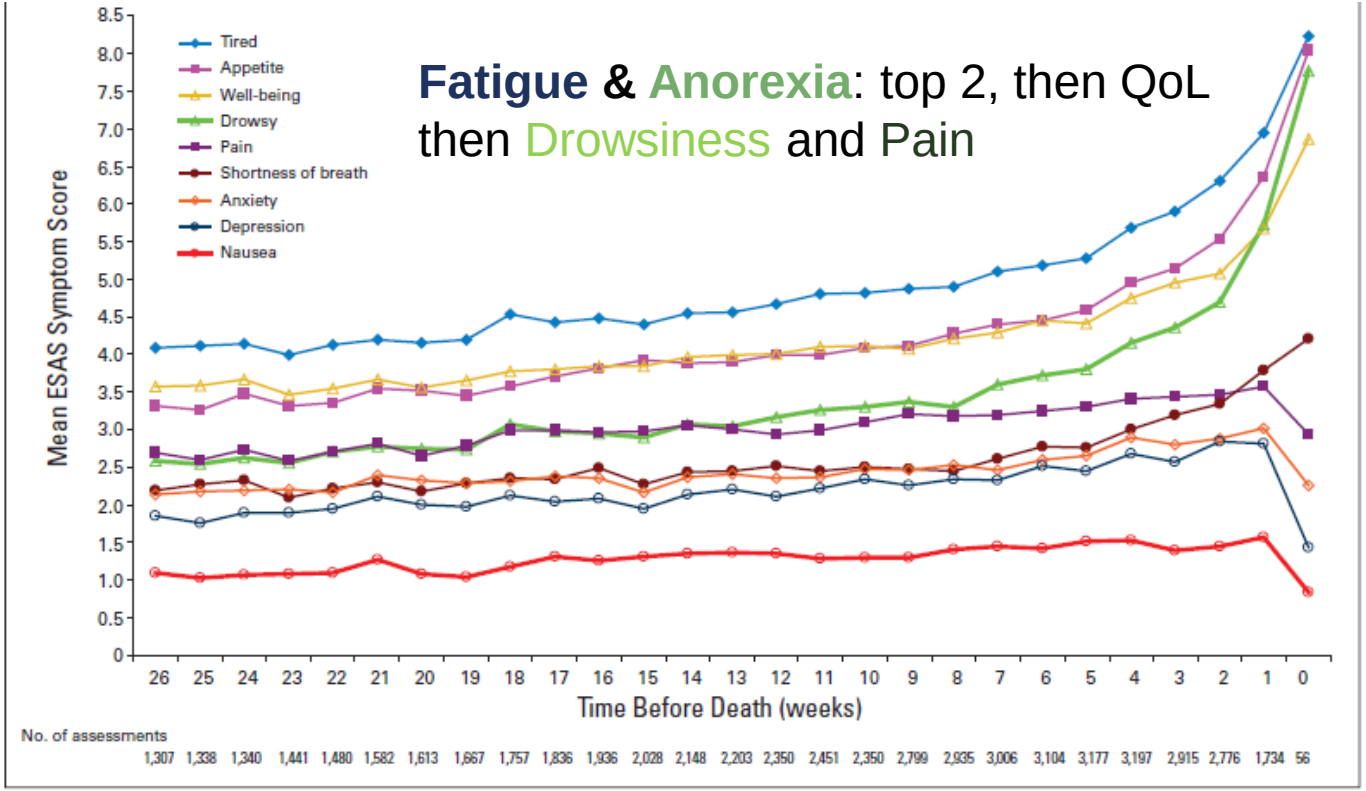

Fig 2. Mean Edmonton Symptom Assessment System (ESAS) symptom scores over time. Number of assessments is maximum number available among all nine symptoms. Missing ESAS values for a given symptom were not included when calculating the mean.

Seow H, et al. J Clin Oncol 2011:1151-8

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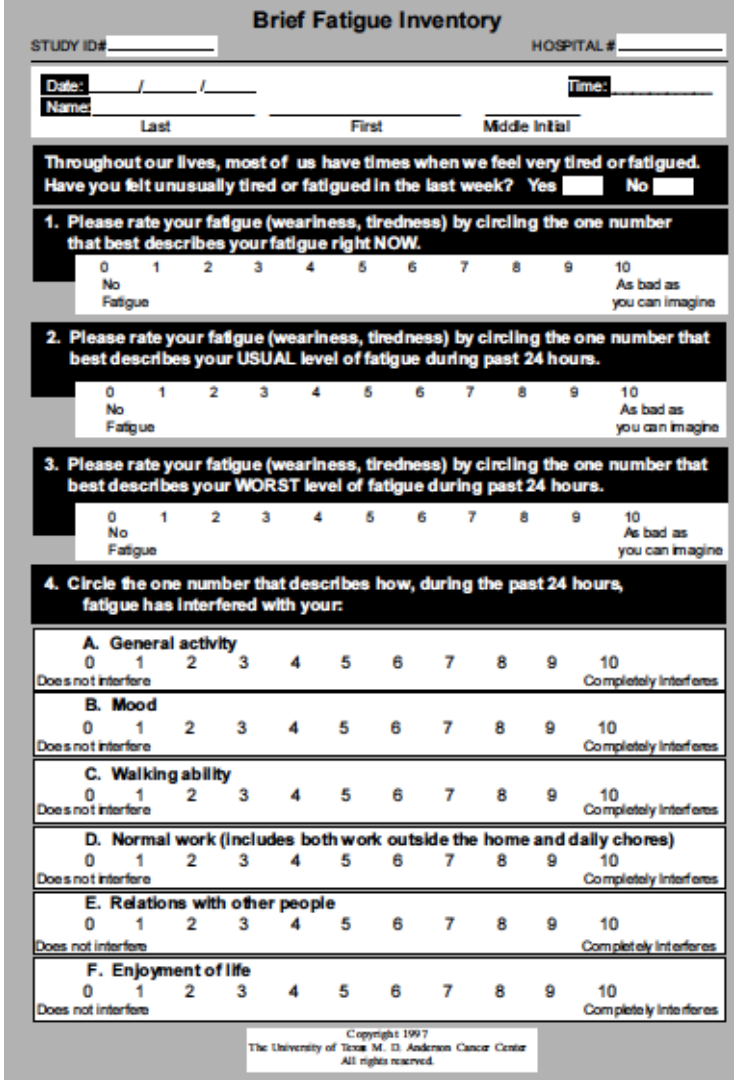
Fatigue Screen by simple Symptom

Fatigue Impact on different domains

BFI, Brief Fatigue Inventory



Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL # _____

Date: ____/____/____ Time: _____

Name: _____ _____ _____

Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

B. Mood
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

C. Walking ability
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

D. Normal work (includes both work outside the home and daily chores)
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

E. Relations with other people
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

F. Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

Slide adapted from Jann Arends 2018

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Cancer (treatment-) related Fatigue Syndrome (CtRF)

- 2-week period significant fatigue
- feel weak all over or heavy all over?
- trouble concentrating or paying attention
- losing your interest or desire to do things
- trouble falling asleep, staying asleep
- don’t feel rested or refreshed
- ….

→ Syndrome occurs as side-effect of anticancer treatments in curative and non-curative situations

→ Causes are not fully understood: inflammatory, «neuro-hormonal»

Fatigue in cancer patients

- Sarcopenia
- Malnutrition
- Cancer cachexia
- Toxicity cancer therapy (CtRF, muscle,..)
- Depression
- Uncertainty
- Pharmacological psychoactive
- Delirium
- Dehydration
- Electrolytes (Ca, Phosp, Na)
- Organ-Dysfunction
- Infection
- Endocrine (Thyroid, Testosterone)
- Anemia
- Sleep-disturbances

In clinical practice: identify main causes of fatigue by phenotypes

Physical

Malnutrition,Sarcopenia, Cachexia,Toxicity

Emotional

Depression, Uncertainity

Cognitive

Delirium, *Psychotropic Medication, CNS-Metastases*

Mixed

Hypercalcemia, Dehydration, Organdysfunction, etc.

«How much are you tired because:»

. **C**ognitive:
Problems thinking, concentrate, dizzy

. **E**motional:
No meaning, no energy, depressed

. **P**hysical:
No strength in the body, muscle weak

Fatigue Phenotypic Approach – Assessments

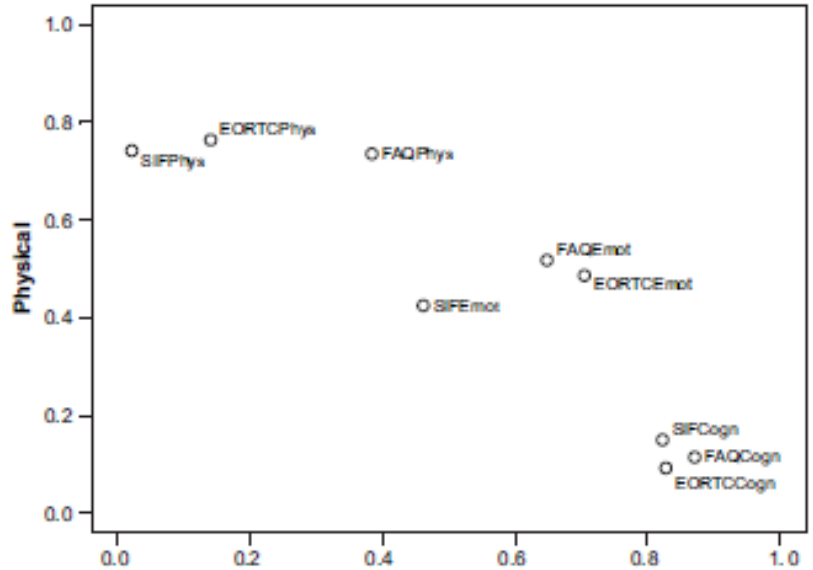
● cognitive	SQIDS, m-MMSQ, DOS, mini-COG
● emotional	HGWS (J.Holland), HADS
● physical	Muscles – Weight loss, physcial Fct.

SQIDS: single question in Delirium[1]
s-MMSW : short mini-mental state exam[2]
DOS: Delirium observation scale[3]
HGWS: Hope, Guilt, Worthlessness, passive suicidal[4]
HADS: Hospital Anxiety Depression Scale[5]
Muscles: weight loss (% in mts) corrected for edema[6]

1: Sands M et al., Pall Med 2011; 24:561-5;
2: Fayers PM et al., JPSM 2005;30:41-50;
3: Wong CL et al., JAMA 2010; 304:779-86;
4: several textbooks; 5: Wateson E et al, Pall Med 2009;23:739-53;
6: Fearon K & Strasser F et al., Lancet Oncol 2011;12:489-95

Phenotypic Approach to Fatigue

Single-Item-Fatigue: 3 questions



SIF: Single-Item Fatigue: emotional (SIFEmot), cognitive (SIFCogn), and physical (SIFPhys)

FAQ: Fatigue Assessment Questionnaire domains: physical (FAQPhys), cognitive (FAQCogn), and affective (FAQEmot)

EORTC: EORTC-QLQ-C30 functional subscales: physical (EORTCPhys), emotional (EORTCEmot), and cognitive (EORTCCogn)

2	Ich fühle mich **müde, weil** ich **„im Kopf“** müde bin, weil ich Mühe habe mich zu konzentrieren, weil meine Auffassungsgabe verlangsamt ist:	Brain

0	1	2	3	4	5	6	7	8	9	10
Nicht müde wegen „dem Kopf“										Sehr stark müde wegen „dem Kopf“

3	Ich fühle mich **müde**, **weil** ich **„keine Freude“** verspüre, weil ich keine Lust habe, keinen Antrieb habe, weil „es“ keinen Sinn (mehr) macht:	Mood

0	1	2	3	4	5	6	7	8	9	10
Nicht müde wegen „keine Freude mehr“										Sehr stark müde wegen „keine Freude“

4	Ich fühle mich **müde**, **weil** ich **„keine Kraft“** mehr habe, weil mein Körper schwac meine Muskeln schwach sind:	Muscle

0	1	2	3	4	5	6	7	8	9	10
Nicht müde wegen „keine Kraft“										Sehr stark müde wegen „keine Kraft“

Useful in clinical practice to roughly classify patients

Strasser F, Käser I , Dietrich D. JPSM 2009;38:505-14

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Mechanistic approach: search causes

See Session 6: cancer cachexia (Jann Arends)

- Side effect cancer-directed therapy: history

- Depression: ESAS, Hospital AnxietyDepression Scale (scores <10, 10-12, >12)
- Uncertainty: illness- and prognosis-understanding

- Pharmacological: history & reality check, opiates, benzod., antidepress., etc.
- Delirium: DOS, other tools, fluctuation during the day

- Dehydration: history (urin, oral intake), skin, neck veins
- Electrolyte: Phosphate, Calcium, Na & ev Osmolality, Glucose, ev Mg
- Organ-Function: kidney, liver, heart, lung (RR, O2-Sat)
- Infection: history, dynamics of CRP (double in 2-3 days), ev. ProCalcitonin
- Endocrine: TSH, free Testosteron (male)
- Anemia (Hb < 10g/dl)
- Sleep-disturbances (e.g. symptoms)

Cancer (treatment-) related Fatigue Syndrome (CtRF)

Careful history taking:

. did Fatigue occur during anticancer treatments?
. often association with CINP

. did patient be active physically during anticancer treatment?

. how did fatigue further develop, namely when starting to work?

. evidence for cofactors?
    . Traumatas
    . Depression
    . Financial burden
    . Misunderstanding from family members
    . Other Fatigue causes?

How do I manage in clincal practice a fatigued patient?

- **«symptomatic» Intervention**
  - → *Patients without «clear» cause*
  - → *often mixed Phenotypes*
  - → *«Cancer-related Fatigue»*

- **Tailored, mechanism-based Intervention**
  - → ***Malnutrition**: nutrition intervention* — *J Arends S6*
    nutrition impact symptoms — *F Scotte, K Jordan S4*
  - → ***Cachexia**: Multimodal therapy* — *J Arends S6*
  - → ***Delirium**: symptomatic & tailored treatment* — *J Wood S2*
  - → ***Depression**: Psychotherapy, counsel, SSRIs* — *(«go visit Maria Die-Trill»)*
  - → ***Anemia:** Blood transfusions, consider EPO* — *M Aapro S6*
  - → ***Electrolytes, Organs, Endocrine, Infection*** — *»Internal Medicine»: but Med Onc need consider (gut) Biome*
    (testosterone, …

see also this preceptorship:

Testosterone replacement for fatigue in hypogonadal ambulatory males with advanced cancer: a preliminary double-blind placebo-controlled trial

Testosteron free <70ng/dl
cancer out-pts, Fatigue
>3/10 (ESAS), Hb >9g/dl

Del Fabbro E et al. Supp Care Cancer 2013;21:2599–2607

i.m. (gluteal) Testosteron enanthate every 14 days, monitoring free testost. (70-270ng/dl)

ESAS Fatigue after 29 days not better, ECOG clearly better (1 vs 0, p=0.02)

	Day 29 vs. baseline			Day 72 vs. baseline		
	Placebo *N*=16 Mean(SD)	Testosterone *N*=13	One sided *p* value	Placebo *N*=6	Testosterone *N*=6	One sided *p* value
PWB_Score	0 (6)	1 (4)	0.21	3 (6)	3 (3)	0.44
SWB_Score	2 (3)	−1 (4)	0.03	1 (3)	1 (4)	0.34
EWB_Score	−2 (3)	2 (3)	0.007	0 (2)	2 (3)	0.21
FWB_Score	−1 (3)	−1 (4)	0.40	0 (5)	−2 (5)	0.26
Fatigue Subscale	−2 (12)	4 (8)	0.11	1 (10)	11 (4)	0.03
FACIT_F Score	−4 (20)	4 (14)	0.14	5 (20)	16 (12)	0.32
FAACT Score	−2 (13)	2 (9)	0.18	4 (15)	13 (5)	0.16

FACIT-F Functional Assessment of Chronic Illness Therapy-Fatigue, *FAACT* Functional Assessment of Anorexia/Cachexia Therapy, *PWB* physical well-being, *SWB* social well-being, *EWB* emotional well-being, *FWB* functional well-being

symptomatic fatigue treatment

Non-drugs	Physical activity Protein rich food	Endurance / strenght Nutrition habits
	Psychoeducation Counselling	Express emotions Communication
	Energy- Management	Rationing energy Relaxation, pleasure
	*C*ognitive *b*ehavioural *t*herapy	Adequate judgment Acceptance disability
drugs	Phytotherapy	Ginseng, Guarana
	Corticosteroids	10-14 days maximal!
	Psychostimulants	Methylphenidate

Anabolic resistance of muscle protein synthesis




Physiological factors	**Clinical factors**
Protein digestion	Lower level of physical activity
Amino acid adsorption	Changes in food intake
Postprandial hormonal response	Bed rest – Hospitalisation
Microvascular perfusion	Insulin resistance - Obesity
Amino acid uptake in muscle	Aging
Intramuscular signaling	Inflammation
Muscle protein synthesis	Medication




Slide (adapted) from van Loon LJC, SCWD Congress Maastricht 2018

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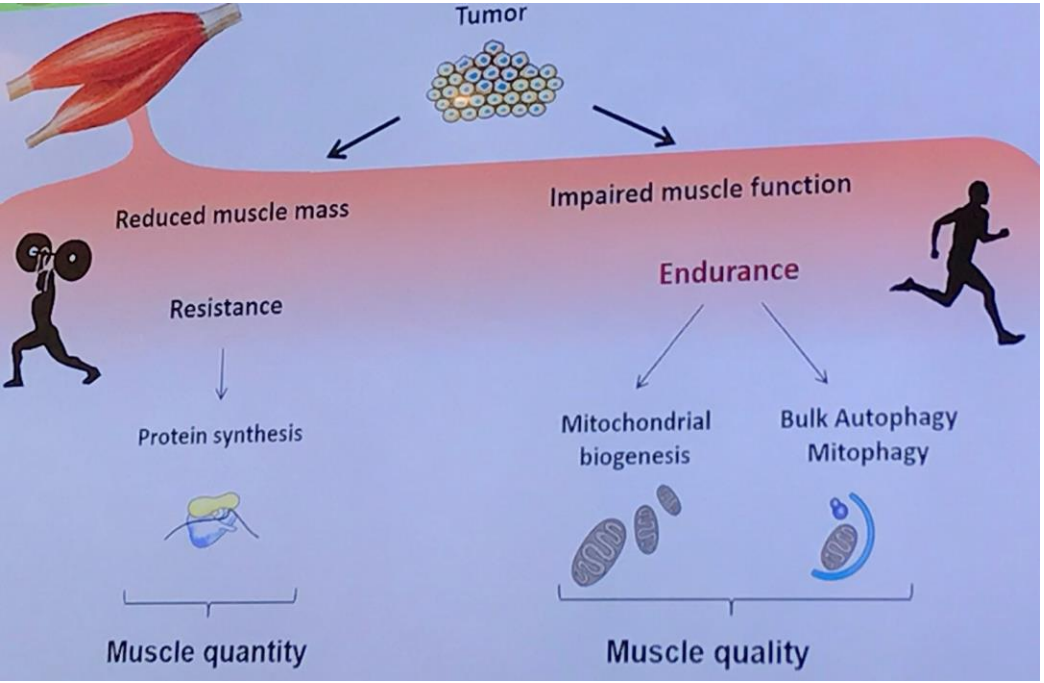
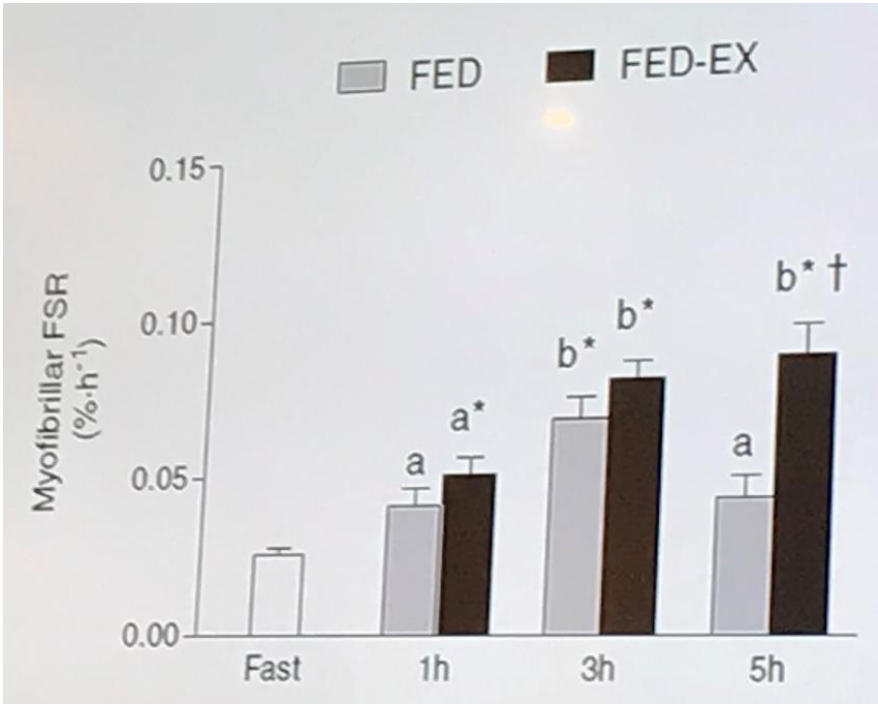
Exercise increases muscle protein synthesis after feeding

Exercise training-regulated pathways
(muscle-centered perspective)



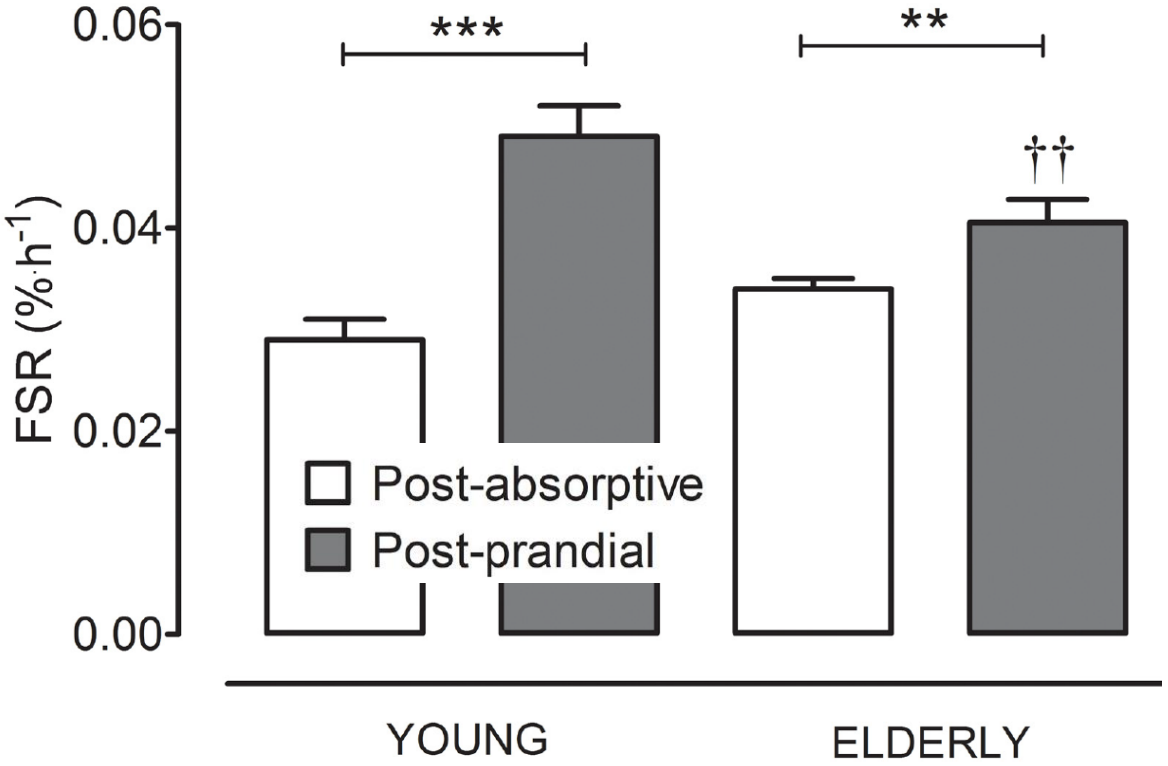
Slide (adapted) from Fabio Pennna
SCWD Congress Maastricht 2018

Muscle protein synthesis after feeding
with & without exercise



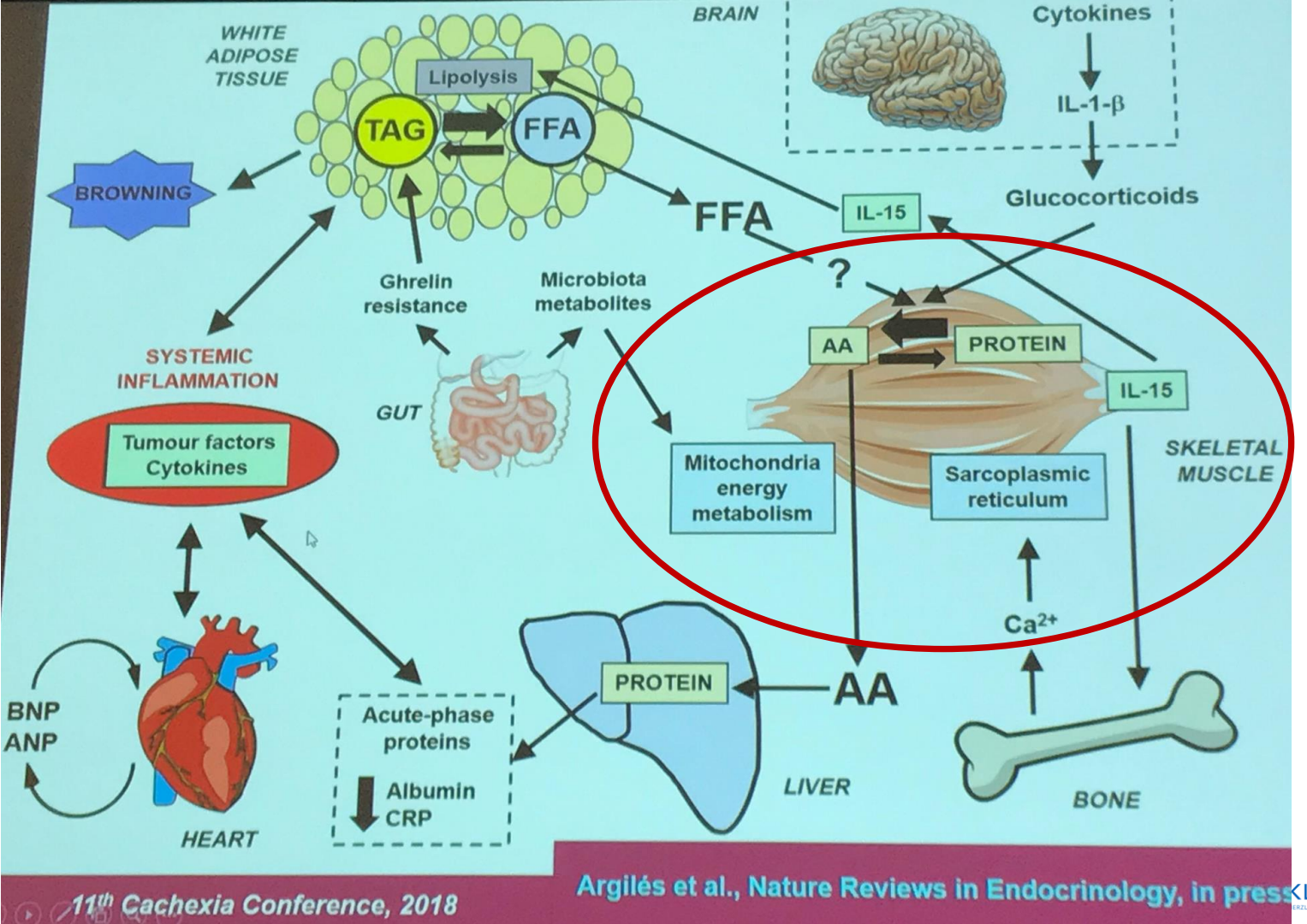
Moore et al. J Physiol 2009

Anabolic resistance in elderly patients



Wall et al. Plos one 2015

Does physical activity work in **patients with active cancer disease and anticancer treatment?**



Active cancer disease causes cachexia through many mechanism

→ Muscle synthesis down

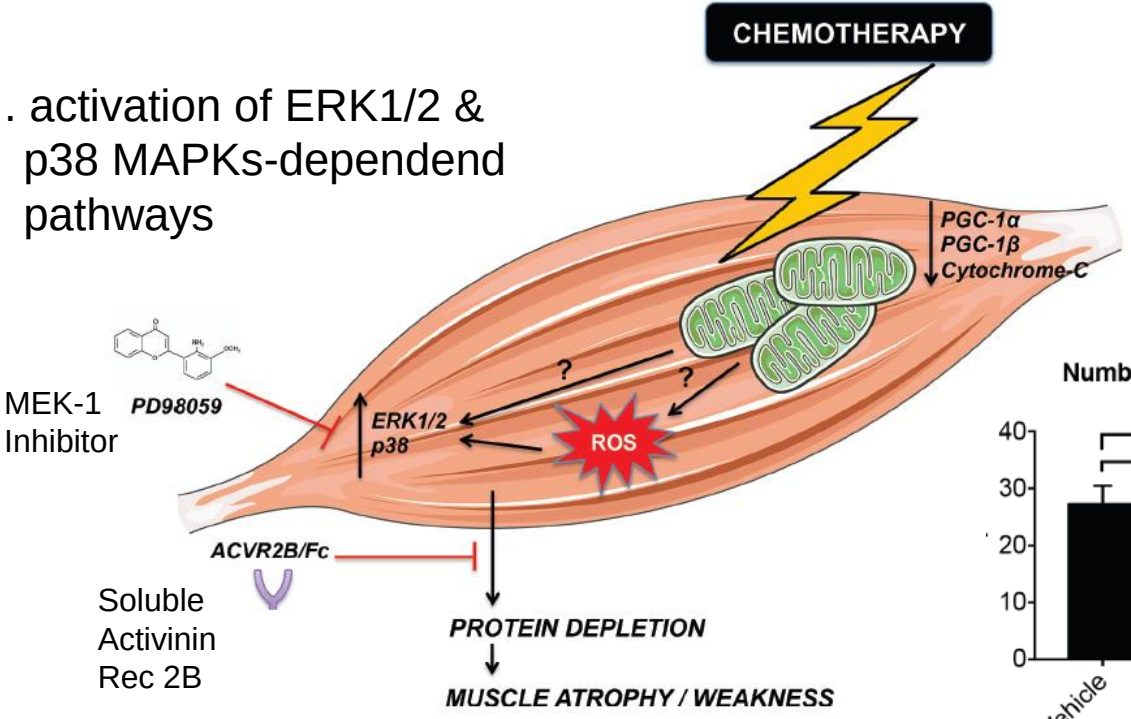
→ Muscle proteolysis up

Argilés et al., Nature Reviews in Endocrinology, in press

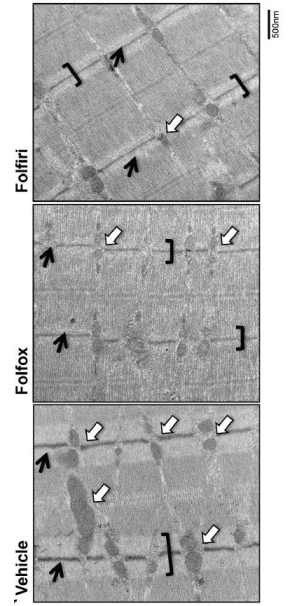
Anticancer treatment → Impact on Muscle

Folfox/Folfiri causes
. **mitochondrial depletion**

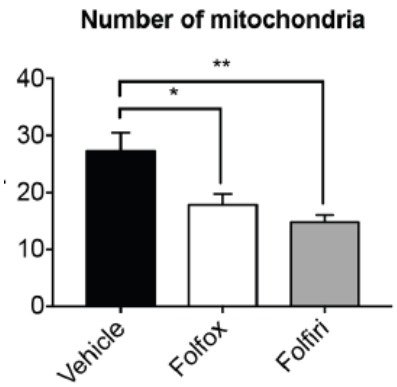
. activation of ERK1/2 & p38 MAPKs-dependend pathways

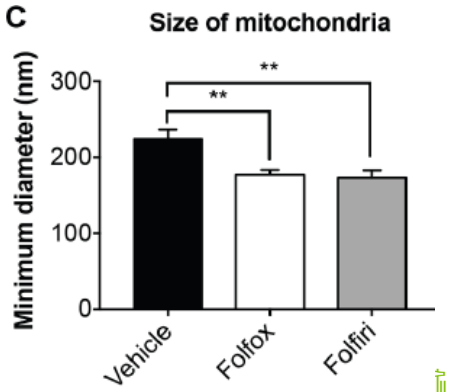


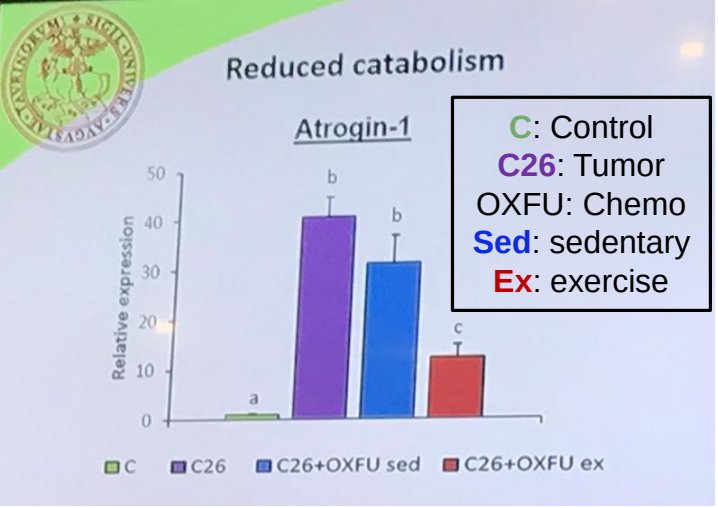
Can exercise improve muscle quality and quantity?



Barreto R Oncotarget 2016;43442-60







Cancer causes catabolism, chemo improves it

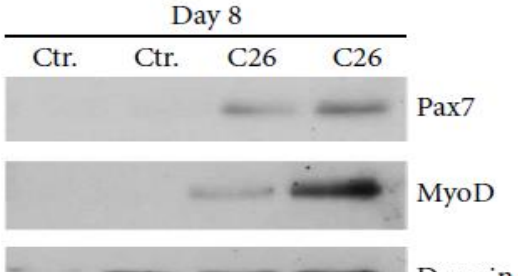
Cancer & chemo cause mitophagy, decrease both energy and biogenesis

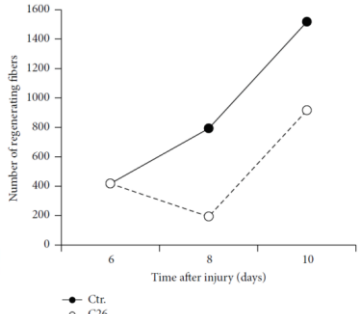
The «drug» exercise

Exercise improves all of them

Slide (adapted) from Fabio Pennna
SCWD Congress Maastricht 2018

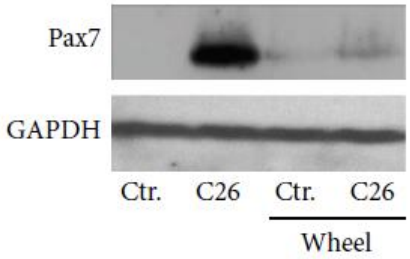
Moderate physical exercise downregulates Pax7 expression and rescues muscle mass and fiber size





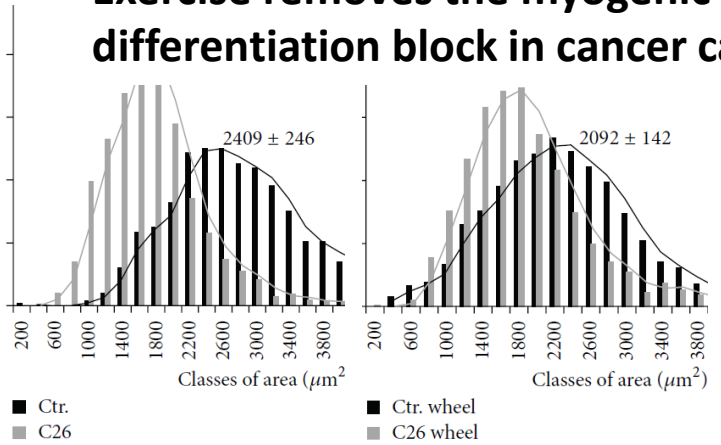
In cachectic mice (C26) less regenerative fibres (impaired myogenic potential) after muscle injury

Early regenerative marker expression in injured muscles



Exercise (wheel) reduces Pax7 overexpression

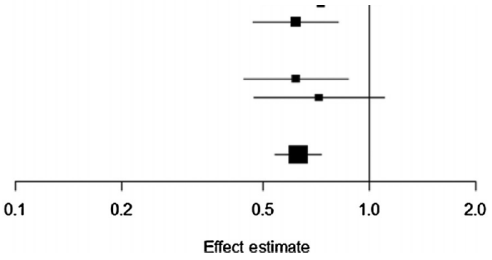
Exercise removes the myogenic differentiation block in cancer cachexia.



Coletti D et al. Stem Cells International 2016, ID 6729268

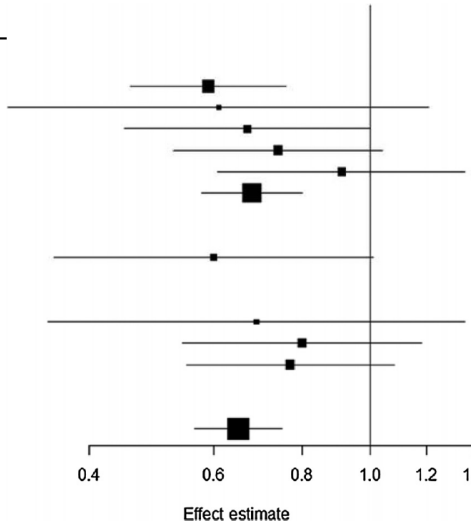
Postdiagnosis physical exercise is associated with lower cancer-specific mortality

Author, year	No. of events/cases	Effect estimate	95% CI
Breast			
Bradshaw, 2014 (10)	195/1,033	0.27	0.17–0.42
Holick, 2008 (26)	109/4,482	0.49	0.27–0.89
Borch, 2015 (9)	155/1,327	0.50	0.15–1.62
Holmes, 2005 (27)	280/2,987	0.60	0.40–0.89
Irwin, 2011 (11)	86/2,910	0.61	0.38–0.99
Irwin, 2008 (28)	115/933	0.65	0.23–1.87
Williams, 2014 (8)	46/986	0.76	0.63–0.92
de Glas, 2014 (12)	39/435	0.77	0.28–2.12
Sternfield, 2009 (29)	102/1,970	0.87	0.48–1.59
Borugian, 2004 (7)	112/603	1.00	0.63–1.60
Pooled estimate ($I^2 = 61.3\%$)	1,239/17,666	0.62	0.48–0.80
Colorectal			
Kuiper, 2012 (13)	51/606	0.29	0.11–0.77
Meyerhardt, 2006 (30)	80/573	0.39	0.19–0.82
Meyerhardt, 2009 (31)	88/661	0.47	0.24–0.92
Arem, 2015 (14)	128/3,797	0.53	0.27–1.03
Campbell, 2013 (15)	379/2,236	0.87	0.61–1.24
Baade, 2011 (16)	345/1,825	0.88	0.67–1.15
Pooled estimate ($I^2 = 56.6\%$)	1,071/9,698	0.62	0.45–0.86
Prostate			
Kenfield, 2011 (17)	112/2,705	0.42	0.20–0.88
Friedenreich, 2016 (18)	170/830	0.56	0.35–0.90
Bonn, 2015 (19)	194/4,623	0.73	0.51–1.05
Pooled estimate ($I^2 = 0.8\%$)	476/8,158	0.62	0.47–0.82
Any			
Lee, 2014 (20)	337/1,021	0.62	0.44–0.87
Inoue-Choi, 2013 (21)	184/2,017	0.72	0.47–1.10
Overall			
Pooled estimate ($I^2 = 47.9\%$)	3,307/38,560	0.63	0.54–0.73



cancer recurrence or progression

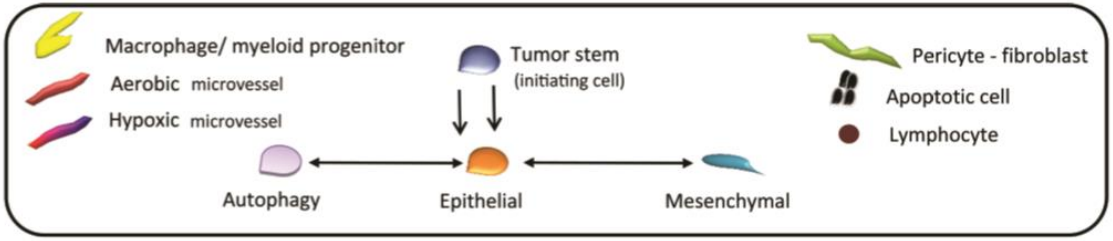
Author, year	No. of events/cases	Effect estimate	95% CI
Breast			
Chen, 2011* (24)	450/4,826	0.59	0.46–0.76
Courneya, 2014* (25)	37/242	0.61	0.31–1.21
Bertram, 2011 (22)	295/2,361	0.67	0.45–1.00
Holmes, 2005* (27)	370/2,987	0.74	0.53–1.04
Sternfield, 2009* (29)	225/1,970	0.91	0.61–1.36
Pooled estimate ($I^2 = 0\%$)	1,377/12,386	0.68	0.58–0.80
Colorectal			
Meyerhardt, 2006 (30)	159/832	0.60	0.36–1.01
Prostate			
Richman, 2011* (23)	117/1,455	0.69	0.35–1.36
Friedenreich, 2016 (18)	239/830	0.80	0.54–1.18
Pooled estimate ($I^2 = 0\%$)	356/2,285	0.77	0.55–1.08
Overall			
Pooled estimate ($I^2 = 10\%$)	1,892/15,298	0.65	0.56–0.75

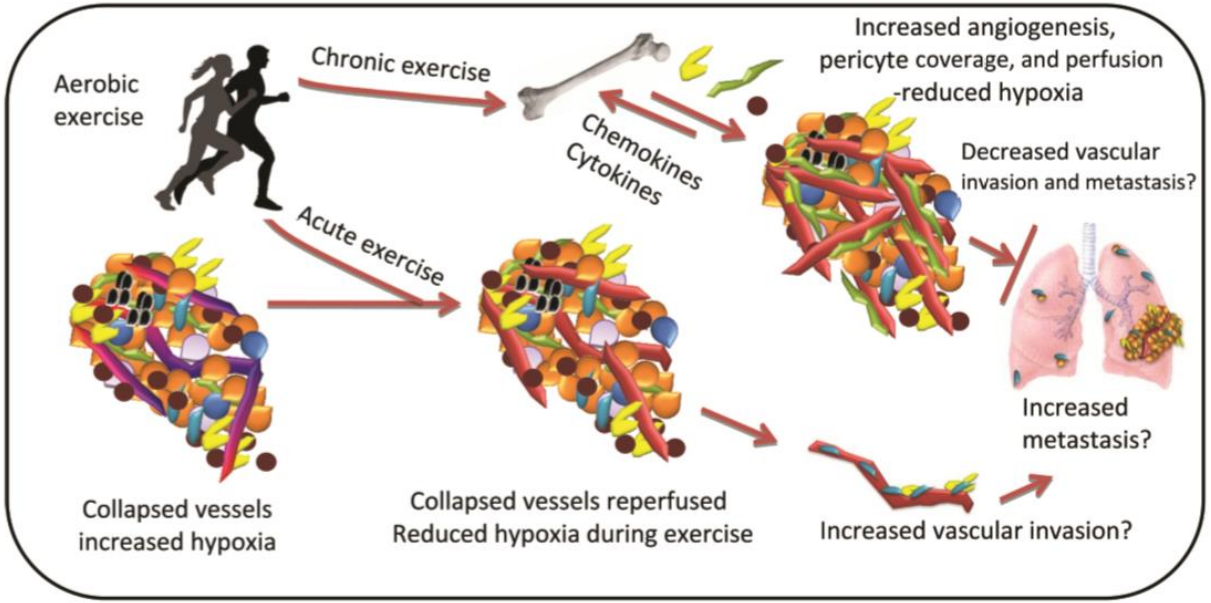


Physical Activity and Cancer Outcomes: A Precision Medicine Approach

Friedenreich CM et al. Clin Cancer Res 2016;22:4766-75

Effects of aerobic exercise on the tumor microenvironment

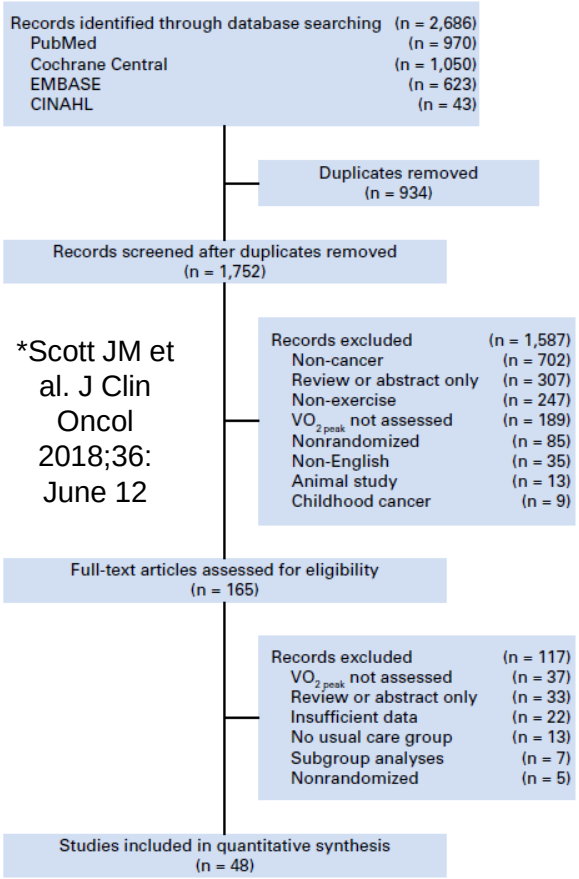




Lee W. Jones, Mark W. Dewhirst. JNCI 2014; 106:1-3

Efficacy of Exercise Therapy on Cardiorespiratory Fitness in Patients With Cancer: A Systematic Review and Meta-Analysis

Search strategy:
- Exercise training intervention
- Cardiovascular Reserve Capacity
- Cancer - RCTs



*Scott JM et al. J Clin Oncol 2018;36: June 12

Aerobic exercise training: chronic (> 3 weeks) repeated sessions of purposeful endurance physical activity of at least 15 min duration
Resistance training: repeated voluntary muscle contractions against a resistance > normally encountered in activities daily living, with objective of improving health

Classic components of exercise prescription:
(1) program length (total number of training weeks)
(2) duration (duration spent on 1 session of exercise)
(3) frequency (mean number of exercise sessions/week)
(4) intensity (% of predetermined physiological parameter, e.g. max heart rate obtained from baseline cardiopulmonary exercise test),
(5) type (modality).

Supervised: all exercise sessions performed under the supervision of, and monitored by a trained professional (non-supervised: e.g., home-based)

Standard prescription: uniform exercise dosing across the intervention period after an initial lead-in period
Nonlinear prescription: nonuniform, alternating exercise doses across the intervention period after an initial lead in

Primary end point:
direct (ie, gas exchange analysis) or estimated (ie, predicted on the basis of submaximal or maximal physiologic parameters)
measurement of VO_{2peak} in mL O_2 x kg^{-1} x min^{-1}

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Why? Impaired VO_{2peak} occurs both during anticancer tx and years after tx cessation, and correlates with heightened symptom burden and poorer clinical outcomes (incl. OAS)

	No. of Trials (%)
Publication year	
2000-2014	23 (48)
2015-2018	25 (52)
Region of origin	
Americas	19 (48)
United States	10
Canada	8
Brazil	1
Europe	22 (46)
Netherlands	5
France	1
Germany	1
Ireland	1
Asia	4 (8)
Iran	2
Korea	1
Taiwan	1
Australia	3 (6)
Sample size	
≤ 50	24 (50)
51-100	13 (27)
≥ 101	11 (23)

	No. of Trials (%)
Group allocation	
Exercise	1,990 (55)
Control	1,642 (45)
Mean age, years (SD)	55 (7.5)
Female sex	2,336 (68)
Cancer site	
Breast	21 (44)
Prostate	6 (13)
Mixed	6 (13)
Lung	4 (8)
Presurgery	5 (10)
During treatment	14 (29)
During and after primary adjuvant ther	2 (4)
After primary adjuvant therapy, years	27 (56)
< 1	9 (19)
1 to 5	9 (19)
> 5	3 (6)
Time not reported	6 (13)

3632 Participants

Only 30% non-curative, mixed tumors with mixed response to anticancer treatment

In summary, exercise therapy is an effective adjunctive therapy to improve VO_{2peak} in patients with cancer.

Pooled effects of exercise training compared with non-exercise control on cardiorespiratory fitness

most trials examined the efficacy of an exercise dose of approximately 100 to 135 minutes per week (three times weekly for 30 to 45 minutes per session)

Exercise

fatigue

Kessels E et al. Neuropsychiatric Dis Treat 2018
SR and MA, 11 RCT in cancer survivors — improved

Fuller JT et al., Br J Sports Med 2017
SR and MA of 140 RCT in cancer survivors — sightly

Repka CP & Hayward R, Integrative Cancer Therapies 2018
CT in 15 cancer survivors — improved

Oberoi S et al., Crit Rev Oncol Hematol 2018
SR and MA of 170 RCT in cancer or after HSCT — improved

Slide adapted from Jann Arends 2018

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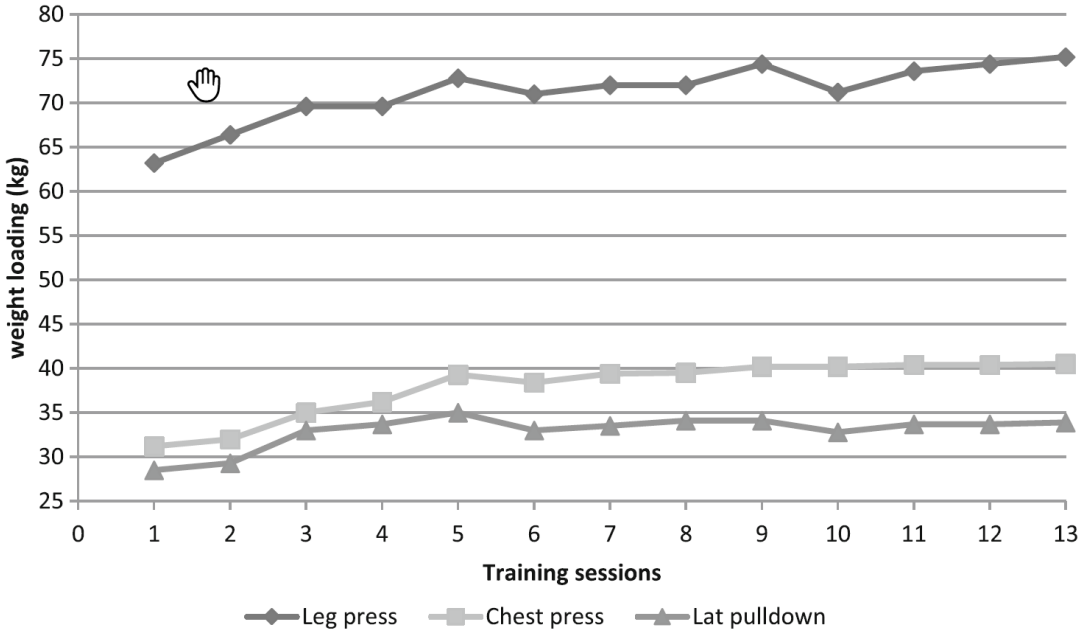
Progressive resistance training in cachectic head and neck cancer patients undergoing radiotherapy: a randomized controlled pilot feasibility trial

N=20, 10 intervention: 3 x weekly 30 min 3 exercises major muscle groups
8–12 repetition maximum for 3 sets each



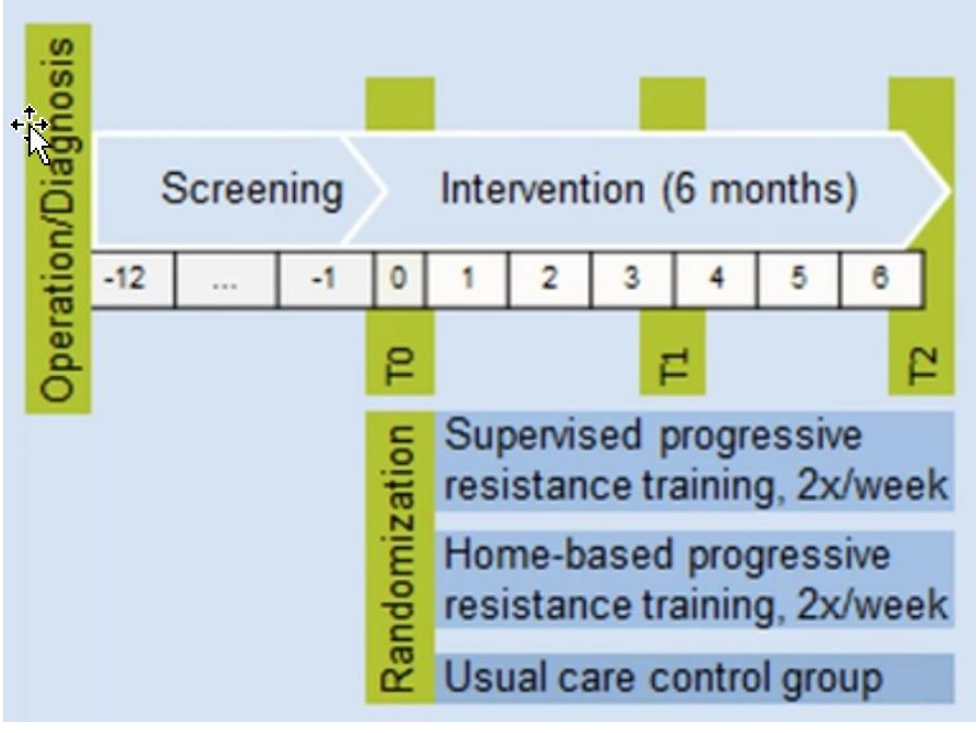
Population Intervention - Control:
Chemoradiation: 8 (80%) 5 (50%)
Neck dissection: 5 (50%) 6 (60%)
Feeding tube: 7 (70%) 4 (40%)

No adverse events, full compliance, trends (?) to better **fatigue** and QoL
Recruitment: 16 «no interest)

Grote M et al. Rad Oncol 2018;13:215

Effects of 6-month exercise training on quality of life in pancreatic cancer patients: results from a randomized controlled trial

N=65 (47 completed)
Most stage IIb, after resectrion and chemotherapy



3 mts
Physical function significantly improved
Better overall QoL, **Fatigue**, Insomnia

6 mts
No difference

Exercise training works in pancreatic cancer pts, but shortly

Tai Chi

Metaanalysis of 6 RCT (373 patients)

2 of 6 RCT included stage IV cancer

Tai Chi reduces fatigue,

8-12 week intervention btter than shorter tretament

effects were more pronounced than after exercise or psychology

Song S et al.Support Care Cancer 2018

Slide adapted from Jann Arends 2018

Cognitive Behavior Therapy (CBT)

Van Gessel LD et al., J Cancer Survivorship 2018

N=78 cancer survivors: *CBT effects recovery from severy fatigue*

50% maintain status over 14 years, 50% relapse

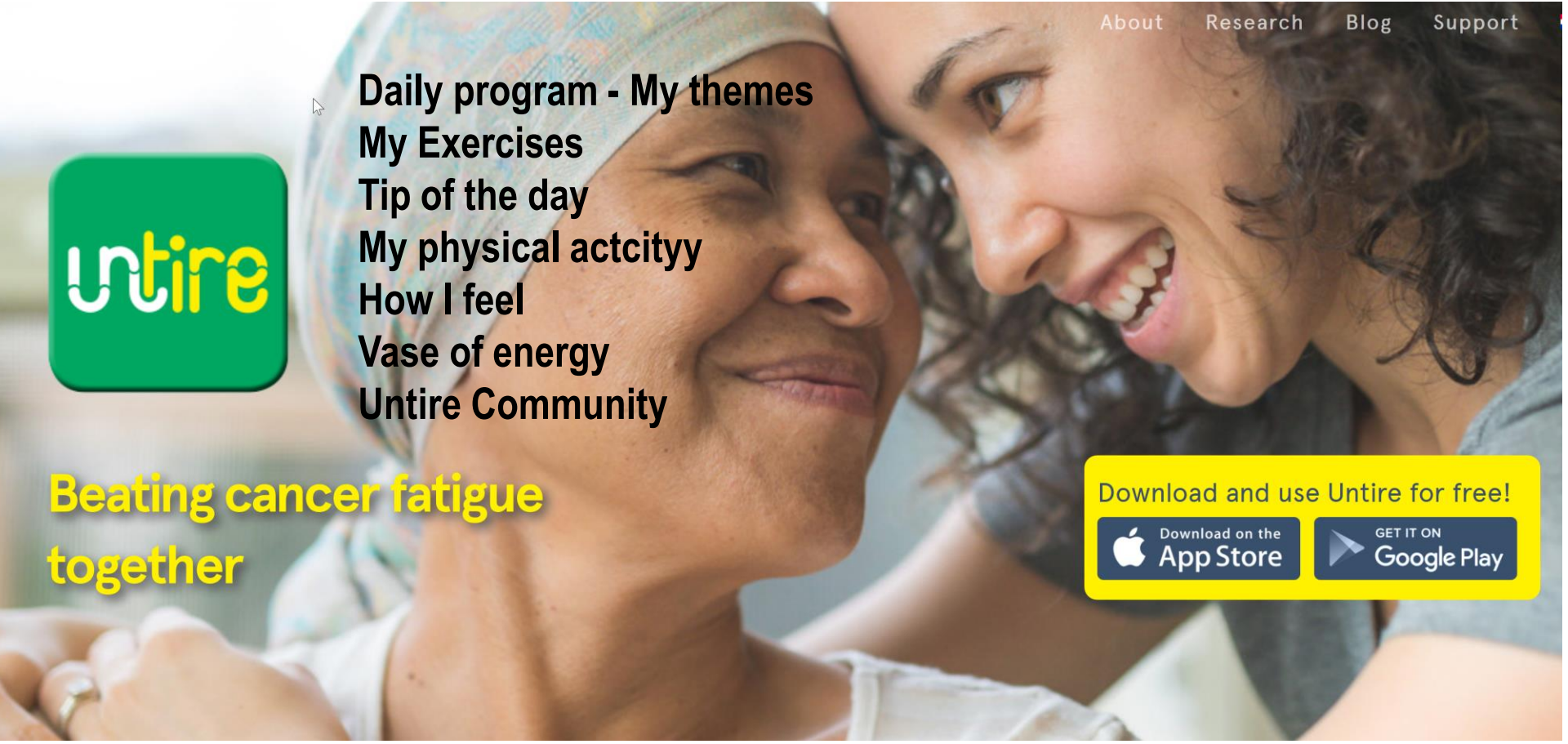
Cobeanu O &David D, J Clin Psychol Medical Setting 2018

Systematic review and metaanalysis of 19 RCT

CBT in breast cancer of different stages

CBT is effective, but no effect on fatigue

Slide adapted from Jann Arends 2018



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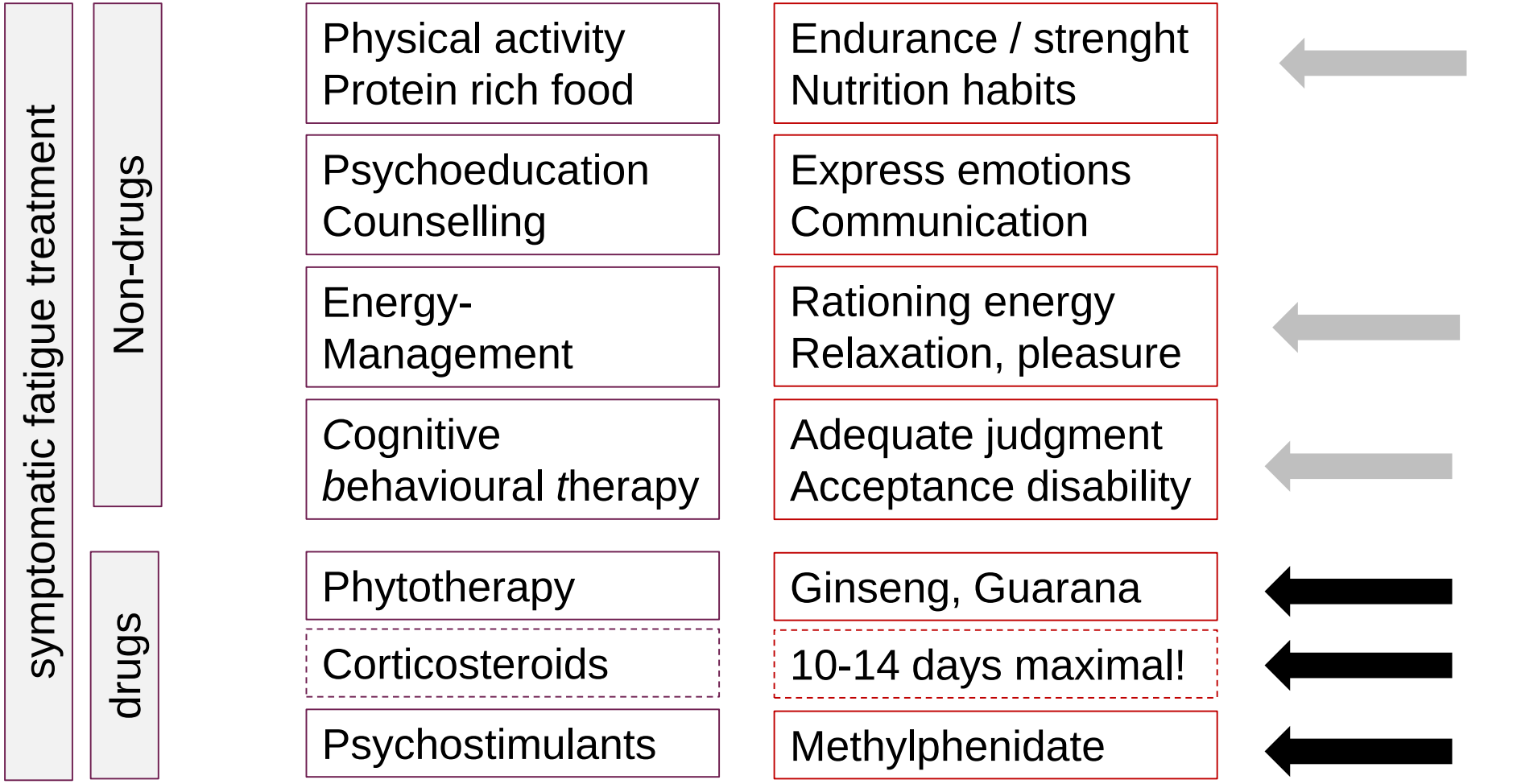
symptomatic fatigue treatment
Non-drugs
drugs
Physical activity
Protein rich food
Endurance / strenght
Nutrition habits
Psychoeducation
Counselling
Express emotions
Communication
Energy-
Management
Rationing energy
Relaxation, pleasure
Cognitive
behavioural therapy
Adequate judgment
Acceptance disability
Phytotherapy
Ginseng, Guarana
Corticosteroids
10-14 days maximal!
Psychostimulants
Methylphenidate

Ginseng to treat fatigue

Korean/Asian ginseng – *Panax ginseng*

American ginseng – *Panax quinquefolius*

Evidence:

. healthy subjects: 4 RCT pos., 1 RCT neg.

. cancer survivors: 1 RCT positive

. cancer-related fatigue: OBS pos., 1 RCT neg

Recommendation:

„..may be used ... Evidence is heterogeneous and very weak.“

<ESMO guidelines on cancer cachexia; submitted>

New Ginseng data

2 neg. RCT in CRF:

Yennu S et al. JNCI 2017, n=127

Martoni AA et al., JNCCN 2018, n=64

Systematic Review of 10 RCT on different types of fatigue, incl. CRF

Arring NM et al, J Altern Comp Med 2018

→ „Ginseng is a promising treatment“

Slide adapted from Jann Arends 2018

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Methylphenidate to treat fatigue

Psychostimulant acting on central nervous system

Blocking dopamine and norepinephrine transporters

Evidence:

pos: 2 small RCT, 1 small CT, 1 retrospective Anal.

neg: 2 large RCT

Recommendation:

„..insufficient evidence ..“

<ESMO guidelines on cancer cachexia; submitted>

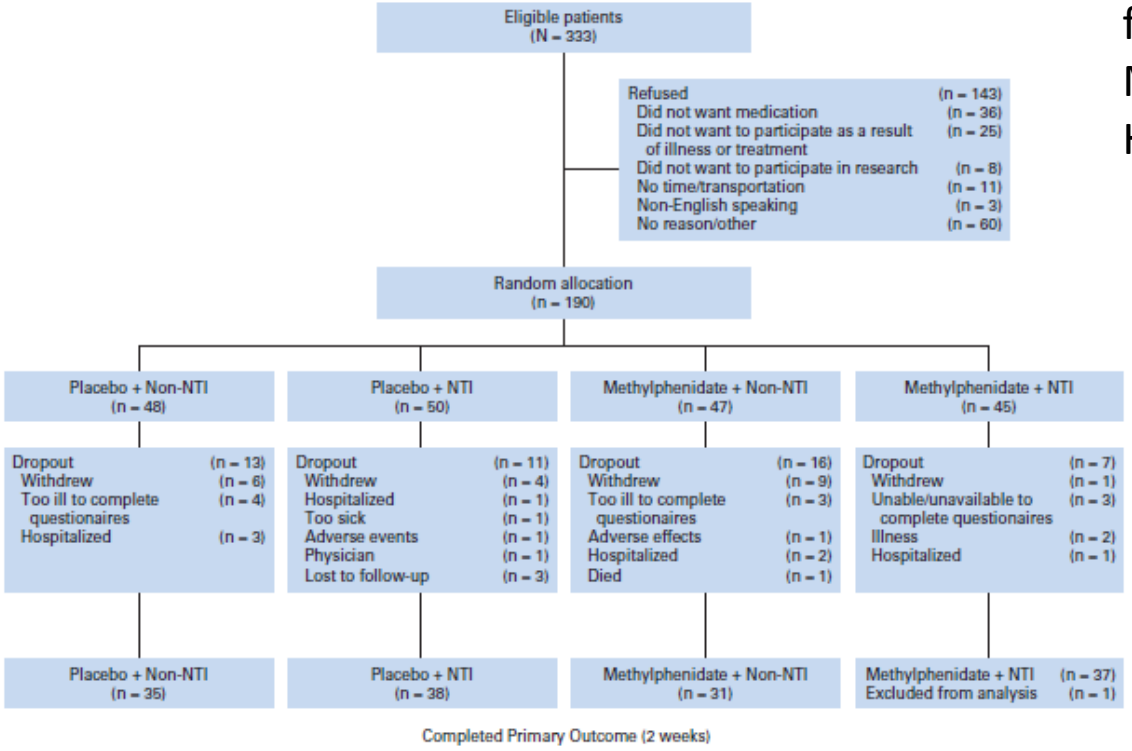
Slide adapted from Jann Arends 2018

Some randomized trials for methylphenidate

Study	N	Setting	Dose	Result
Lower EE (2009)	168	various tumor entities after chemotherapy	10-50 mg/d	Significant improvement in FACIT-F at week 8 (p=0.02) Reduction in fatigue also reflected in a dose in other scales
Bruera E (2006)	112	palliative patients with various malignancies	5-20	icant difference in FACIT-F
Moraska AR (2010)	148			ant difference in BFI
Roth AJ (2010)	39			BFI total scores significantly decreased for both groups Significant benefit for BFI severity subscale (p=0.03)
Mar Fan HG (2008)	59	resected breast cancer, standard adjuvant chemotherapy	10-20 mg/d	No significant difference in FACIT-F

Mixed populations with also different other reasons for fatigue and insufficient understanding of mechanism

Methylphenidate and/or a Nursing Telephone Intervention for Fatigue in Patients With Advanced Cancer: A Randomized, Placebo-Controlled, Phase II Trial



Patient population

Advanced cancer

fatigue ≥ 4 ESAS

Mini-Mental State normal (>24/30)

Hb> 8 g/dL

5 mg Ritalin every 2 hours max 20 mg per day for 14 d

Nurse practitioner phone 4-6 x in 14 days

→ Both same effect, together not better

Bruera E et al. J Clin Oncol 2013;31:2421-2427

Methylphenidate - Ritalin

10mg Pills, breakable (require special triplicates)

Start: 5 mg Testdose (Anxiety, Tachykardia, [may cause Epilepsia])

If after 1 hour Fatigue VAS better (2/10) → >80% likely, that after 1 week better

Then: 5-10mg morning, midday, ev. evening
After weeks: personality disorders may (rarely) develop

Own experience → may be effective: Fatigue in far advanced Patients, when no other severe Fatigue-cause present

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

Patients with ≥ 3 Symptoms ESAS ≥ 4/10
Dexamethasone 4 mg 2 x day / 14 d

	Day 15 From Baseline					Day 8 From Baseline				
	Dexamethasone (n = 43)		Placebo (n = 41)			Dexamethasone (n = 43)		Placebo (n = 41)		
Instrument	Mean	SD	Mean	SD	*P*	Mean	SD	Mean	SD	*P*
FACIT-F subscale	9.0	10.30	3.1	9.59	.008	8.01	7.81	3.06	7.28	.005
FACIT physical	5.25	6.01	1.32	5.52	.002	4.37	5.14	1.34	4.50	.007
FACIT social/family	−0.05	5.50	0.2	4.77	.820	−0.22	4.06	0.52	3.58	.40
FACIT emotional	1.85	4.93	1.18	4.49	.490	0.59	3.57	1.44	4.07	.33
FACIT functional	1.3	6.21	1.51	5.17	.820	0.55	5.20	1.11	4.80	.56
FACIT-F total score	18.16	22.88	7.87	19.93	.030	13.37	13.22	7.5	14.04	.06
ESAS pain	−1.35	3.11	−0.17	2.66	.09	−1.77	2.89	−0.13	2.80	.014
ESAS fatigue	−2.70	2.85	−1.61	2.69	.158	−1.97	2.78	−0.82	2.85	.056
ESAS nausea	−1.08	2.95	−0.36	3.17	.32	−1.18	2.91	−0.45	2.81	.09
ESAS depression	−0.89	2.58	−0.80	2.67	.54	−0.90	2.67	−1.03	2.90	.89
ESAS anxiety	−0.72	2.81	−1.17	2.45	.77	−1.20	2.44	−0.84	2.79	.49
ESAS drowsiness	−1.59	3.46	−0.89	2.94	.35	−1.00	2.77	−0.45	2.54	.37
ESAS shortness of breath	−2.16	2.92	−0.89	2.40	.06	−1.56	2.44	−0.58	2.37	.07
ESAS appetite	−2.19	3.78	−0.63	3.11	.06	−1.74	3.42	−0.83	3.71	.27
ESAS sleep	−0.22	3.22	−0.14	2.93	.91	−0.13	2.87	−0.11	2.45	.97
ESAS feeling of well-being	−0.32	3.03	−1.22	3.38	.24	−1.31	3.43	−0.73	2.86	.43
ESAS physical	−10.86	9.55	−4.78	10.86	.013	−9.10	7.50	−3.42	10.79	.009
ESAS psychological	−1.48	4.67	−2.08	4.73	.65	−1.26	4.68	−1.81	5.01	.65
ESAS symptom distress	−12.2	13.49	−8.86	15.91	.15	−10	12.28	−6.95	16.38	.15
HADS anxiety	−0.66	3.45	−1.00	3.54	.75	−0.85	3.16	−1.09	2.32	.59
HADS depression	−1.39	3.59	−0.31	3.90	.29	−1.23	4.02	−0.43	3.12	.65
FAACT	6.82	8.95	1.95	8.54	.013	4.78	8.44	1.49	8.23	.08

Abbreviations: ESAS, Edmonton Symptom Assessment Scale; FAACT, Functional Assessment of Cancer Therapy–Anorexia-Cachexia; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; HADS, Hospital Anxiety Depression Scale; SD, standard deviation.

FACIT-F but not ESAS-Fat better

FAACT but not ESAS-App better

Yennu S et al.
J Clin Oncol
2013:31:3076-82

IKGAIS Kantonsspital St.Gallen

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

Side effects

	Grade ≥ 3*			Grade < 3		
Adverse Event	Total No. of Patients	Dexamethasone (n = 17)	Placebo (n = 11)	Total No. of Patients	Dexamethasone (n = 24)	Placebo (n = 33)
Pain	7	5	2	22	13	9
Insomnia	6	2	4	3	1	2
Fatigue	5	5	0	9	3	6
Infection	2	2	0	3	2	1
Cough	1	0	1	1	0	1
Death NOS	1	1	0	0	0	0
Dysphagia	1	1	0	0	0	0
Dizziness	1	0	1	1	1	0
Dyspnea	1	0	1	5	0	5
Edema	1	0	1	4	1	3
Neuropathy	1	1	0	0	0	0
Somnolence	1	0	1	3	0	3
Nausea/vomiting	0	0	4	4	1	3
Blurred vision	0	0	1	1	1	0
Depression	0	0	1	1	1	0

→Dexamethasone not more side-effects than Placebo.

→ Effect on Fatigue, Appetita maximum 14 days

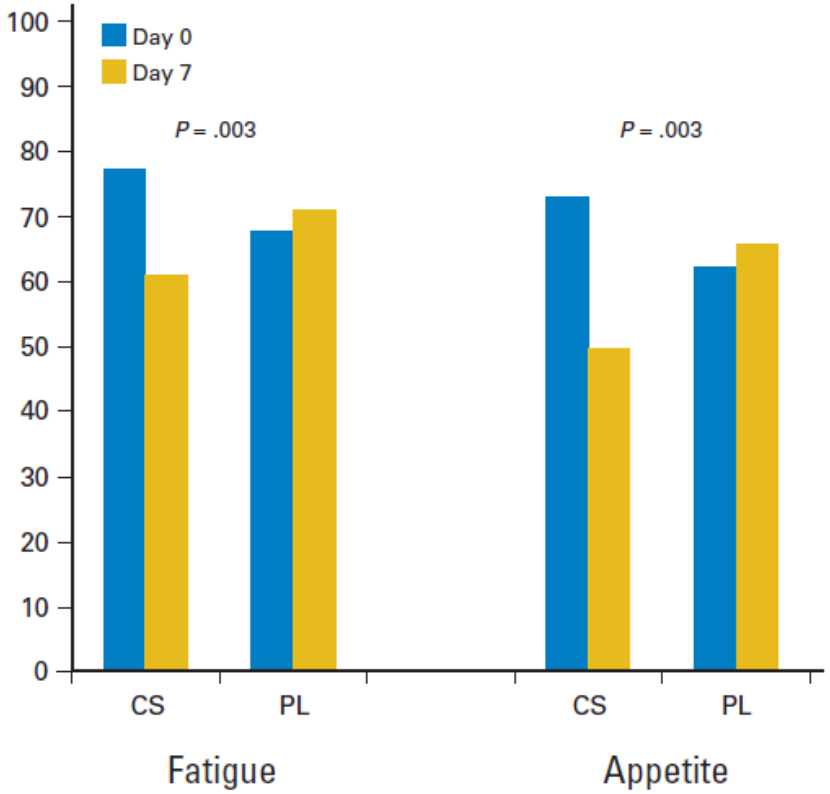
Yennu S et al. J Clin Oncol 2013:31:3076-3082

Efficacy of Methylprednisolone on Pain, Fatigue, and Appetite Loss in Patients With Advanced Cancer Using Opioids: A Randomized, Placebo-Controlled, Double-Blind Trial

Ørnulf Paulsen, Pål Klepstad, Jan Henrik Rosland, Nina Aass, Eva Albert, Peter Fayers, and Stein Kaasa

Patients Pain 4/10 in 24 h, opioid-Analgesia, survival >4wks

Paulsen O et al. J Clin Oncol 2014;32:3221-8



Methylprednisolone 16 mg 2 x day for 7 days

Fatigue and Appetit become better after 7 days, few side-effects

	Methylprednisolone (n = 25)		Placebo (n = 22)	
Predefined AE Category	No.	%	No.	%
Oral symptoms	6	24	7	32
Restlessness	6	24	3	14
Psychic change	2	8	3	14
Anxiety	2	8	3	14
Edema	1	4	5	23
Muscle weakness	1	4	3	14
Sleeplessness	4	16	3	14
Dyspepsia	3	12	4	18
Other	2	8	3	14
Total	27		34	
Mean No. of AEs	1.08		1.55	
P		.28		

Fatigue and Appetit but not pain become better after 7 days, few side-effects

Table 3. Primary and Secondary Outcomes

Outcome	Methylprednisolone (n = 25) Mean	Methylprednisolone (n = 25) 95% CI	Placebo (n = 22) Mean	Placebo (n = 22) 95% CI	P*
Average pain intensity†‡					
Day 0	4.76	4.33 to 5.19	4.36	3.88 to 4.85	.21
Day 7	3.60	2.79 to 4.41	3.68	2.99 to 4.37	.88
Mean difference	−1.16	−1.96 to −0.35	−0.68	−1.28 to −0.08	.50
Morphine consumption (OMEs), mg§					
Day 0	273.8	167.8 to 379.8	165.8	93.1 to 238.5	.09
Day 7	318.6	192.3 to 444.8	188.2	103.2 to 273.2	.08
Mean difference	44.8	−16.0 to 105.6	22.4	−5.6 to 50.4	.51
Relative difference (day 7/day 0)	1.19	1.00 to 1.38	1.20	0.90 to 1.51	.95
Pain intensity at rest (day 1 to 7)‡§‖					
AUC	19.9	14.4 to 25.4	17.9	12.2 to 23.6	.60
Fatigue§‖¶					
Day 0	77.1	68.3 to 85.9	67.2	56.3 to 78.1	.15
Day 7	60.4	49.7 to 71.2	70.5	61.4 to 79.6	.16
Mean difference	−16.7	−27.0 to −6.3	3.3	−4.5 to 11.1	.003
Appetite loss§‖¶					
Day 0	73.3	60.2 to 86.5	63.6	50.8 to 76.5	.28
Day 7	49.3	34.9 to 63.7	65.2	51.9 to 78.4	.10
Mean difference	-24.0	−37.5 to −10.5	1.5	−8.1 to 11.2	.003
Patient satisfaction with treatment‡§	5.4	4.05 to 6.70	2.0	0.71 to 3.29	.001

Paulsen O et al. J Clin Oncol 2014;32:3221-8

In summary: Symptomatic Fatigue treatment

- Methylphenidate (Ritalin) yes, start slow, watch anxiety
  Antidepressants not for CRF but for Depression
  Modafinil maybe, one trial[1], Phytotherapeutics may be promising[2]
- Behavioural interventions (cancer advocacy education)
  - Regular physical Activity
  - Sleep-Hygene (but not too much)
  - Energy planing (Expectations – Reality)
  - Restorative Activities
- Corticosteroids: yes (most often), but ONLY <2 weeks!
  Tox: myopathy (proximal), infections (candidiasis), insulin resistance, bones
- Testosterone if hypogonadism (Men, not Prostata-Ca)
- Physical activity and strenght training: define expecations & goals
- «Psychosocial» Interventions[3]: controversial, many methods (Yoga, Acupuncture[4]), v.a. in postcurative „survivors“

1: Hovey E Support Care Cancer 2014;22:1233-42
2: Bar-Sela G Support Care Cancer 2015;23:1979-8
3: Larkin D Int J Nurs Pract 2014;20:549-60
4: Zeng Y Integr Cancer Ther 2014;13:193-200

Conclusion

Assess fatigue in daily practice, consider emotional, cognitive and physical fatigue, assess impact of fatigue

Consider all reasons and treat reversible reasons for fatigue

«always» use exercise and protein-rich nutrition, discuss impairment and reversibility of disability, support patients to cope with it (Calman Gap)