Treatment of Fatigue in Advanced Cancer

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UCSD/Scripps Hospice and Palliative Medicine Fellow

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Objectives

- Review mechanism and contributing factors to fatigue in advanced cancer
- Review guidelines for treatment of cancer-related fatigue
- Review evidence for use of methylphenidate and corticosteroids in cancer-related fatigue

Background

- Fatigue in cancer patients is ‘a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion that is not proportional to recent activity and interferes with usual functioning’.
- Most people with advanced cancer rank fatigue as their most important symptom, up to 80% are affected
- Majority of patients feel they do not get the help they want with this symptom

Proposed pathophysiology of Cancer-Related Fatigue

- Mental fatigue
  - HPA axis: IL-1, IL-6, and TNF-a associated with tumor affect HPA axis functioning
  - Suprachiasmatic nucleus – circadian rhythm; influenced by tumor-derived peptides and cytokine deregulation
  - Basal and frontal ganglia – decreased perfusion
- Physical fatigue
  - Changes in mitochondrial and sarcoplasmic reticulum functioning
    - Impairment of ATP generation of mitochondria during muscle contraction
  - Failure of central activation → impaired skeletal muscle activity
  - Cancer and treatment → peripheral release of serotonin and several cytokines → vagal activation → inhibition of skeletal muscle activity → generalized weakness

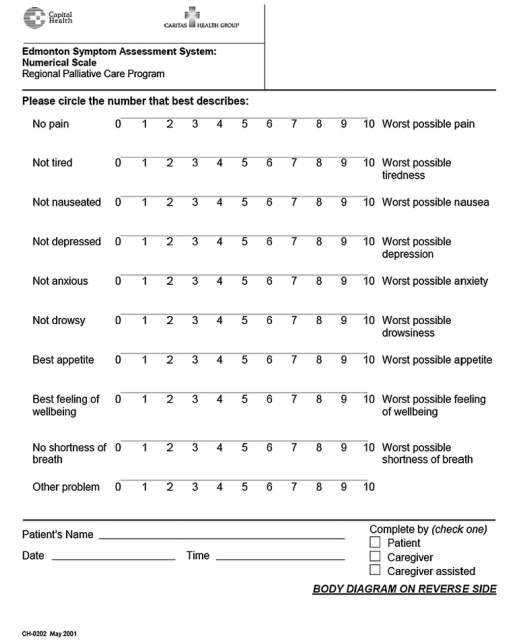
Neefjes EC, van der Vorst MJ, Blauwhoff-Buskermolen S, Verheul HM. Aiming for a better understanding and management of cancer-related fatigue. Oncologist. 2013;18(10):1135-43. doi: 10.1634/theoncologist.2013-0076. Epub 2013 Sep 13. PMID: 24037979; PMCID: PMC3805156.

Fatigue is hard to study

- Lack of consensus on definition
- Subjective and multidimensional nature
- Culture and language differences
- RCTs often can’t be performed due to fluctuating symptom intensity, declining performance status, rapid disease trajectory, short prognosis

Scales

- ESAS: Edmonton Symptoms Assessment System
- FACT-F: Functional Assessment of Cancer Therapy-Fatigue
- FQ: Fatigue Questionnaire
- MFI-20: Multidimensional Fatigue Inventory
- EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 fatigue subscale



Capital Health — Caritas Health Group

Edmonton Symptom Assessment System:
Numerical Scale
Regional Palliative Care Program

Please circle the number that best describes:

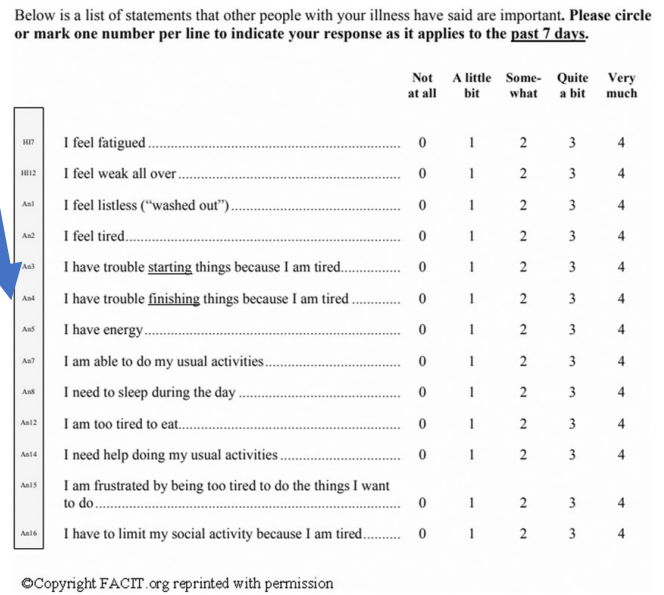
No pain	0 1 2 3 4 5 6 7 8 9 10	Worst possible pain
Not tired	0 1 2 3 4 5 6 7 8 9 10	Worst possible tiredness
Not nauseated	0 1 2 3 4 5 6 7 8 9 10	Worst possible nausea
Not depressed	0 1 2 3 4 5 6 7 8 9 10	Worst possible depression
Not anxious	0 1 2 3 4 5 6 7 8 9 10	Worst possible anxiety
Not drowsy	0 1 2 3 4 5 6 7 8 9 10	Worst possible drowsiness
Best appetite	0 1 2 3 4 5 6 7 8 9 10	Worst possible appetite
Best feeling of wellbeing	0 1 2 3 4 5 6 7 8 9 10	Worst possible feeling of wellbeing
No shortness of breath	0 1 2 3 4 5 6 7 8 9 10	Worst possible shortness of breath
Other problem	0 1 2 3 4 5 6 7 8 9 10	

Patient's Name _____
Date _____ Time _____

Complete by *(check one)*
☐ Patient
☐ Caregiver
☐ Caregiver assisted

BODY DIAGRAM ON REVERSE SIDE

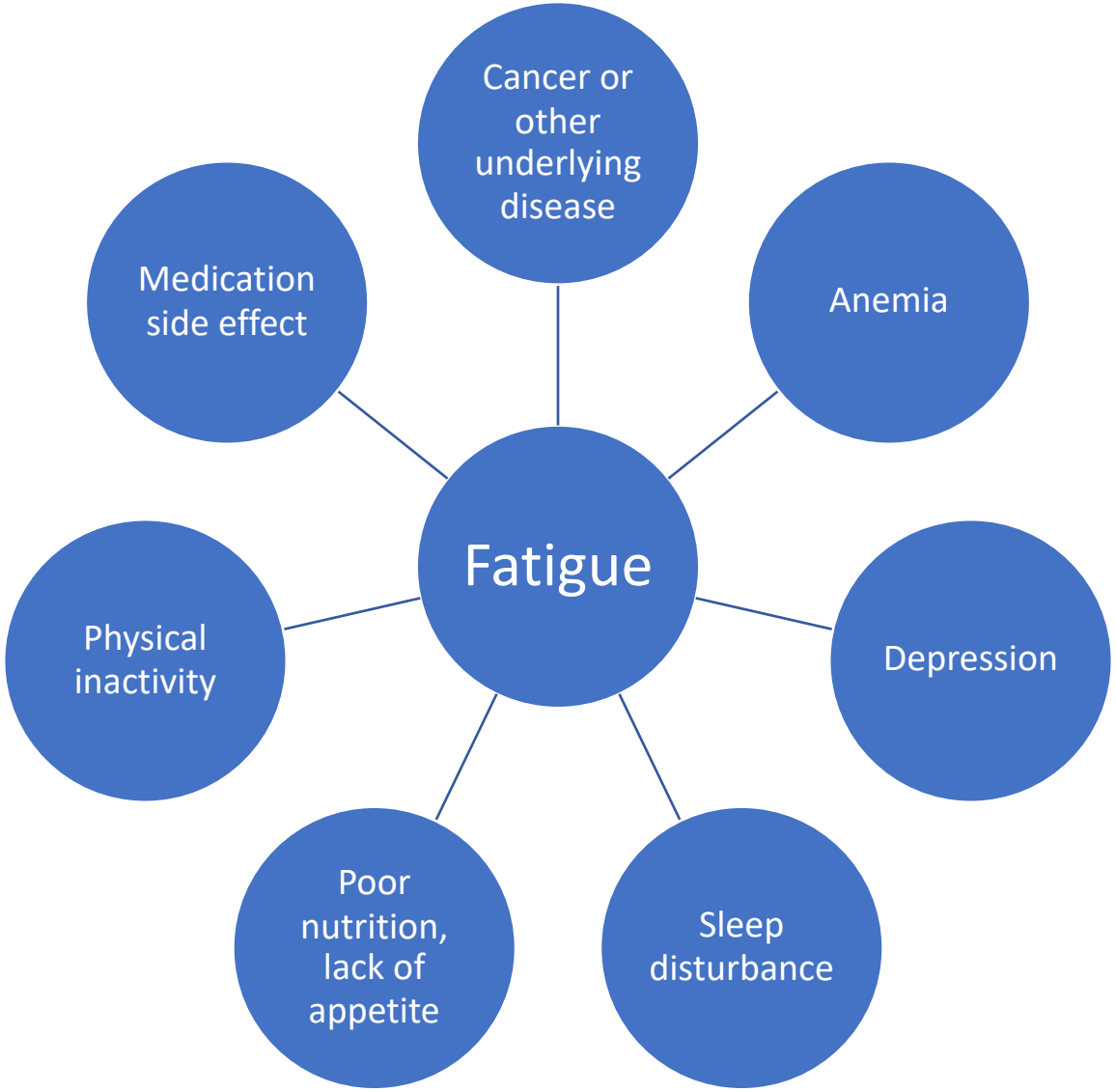
CH-0202 May 2001



Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Contributing Factors



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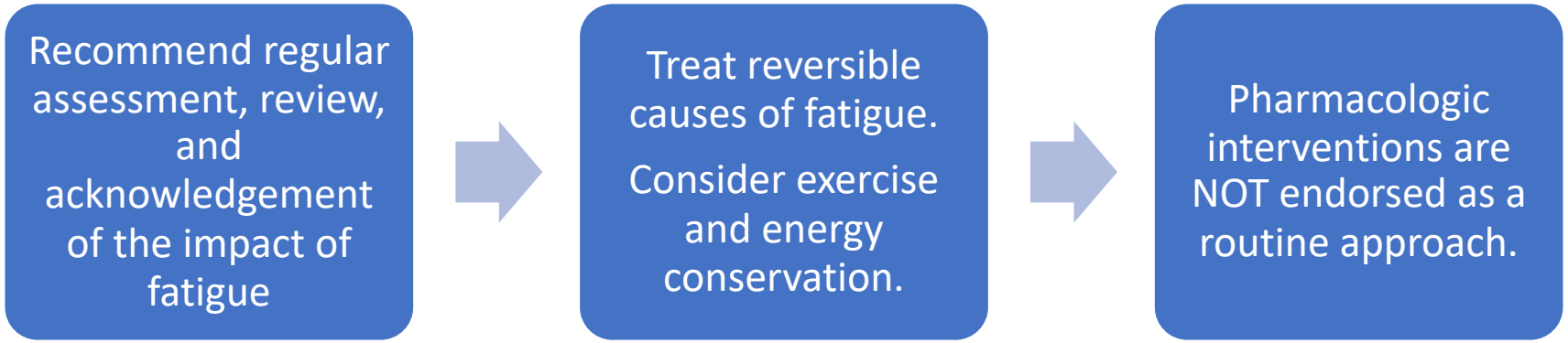
Palliat Med. 2022 Jan; 36(1): 7–14. PMCID: PMC8793304
Published online 2021 Dec 14. doi: 10.1177/02692163211046754 PMID: 34903113

Practice review: Evidence-based and effective management of fatigue in patients with advanced cancer

Emma J Chapman,[1,*] Erica Di Martino,[2,*] Zoe Edwards,[1] Kathryn Black,[3] Matthew Maddocks,[4] and Michael I Bennett[1]

- Practice review in the Journal of Palliative Medicine, 2022:



Many interventions currently recommended by guidelines are not supported by a robust evidence base; further study is needed. Further study also needed on psychological, nutritional, sleep optimization, and complementary therapies.

Chapman EJ, Martino ED, Edwards Z, Black K, Maddocks M, Bennett MI. Practice review: Evidence-based and effective management of fatigue in patients with advanced cancer. *Palliat Med*. 2022;36(1):7-14. doi:10.1177/02692163211046754

A look at the guidelines for management of cancer-related fatigue

Table 2.

Summary of approaches for the management of cancer-related fatigue supported by the guidelines included in the review.

	European Society for Medical Oncology (ESMO) 2020	Scottish Palliative Care (SPC) 2019	National Comprehensive Cancer Network (NCCN) 2021	Oncology Nursing Society (ONS) 2017	Canadian Association of Psychosocial Oncology (CAPO) 2015
Assess	√	√	√		√
Re-assess	√		√		√
Acknowledge	√	√			
Inform and educate	√		√		√
Reversible causes	√	√	√	√	√
Physical activity	√	√	√	√	√
Energy conservation	√	√	√	√	√
Nutrition		Anorexia	√		√
Sleep optimization		√	√	√	√
Psychological support	√	√	√	√	√
Complementary therapies	*Mindfulness and Yoga*	√	√	*Mindfulness, Massage, Ginseng*	*Mindfulness, Yoga*
Psychostimulant medication	*No consensus*		*Selected patients*		
Corticosteroids	*Short term*		*Short term*	*Benefit to be balanced with harms*	

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Table 4.

Summary of recommendations for addressing fatigue in advanced cancer patients and strength of evidence.

	Strength of evidence
Do	
1. Regularly assess and review	Tentative
2. Acknowledge the problem	Tentative
3. Inform and educate	Tentative
4. Address reversible causes	Tentative
5. Agree upon a tailored management plan	
(a) Exercise activity	Moderate
(b) Energy conservation	Tentative
** Do not	
1. Routinely use psychostimulant medication (methylphenidate, modafinil)	Moderate
Don't know if there is a benefit of	
1. Corticosteroids	
2. Psychological interventions	
3. Nutrition	
4. Sleep optimization	
5. Complementary therapies	

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Regularly Assess and Review; Acknowledge (tentative recommendation)

- Screen, and follow up with a more in-depth assessment for moderate to severe fatigue
- Acknowledge burden on QOL
- Low potential for harm

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Inform and educate the patient and people important to them (tentative recommendation)

- Cochrane Review 2016:
  - 14 RCTs of educational interventions for cancer-related fatigue where fatigue was a primary outcome
  - Moderate quality evidence of a small reduction in fatigue intensity from a meta-analyses of eight studies (1524 participants; standardized mean difference (SMD) -0.28, 95% confidence interval (CI) -0.52 to -0.04) comparing educational interventions with usual care or attention control.
  - Low quality evidence for reduction of fatigue distress and fatigue interference with daily life

Cochrane Database Syst Rev. 2016 Nov; 2016(11): CD008144. PMCID: PMC6464148
Published online 2016 Nov 24. doi: 10.1002/14651858.CD008144.pub2 PMID: 27883365

Educational interventions for the management of cancer-related fatigue in adults

Monitoring Editor: Sally Bennett,[✉] Amanda Pigott, Elaine M Beller, Terry Haines, Pamela Meredith, Christie Delaney, and Cochrane Pain, Palliative and Supportive Care Group
The University of Queensland, Division of Occupational Therapy, School of Health and Rehabilitation Sciences,

Inform and educate the patient and people important to them (tentative recommendation)

- Educational interventions are defined as any information given to help people understand and manage cancer-related fatigue. Information *about* strategies (relaxation, CBT, exercise).

Table 3
Patient education for the management of cancer-related fatigue [44,73–75].

Plan and organize your work	Develop a routine and schedule energy-consuming activities at times of the day or on days of the week when you tend to have more energy. Stop to rest before you are tired. Defer tasks that are not important.
Delegate	Delegate as much as possible. For example, teach grandchildren to make a game out of household chores.
Sleep well	Limit naps to <1 h per day. Turn off the TV at least 1 h before bedtime. Use your bedroom for sleep and intimacy only.
Use devices	Use helpful devices if needed, like walkers, scooters, canes, handrails, and grab bars. Ask for a referral to occupational therapy for additional devices to help you manage your self-care.
Position comfortably	Sit to do tasks as much as possible. Avoid heavy lifting.
Minimize meal preparation	Assemble all ingredients beforehand. Use mixes or prepackaged food. Consider non-profit meal delivery services.
Prioritize	Focus on performing activities you enjoy and try to delegate the rest.

Soones T, Ombres R, Escalante C. An update on cancer-related fatigue in older adults: A narrative review. J Geriatr Oncol. 2022 Mar;13(2):125-131. doi: 10.1016/j.jgo.2021.07.006. Epub 2021 Aug 2. PMID: 34353750.
https://pubmed.ncbi.nlm.nih.gov/34353750/

Cochrane Library

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Patient Resources for Education, Exercise, Energy Conservation

Tips for Saving Your Energy

Following the tips in this section can help you save energy when doing your daily activities. This may help with fatigue. If you have questions, talk with your nurse, OT, or PT.

General activities

- Use a transport chair or wheelchair while traveling longer distances.
- Take your time with your activities and sit while you work. Remember to keep breathing normally (don't hold your breath) and stop and rest often if you feel tired.
- Sit on higher seats. They are easier to stand up from than low seats.
- Organize and store your work items where you use them and can get them easily.
- Maintain good posture. Sit up straight and try not to slouch.
- If you need to bend over to reach for something, exhale (breathe out) when you bend over and inhale (breathe in) when you reach.

Showering

- Install grab bars in your shower.
- Use a shower bench to sit in the tub while you shower.
- Use a sponge or brush with a long handle (such as a back brush) to scrub your feet and other areas that may be hard to reach.
- Sit in front of a mirror or sink for activities that take more time, such as putting on makeup or shaving.
- Keep your hair in a style that's easy to care for.

Getting dressed

- Sit on a chair or at the edge of your bed to get dressed.
- Dress the lower part of your body first.
- To put on your socks and shoes, sit and bring your foot to the opposite knee instead of bending over.
- Choose shirts or blouses that button at the front and bottoms that fit loosely. These are easier to get on and off.

Memorial Sloan Kettering Cancer Center

https://www.mskcc.org/cancer-care/patient-education/managing-related-fatigue

Address reversible causes (tentative recommendation)

- Overall, evidence is limited
- Some evidence that satisfactory analgesia improves fatigue in patients with severe pain
- Insufficient evidence to support addressing anemia with blood transfusion for fatigue management, in advanced cancer

Preston NJ, Hurlow A, Brine J, Bennett MI. Blood transfusions for anaemia in patients with advanced cancer. Cochrane Database Syst Rev. 2012 Feb 15;2012(2):CD009007. doi: 10.1002/14651858.CD009007.pub2. PMID: 22336857; PMCID: PMC7388847.

Exercise (moderate recommendation)

- Strong evidence for exercise for cancer-related fatigue during/after treatment in non-advanced disease, but results inconsistent or preliminary in advanced cancer
- 2020 meta-analysis in Journal of Pain and Symptom Management, including 15 RCTs, showed small improvement in fatigue with exercise compared to normal care (Standardized mean difference −0.25; 95% CI −0.45 to −0.04; $p = 0.02$).

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Peddle-McIntyre CJ, Singh F, Thomas R, Newton RU, Galvão DA, Cavalheri V. Exercise training for advanced lung cancer. Cochrane Database Syst Rev. 2019 Feb 11;2(2):CD012685. doi: 10.1002/14651858.CD012685.pub2. PMID: 30741408; PMCID: PMC6371641.

Exercise (moderate recommendation)

- What to recommend?
  - No specific exercise regimen recommended by guidelines
  - 2019 RCT in the Journal of Pain and Symptom Management, in women with metastatic breast cancer:
    - Primary outcomes: feasibility and safety of partially supervised exercise program
    - n=14; ECOG 0-2; 8 week home based exercise program, twice weekly resistance training, unsupervised walking program
    - Not powered to detect statistical significance, but improvements were seen in Functional Assessment of Chronic Illness Therapy: Fatigue Score, VO2 max, and 6 min walk test, with no adverse events
    - Adherence to the unsupervised walking portion was only 25%, supervised resistance training adherence 100%

Do not use psychostimulants (moderate recommendation)

- Lack of high-quality evidence to support use for fatigue in advanced cancer
- Cochrane review 2015 concluded insufficient evidence to recommend any specific drug treatment for fatigue in palliative care
  - Examined stimulants, corticosteroids, donepezil, SSRIs, acetylsalicylic acid, megestrol, alfacalcidol, acytyl-L-carnitine
  - Two methylphenidate RCTs were included in meta-analysis, showing slight superior effect of methylphenidate, but study authors concluded further study needed

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Mücke M; Mochamat, Cuhls H, Peuckmann-Post V, Minton O, Stone P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. Cochrane Database Syst Rev. 2015 May 30;2015(5):CD006788. doi: 10.1002/14651858.CD006788.pub3. PMID: 26026155; PMCID: PMC6483317.

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Methylphenidate

- Central nervous system stimulant, with dopaminergic effects on basal ganglia, and dopaminergic and noradrenergic effects on the cerebral cortex
- Peak plasma level at 1-2 hours, half life 2-7 hours

Methylphenidate

- Lack of high-quality evidence to support use for fatigue in advanced cancer. Many studies have small sample sizes and little power.
- Small 2020 double blind study (n=28) in Journal of Pain and Symptom Management; patients with advanced cancer, methylphenidate 10 mg PO TID PRN, significantly relieved fatigue after 2 and 5 hours
  - Mean decrease on VAS (0-100) after two and five hours was 20 and 17 for methylphenidate; 8 and 5 for placebo. Comparing mean differences, methylphenidate to placebo difference in 2 hours p=0.004; for five hours p=0.001
- 2020 RCT from Spain published in BMJ Supportive and Palliative Care found **methylphenidate to be no better than placebo for cancer related fatigue**
  - n=77; results using FACT-F and ESAS scales were congruent, difference between groups not statistically significant
  - This sample size was three times larger than average size in trials with similar characteristics in the last 6 years

Table 2 Response assessment: mean improvement in fatigue (ESAS) on day 6

	Placebo n=34	Methylphenidate n=43	P value
Mean	−1.9	−2.3	0.5
SD	(2.5)	(2.6)	
P value	<0.001	<0.001	

*ESAS (Edmonton Symptoms Assessment System) 10/10: the most intense fatigue.

Centeno C, *et al*. *BMJ Supportive & Palliative Care* 2020;**0**:1–9. doi:10.1136/bmjspcar

Figure 2 Evolution of mean fatigue (mean; ESAS). ESAS, Edmonton Symptoms Assessment System. ESAS 10/10: the most intense fatigue.

Pedersen L, Lund L, Petersen MA, Sjogren P, Groenvold M. Methylphenidate as Needed for Fatigue in Patients With A[illegible]dy. J Pain Symptom Manage. 2020 Nov;60(5):992-1002. doi: 10.1016/j.jpainsymman.2020.05.023. Epub 2020 May 26. PMID: 32[illegible]

Centeno C, Rojí R, Portela MA, De Santiago A, Cuervo MA, Ramos D, Gandara A, Salgado E, Gagnon B, Sanz A. Improve[illegible]o better than placebo. BMJ Support Palliat Care. 2020 Nov 9:bmjspcare-2020-002454. doi: 10.1136/bmjspcare-2020-002454. Epub ahead of print. PMID: 33168668.

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2. Psychological interventions	
3. Nutrition	
4. Sleep optimization	
5. Complementary therapies	

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Corticosteroids—practice recommendation of ‘don’t know’

VOLUME 31 · NUMBER 25 · SEPTEMBER 1 2013
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

- Mixed conclusions; limitations in data quality, studies mostly evaluate short term use
- Proposed mechanism in fatigue is that steroids would reduce fatigue via peripheral effects of proinflammatory cytokines
- Little evidence available regarding optimal dose and duration
  - Some studied regimens include dexamethasone 4 mg PO BID x14 days, methylprednisolone 32 mg PO daily x7 days

- 2013 RCT in Journal of Clinical Oncology is cited by guidelines, examining dexamethasone for cancer-related fatigue
  - n=84; primary outcome was change in FACIT-F at day 15, after 14 days of dexamethasone
  - Mean (± standard deviation) improvement in the FACIT-F subscale at day 15 was significantly higher in the dexamethasone than in the placebo group (9 [± 10.3] v 3.1 [±9.59]; P .008).
  - No significant adverse effects of dexamethasone compared to placebo at the 15 day mark

Yennurajalingam S, Frisbee-Hume S, Palmer JL, Delgado-Guay MO, Bull J, Phan AT, Tannir NM, Litton JK, Reddy A, Hui D, Dalal S, Massie L, Reddy SK, Bruera E. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. J Clin Oncol. 2013 Sep 1;31(25):3076-82. doi: 10.1200/JCO.2012.44.4661. Epub 2013 Jul 29. PMID: 23897970.

Corticosteroids—practice recommendation of ‘don’t know’

- 2015 pilot RCT in Journal of Palliative and Supportive Care examined methylprednisolone for cancer-related fatigue
  - n=35, multicenter RCT
  - No improvement in fatigue, appetite, or QOL with methylprednisolone
  - Authors called for larger study

- European Society for Medical Oncology 2020 and National Comprehensive Cancer Network 2021 guidelines: **can consider short term use; avoid long term use**

- Further study needed regarding whether there is benefit to routine or long-term use of corticosteroids

Eguchi K, Honda M, Kataoka T, Mukouyama T, Tsuneto S, Sakamoto J, Oba K, Saji S. Efficacy of corticosteroids for cancer-related fatigue: A pilot randomized placebo-controlled trial of advanced cancer patients. Palliat Support Care. 2015 Oct;13(5):1301-8. doi: 10.1017/S1478951514001254. Epub 2014 Nov 5. PMID: 25370595.

Complementary and Alternative Medicine—practice recommendation of ‘don’t know’

- Guidelines specifically recommend mindfulness, massage, and ginseng
- Very few studies recruited only patients with advanced cancer
- Lack of high-quality evidence

Ginseng

- Panax quinquefolius – American ginseng; Panax ginseng – Korean ginseng
- 2017 RCT published in the Journal of the National Comprehensive Cancer Network examined Panax ginseng on cancer-related fatigue
  - n=112; Panax ginseng 400 mg PO BID
  - **No difference in mean improvement between groups on FACIT-F subscale after 4 weeks**, though both placebo and ginseng group with significant improvement in fatigue.

- *2013 RCT in the Journal of the National Cancer Institute on American ginseng*
  - *Patients undergoing or completed cancer treatment* ***with curative intent***
  - *n=364 from 40 institutions, Wisconsin ginseng 1000 mg PO BID (AM and lunch) x8 weeks*
  - *Difference in fatigue score using Multidimensional Fatigue Symptom Inventory Short Form not statistically significantly different at 4 weeks, but* ***decreased at 8 weeks*** *[change score of 20 for the ginseng group (SD = 27), and 10.3 (SD = 26) for placebo group, p=0.003]*

Yennurajalingam S, Tannir NM, Williams JL, Lu Z, Hess KR, Frisbee-Hume S, House HL, Lim ZD, Lim KH, Lopez G, Reddy A, Azhar A, Wong A, Patel SM, Kuban DA, Kaseb AO, Cohen L, Bruera E. A Double-Blind, Randomized, Placebo-Controlled Trial of *Panax Ginseng* for Cancer-Related Fatigue in Patients With Advanced Cancer. J Natl Compr Canc Netw. 2017 Sep;15(9):1111-1120. doi: 10.6004/jnccn.2017.0149. PMID: 28874596.

Barton DL, Liu H, Dakhil SR, et al. Wisconsin Ginseng (Panax quinquefolius) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2. *J Natl Cancer Inst*. 2013;105(16):1230-1238. doi:10.1093/jnci/djt181

Acupuncture

Review > Support Care Cancer. 2018 Feb;26(2):415-425. doi: 10.1007/s00520-017-3955-6. Epub 2017 Nov 11.

Effects of acupuncture on cancer-related fatigue: a meta-analysis

Yan Zhang [1], Lu Lin [2], Huiling Li [2], Yan Hu [3], Li Tian [4]

- *2018 meta-analysis with 10 RCTs, n = 1327, published in Supportive Care Cancer*
  - *Only 4 studies reported cancer stage; **most patients stage I-III***
  - *Acupuncture regimens 20-30 minutes per session, 1-3x per week for 2-6 weeks*
  - *Studies used sham acupuncture or usual care as control intervention*
  - *Significant reduction in cancer-related fatigue scores with acupuncture (standard mean difference = negative 1.26; 95% CI (-1.80, -0.71), P < 0.01*

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Summary

- Evidence supports routine use of physical exercise and energy conservation, for fatigue in advanced cancer
- Psychostimulants should not routinely be prescribed for fatigue in advanced cancer
- Inconclusive data regarding corticosteroids for fatigue in advanced cancer
  - Can consider short-term corticosteroid use on an individualized basis, but no established optimal dose and duration

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