

**11th Guildford
Advanced Pain &
Symptom
Management
Course – Fatigue**

09:40-10:20am

5th/19th Sept 2023

Prof Paddy Stone

p.stone@ucl.ac.uk



My post and research department receive core funding from Marie Curie.

I also receive funding from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) fund.

- What is fatigue?
- What causes fatigue?
- How can fatigue be assessed?
- How can fatigue be treated?
- Guidelines?

- What is fatigue?
- What causes fatigue?
- How can fatigue be assessed?
- How can fatigue be treated?
- Guidelines?

A distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity, and significantly interferes with usual functioning

National Comprehensive Cancer Network (NCCN)

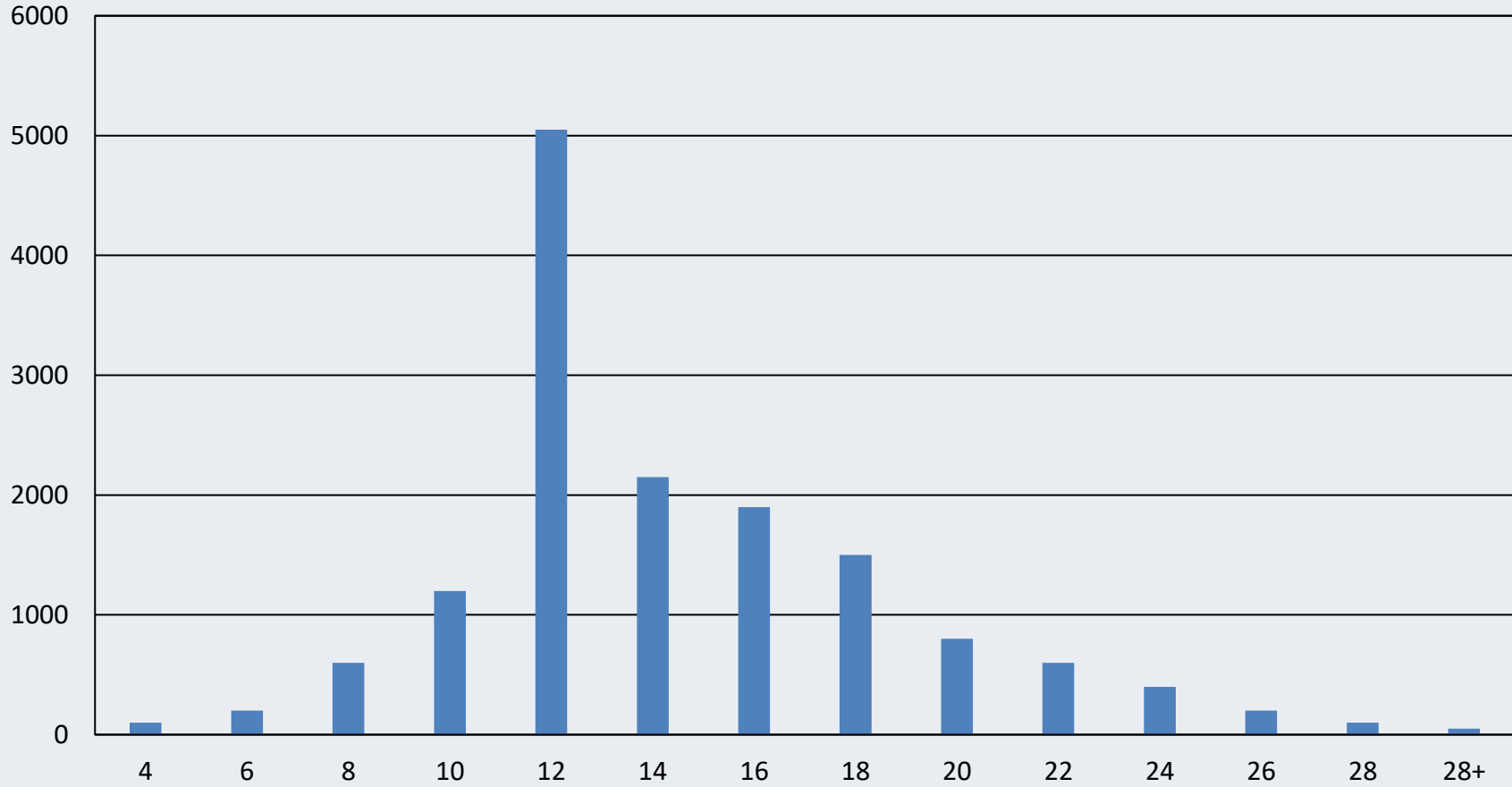
A subjective feeling of tiredness, weakness or lack of energy

European Association of Palliative Care

Prevalence of fatigue in the population



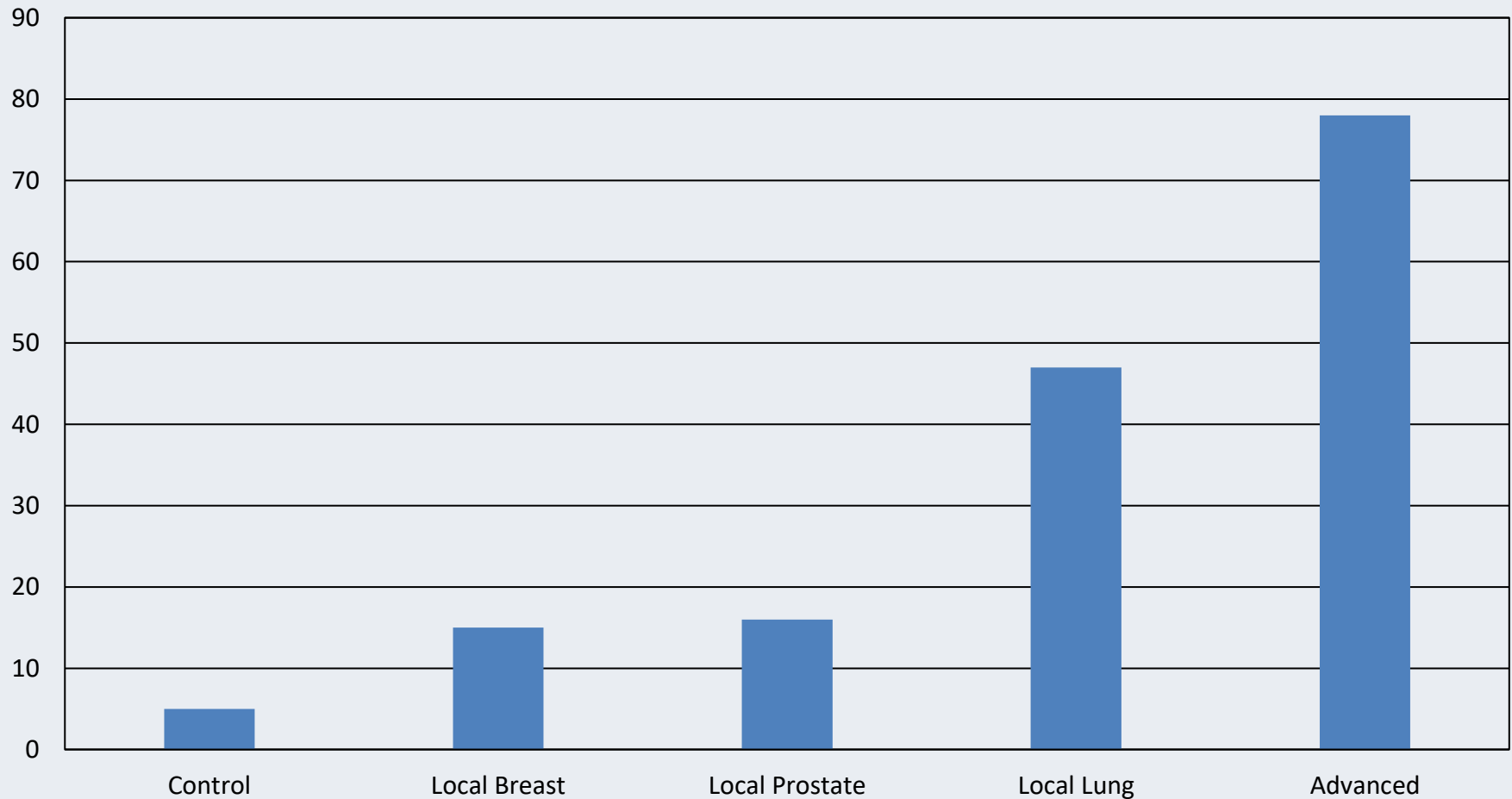
Chalder Fatigue Score



Pawlikowska T et al. BMJ 1994; 308; 763-6 *n* = 15283

Prevalence of severe fatigue

Prevalence of severe fatigue (%)



Stone et al Annals of Oncology, 2000. 11(5): 561-7

- Meta-analysis of 129 studies
- Prevalence = 49% (34,947 of 71,656 participants)

Maqbali et al. British
Journal of Nursing.
2021;30(4):S36-S43

Prevalence = 46.7%

Prevalence of cancer fatigue (advanced)

Prevalence = 60.6%

- Cancer-related fatigue: 49%
- Systolic heart failure: 50 - 96%
- COPD: 43 – 58%
- End-stage renal disease: 71%

- What is fatigue?
- What causes fatigue?
- How can fatigue be assessed?
- How can fatigue be treated?
- Guidelines?

Causes of fatigue in the general population?



- Depression
- Sleep disturbance
- Anxiety
- Stress
- Somatisation

- Psychological distress
- Deconditioning
- Anaemia
- Inflammation
- Metabolic disturbances
- Multiple symptomatology

Causes of fatigue specific to cancer?



- Bower et al. 2005 – no decrease in morning cortisol in patients with CRF (n = 13) compared to controls (n = 16)
- Alexander et al 2009 – no difference in 24-hr urinary free cortisol in patients with CRF (n = 60) compared to controls (n = 104)

Altered HPA-axis activity?



J Bower et al. Psychoneuroendocrinology (PNEC) 2005; 30: 92 - 100

Altered HPA-axis activity?



J Bower et al. Psychosomatic Med 2005; 67: 277 - 280

- What is fatigue?
- What causes fatigue?
- **How can fatigue be assessed?**
- How can fatigue be treated?
- Guidelines?

- Single items
- Uni-dimensional
- Multi-dimensional
- CRFS

- NCCN guidelines (<http://www.nccn.org>)
- How would you rate your fatigue on a scale of 0-10 over the past 7 days?
 - None to mild (0 – 3)
 - Moderate (4 – 6)
 - Severe (7 – 10)

- FACT-F*
- EORTC QLQc30
- Brief Fatigue Inventory
- FSS
- POMS

- Chalder Fatigue Scale* (mental and physical)
- EORTC QLQ-FA13 (physical, emotional and cognitive)
- Fatigue Symptom Inventory
- Lee Fatigue Scale
- Multi-dimensional assessment of Fatigue
- Multi-dimensional Fatigue Inventory
- Multi-dimensional Fatigue Symptom Inventory
- Revised Piper Fatigue Scale
- Schwartz cancer fatigue scale
- Wu cancer fatigue scale

Cella's diagnostic criteria for Cancer Related Fatigue Syndrome



A1	Significant fatigue
A2 – A11	5 other associated symptoms
B	Fatigue impact
C	Due to cancer or cancer treatment
D	Not due to co-morbid psychopathology

- What is fatigue?
- What causes fatigue?
- How can fatigue be assessed?
- How can fatigue be treated?
- Guidelines?

- What is fatigue?
- What causes fatigue?
- How can fatigue be assessed?
- How can fatigue be treated?
 - Exercise
- Guidelines?

- 72 RCTS; 5367 participants
- Exercise had a moderate effect (SMD -0.45; 95% CI -0.57 to -0.32; n = 56 studies; P = 0.001) on reducing fatigue compared with control interventions
- Type of exercise did not significantly influence the effect

- Systematic review and meta-analysis
- 22 included studies (13 low and 9 high quality)
- Duration 2 weeks to 6 months
- Exercise types
 - Aerobic (n = 3), resistance (n = 4), mixed-mode (n = 14) and other (n = 1)
- Cancer types
 - lung (n = 6), breast (n = 3), prostate (n = 2), multiple myeloma (n = 1) and mixed (n = 10)

Adverse effects in advanced cancer



Navigante et al BMJ SPC . doi:10.1136/
bmjcare-2021-003516

Advanced GI cancer (n=64); post chemo; with weight loss

PDPE = Programmed and directed physical exercise
Weekly sessions over 12-weeks

Significant improvement in fatigue ($p < 0.001$)

- RCT
- N = 279 (60% with advanced cancer)
- Four-week tablet based multi-media education programme with focus on exercise as a therapy (or usual care)
- Significantly lower fatigue intensity ($p=0.02$)

Yoga – breast cancer patients



Walking – all cancer patients



Wang et al. Cancer Nursing 2021, 45(1):E270-278

12 studies

1064 patients

- Good evidence of effectiveness in patients across the disease spectrum
 - Early disease
 - On treatment
 - Palliative Care
- Evidence of safety even in advanced disease
 - But need to consider practicalities of exercise in advanced cancer groups
 - Yoga
 - Walking

- What is fatigue?
- What causes fatigue?
- How can fatigue be assessed?
- How can fatigue be treated?
 - Exercise
 - Psycho-educational treatment
- Guidelines?

- 14 RCTs (n = 2213)
- Not restricted to palliative cancer care
- Information-giving ± problem-solving, reinforcement, or support

- Systematic review
- 33 trials (n=4525)
- 11 interventions reported a significant effect on fatigue, compared to wait-list control or usual care
 - 5/5 CBT studies reported benefit
 - 4/6 Mindfulness studies reported benefit
- Heterogeneous and poor quality

- Systematic review
- 14 studies; 3077 participants
- Restricted to patients with incurable cancer receiving cancer treatment with palliative intent
- Findings do not support the effectiveness of psychosocial interventions for reducing fatigue (SMD -0.25; 95% CI - 0.50 to 0.00; not significant; 535 participants; 12 studies; very low-quality evidence)
- No benefit immediately post-intervention, benefit at first follow-up but not maintained at second follow-up

Psychological interventions - metastatic breast cancer



- Systematic review
- 15 RCTs (n=1638)
- Improved
 - Distress (8/13 trials)
 - Coping (4/5 trials)
 - Pain (4/5 trials)
- Fatigue
 - Group therapy trials (1/5 showed benefit)
 - Individual therapy trials (0/1 showed benefit)
 - Low intensity trials (0/2 showed benefit)

- RCT
- 12 weeks CBT; GET; or TAU
- N=134
- Compared to TAU
 - CBT significantly reduced fatigue
 - 10 individual 1-hour sessions
 - GET did not
 - Weekly individual 2-hour sessions

- Weak to moderate evidence of benefit for information provision
- Some evidence of effectiveness for psychological approaches in patients on treatment and in survivors
- Less evidence of effectiveness in advanced cancer patients

- What is fatigue?
- What causes fatigue?
- How can fatigue be assessed?
- How can fatigue be treated?
 - Exercise
 - Psycho-educational treatments
 - Pharmacological treatment
- Guidelines?

Placebo response



Yennurajalingham S,
et al. *The Oncologist*,
2022; 27: 1081–1089
<https://doi.org/10.1093/oncolo/oyac184>

Psycho-stimulants - systematic review of systematic reviews



Methylphenidate - systematic review of systematic reviews



Belloni et al Crit Review Oncol Haematol 2021

Methylphenidate adverse effects - systematic review of systematic reviews



- Methylphenidate versus placebo for fatigue in advanced cancer
- Individually tailored dose
- Titrated over six weeks
- Administered for further two weeks then tapered
- Recruitment finished April 2023
- Revised recruitment target met (n=162)
- Results due in October 2023

- **Jean-Pierre 2010**
- N=877 mixed solid tumours on chemotherapy
- Beneficial effect only seen in severe fatigue (based on a 0-10 scale) 8-10 only
- **Spathis 2014**
- N = 207 NSCLC off treatment
- No benefits in any subgroup

Jean-Pierre et al. Cancer 2010;116:3513–20

Spathis et al JCO 2014

- Placebo-controlled
- N = 364
- Primary outcome; fatigue at 4 weeks
- Panax quinquefolius 2000mgs

Ginseng – all patients



Ginseng – during and after treatment



- Panax ginseng 400mgs bd versus placebo
- Four weeks
- Advanced cancer
- N = 112

Ginseng in advanced cancer



High heterogeneity; high risk of bias
10 open label studies
2 double-blind placebo-controlled trials

- Double blind, placebo controlled, crossover
- N = 31 “advanced cancer”
- Oral methylprednisolone 32mg/day
- After 5 days:
 - Improved “activity levels” in 61% of patients on MP vs 16% of patients on placebo ($p < 0.01$)

- Double blind, placebo controlled RCT
- N = 403 “advanced” cancer
- I.V. Methylprednisolone 125mg/day
- Over 8 week study period:
 - No improvement in “weakness”
- Higher mortality rate in female patients receiving placebo

- Double blind, placebo controlled, RCT
- N = 173 women with “advanced” cancer
- I.V. Methylprednisolone 125mg/day
- For first two weeks:
 - Significant improvement in “weakness”
- Improvement not maintained
- No excess mortality in treatment group

- Double-blind placebo-controlled RCT
- Dexamethasone 4mgs bd vs placebo
- N=84
- Significant improvement in fatigue and QoL at 15 days

- Weak to moderate evidence
 - Dexamethasone (advanced cancer)
 - Ginseng (patients on treatment)
 - Methylphenidate (ongoing trials)
 - Modafanil (severe fatigue)
 - Open-label placebo (selected patients)
 - Mistletoe (only at Christmas)

- What is fatigue?
- What causes fatigue?
- How can fatigue be assessed?
- How can fatigue be treated?
- **Guidelines?**

- <https://www.nccn.org/guidelines>
- Freely available
- Consensus statement
 - First published 2000, revised annually
- Evidence-based when possible

- Prevalence and impact
- Psychological therapies
- Exercise
- Pharmacological therapies
- **Conclusions**

- Fatigue is common and adversely affects QoL
- Ask about (and measure) it
- Treat treatable causes
- Consider other management approaches
 - Education
 - Exercise (including walking and yoga)
 - Dexamethasone (short-term; advanced cancer)
 - Ginseng
 - Psychological therapies
 - Methylphenidate
 - Modafanil
 - Open-label placebo