Cambridge University Hospitals NHS
NHS Foundation Trust

Fatigue in the teenage and young adult population

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Overview

1. Why is this important?
2. Why does it happen?
3. What can we do about it?

1. Why is this important?

Fatigue is a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness ... that is not proportional to recent activity and interferes with usual functioning *(NCCN 2013)*

It's a horrible feeling you don't belong anymore... Life goes on without me.

...just getting through each day... I did not have the physical or emotional energy to give to anyone else... a very humbling and isolating experience

I feel like someone let the plug out

I am just not myself

Why can't I be me again?

Like wet cement

Cancer-related fatigue in adults

1. Most prevalent
2. Most negative effect on quality of life
3. Most neglected symptom
   - Considered inevitable and unavoidable
   - Under-reported by patients
   - Under-researched by HCP

Increasing consensus that fatigue is "the most important untreated symptom in cancer today"

Curt 2001

Cancer-related fatigue in adults

Fatigue in non-malignant disease in adults

Cancer-related fatigue in teenagers and young adults

Cancer-related fatigue in children

Fatigue in non-malignant disease in teenagers, young adults and children

"Teenage and young adult cancer-related fatigue is prevalent, distressing and neglected: it is time to intervene."
A systematic literature review and narrative synthesis.

UNIVERSITY OF CAMBRIDGE

Anna Spathis,[1] Sara Booth,[2] Sarah Grove,[1] Helen Hatcher,[1] Isla Kuhn,[2] Stephen Barclay[2]

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Search strategy

#1. exp fatigue/
#2. fatigue* or tire* or exhaust* or lethargy* (title or abstract)
#3. exp neoplasm/
#4. neoplasm* or cancer* or carcinoma* or lymphoma* or leukaemia* or leukemia* (title or abstract)
#5. 1 or 2
#6. 3 or 4
#7. 5 and 6
#8. limit 7 to adolescent
#9. tya* or teenage* or "young adult"* (title or abstract)
#10. 7 and 9
#11. 8 or 10

PRISMA flow chart

Data base searches	Other searches
Titles n=2388	
Abstracts n=566	
Papers n=343	
Included papers n=55	Included papers n=5
Total included papers n=60	

Results

- Of 60 selected papers, 36 were cross-sectional/observational, and 24 longitudinal. 57 were poor/medium quality. Fatigue was the focus of only 18 of the 60 studies.
- Fatigue prevalence was 7-100% during treatment and 8-67% after treatment. On 17 out of 20 occasions it was the first or second most prevalent symptom.
- Distress was the most commonly described impact of fatigue; in 3 of the 8 studies comparing fatigue with other symptoms, it was the most distressing symptom. Being a barrier to exercise and to other social activities were the next two commonest impacts.
- Poor sleep, receiving chemotherapy, low mood and distress/anxiety were the main correlates with CRF. No studies examined the experience of parents.
- Of the 5 interventional clinical trials, 2 uncontrolled studies found benefit from intensive gym exercise, and 3 (of which 2 evaluated inpatient exercise) were negative.

Conclusions

- Fatigue is one of the most prevalent and distressing symptoms experienced by teenage and young adult cancer patients.
- Despite this, there is very limited research evaluating interventions for TYA CRF.

Most prevalent **Most distressing** **Even more neglected...**

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"Eight studies compared fatigue severity between younger children and teenagers treated for cancer.... In all but one study, fatigue was reported as being more severe in adolescents than in younger children."

Comparison of fatigue descriptions (Hinds 1999)

Age 7-12	• Weak or tired • Difficulty with movement • Hard to play, concentrate • Anger and sadness • Made worse by being active
Age 13-18	• Complex, changing • Physical and mental components • Loss of usual involvement with friends, academics, sports • Anger, prefer ‘not to be bothered’ • Made worse by doing to much, being bored, having fears

"I can't walk straight and my balance is dreadful."

"It's like a giant hoover has come down out of the sky and sucked out all my energy."

"My energy is used up so quickly, even on simple tasks like sitting up, or getting dressed."

"On bad days it can be hard work just lifting a spoon to your mouth."

"Words come out all wrong and you forget what you're saying in the middle of a sentence."

"I can't concentrate on any kind of reading, writing, or watching television for more than ten minutes."

"My legs ache continuously; the muscles twitch and jump. I start off walking quite well but soon my legs grow heavier until they can't straighten under my weight."

"All my senses are hypersensitive. And noise is painful and bright lights hurt my eyes."

"I sleep all day and am awake all night. I try to sleep, but the inside of my head just goes round and round."

"Even on the hottest day I feel cold, especially my hands and feet. They tingle and sometimes I can't feel my fingers."

Acknowledgement: Helen Hatcher

‘Neurasthenia [nervous exhaustion] has been the central Africa of medicine – an unexplored territory into which few may enter and those few have been compelled to bring back reports that have been neither credited or comprehended’

Beard, 1880

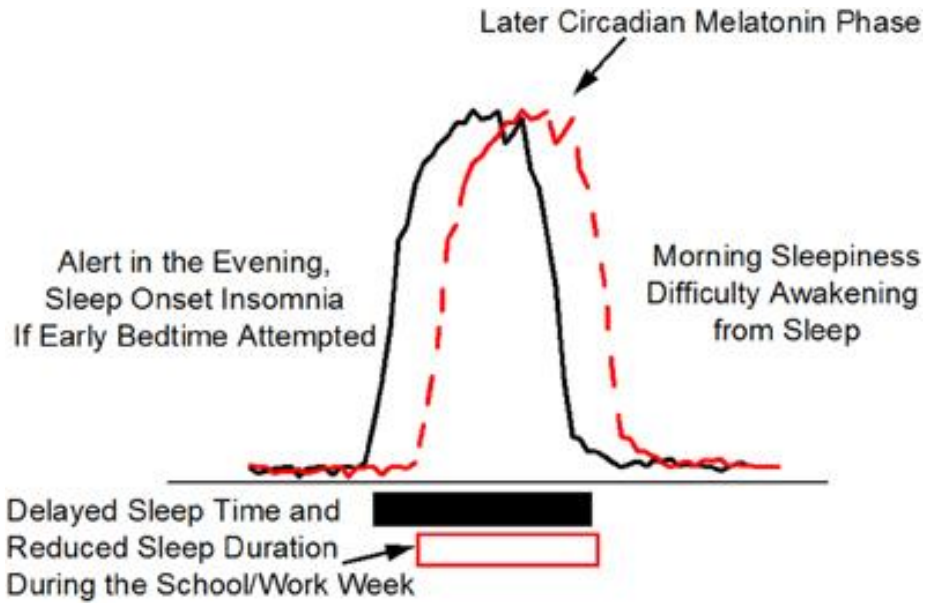
Developmental needs of adolescence

- Autonomy
- Independence and responsibility
- Development of peer relationships
- Self-definition
- Education, work, personal vision
- Competency and achievement
- Physical activity

Fatigue has the potential for a long-term adverse impact at this formative stage of life

2. Why does it happen?

Biological and behavioural sleep deprivation



Symptom clusters

Life-limiting condition

Fatigue

Breathless

Depression

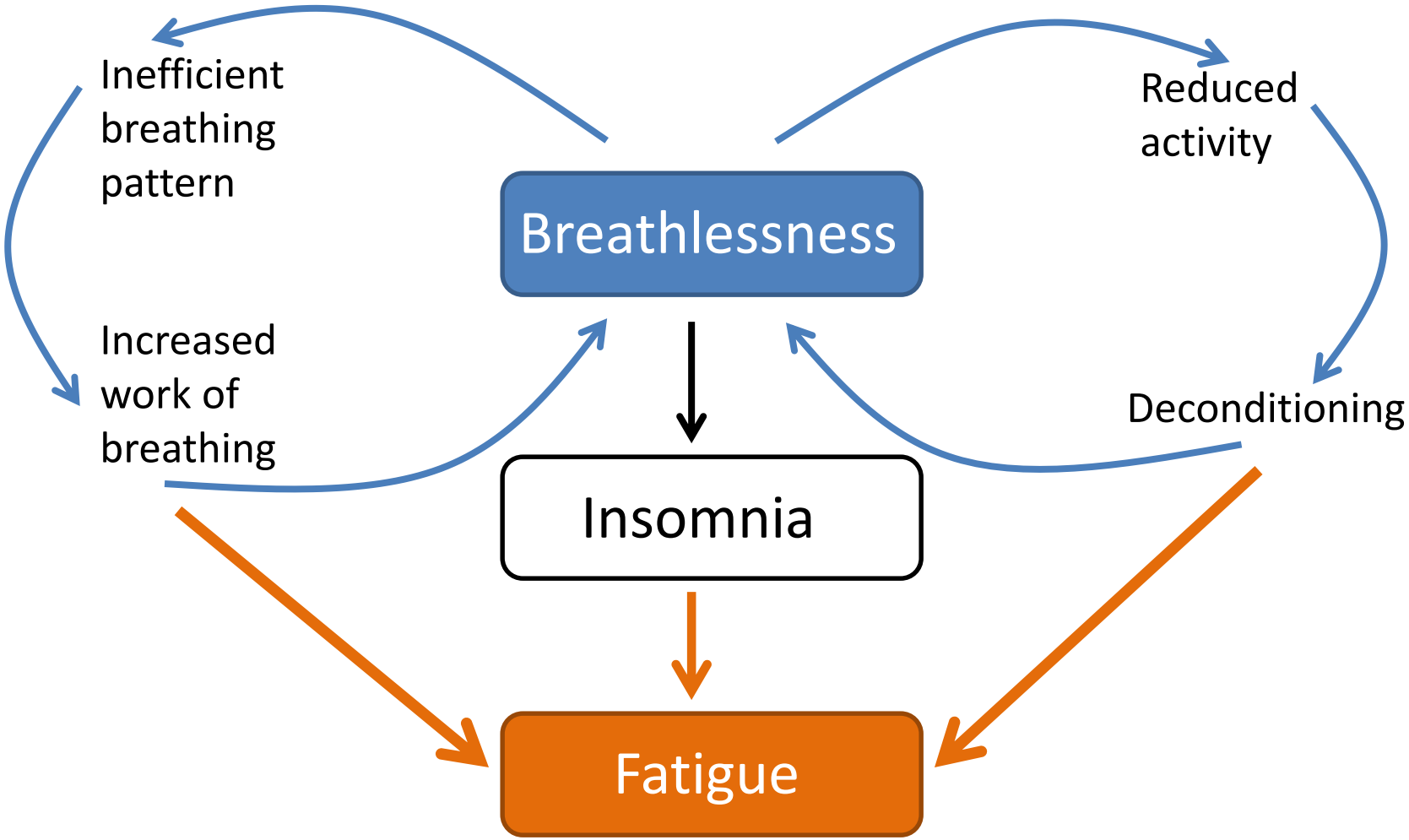
Insomnia

Pain

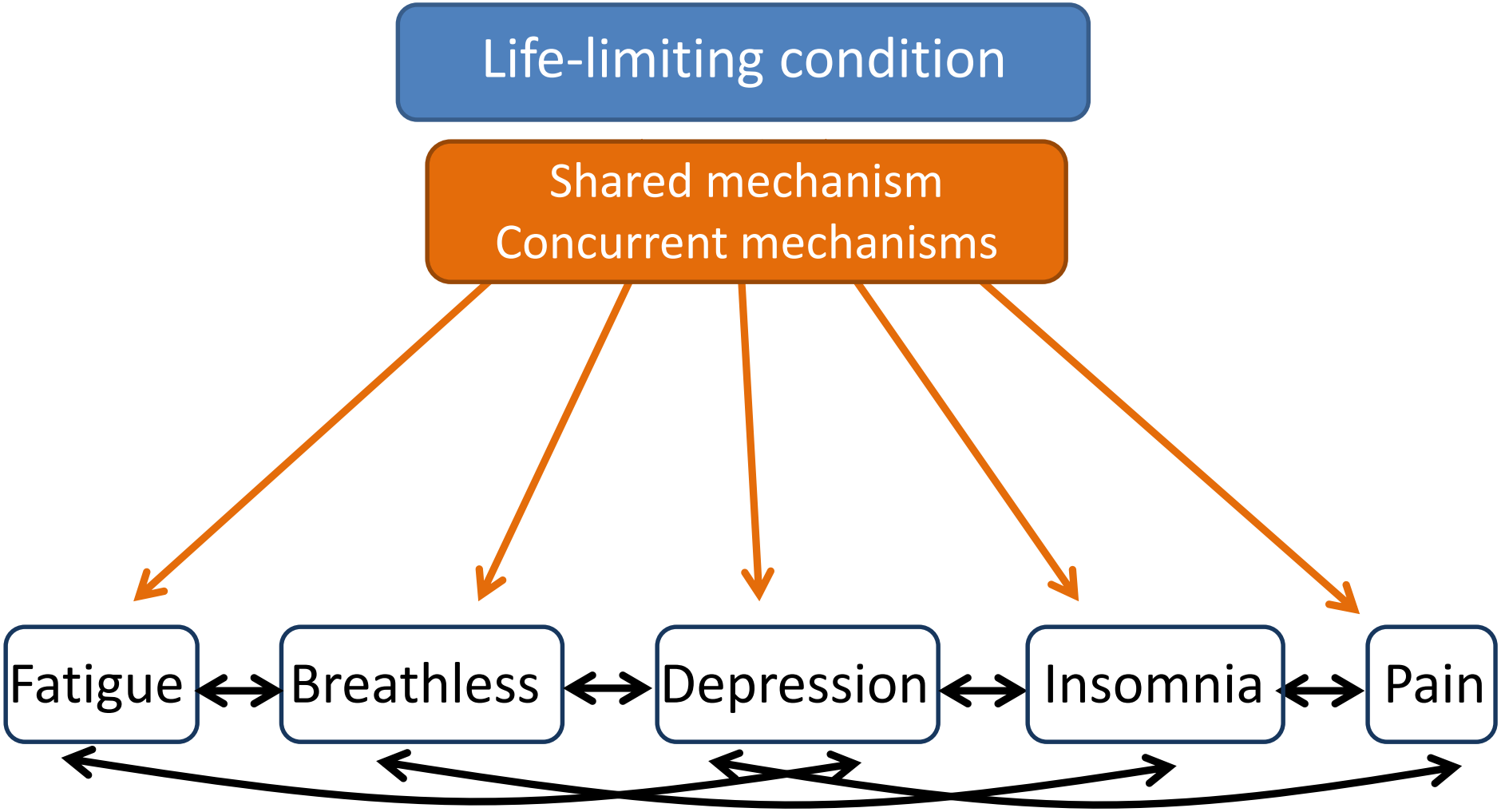
Symptom clusters

Life-limiting condition

Symptom interaction



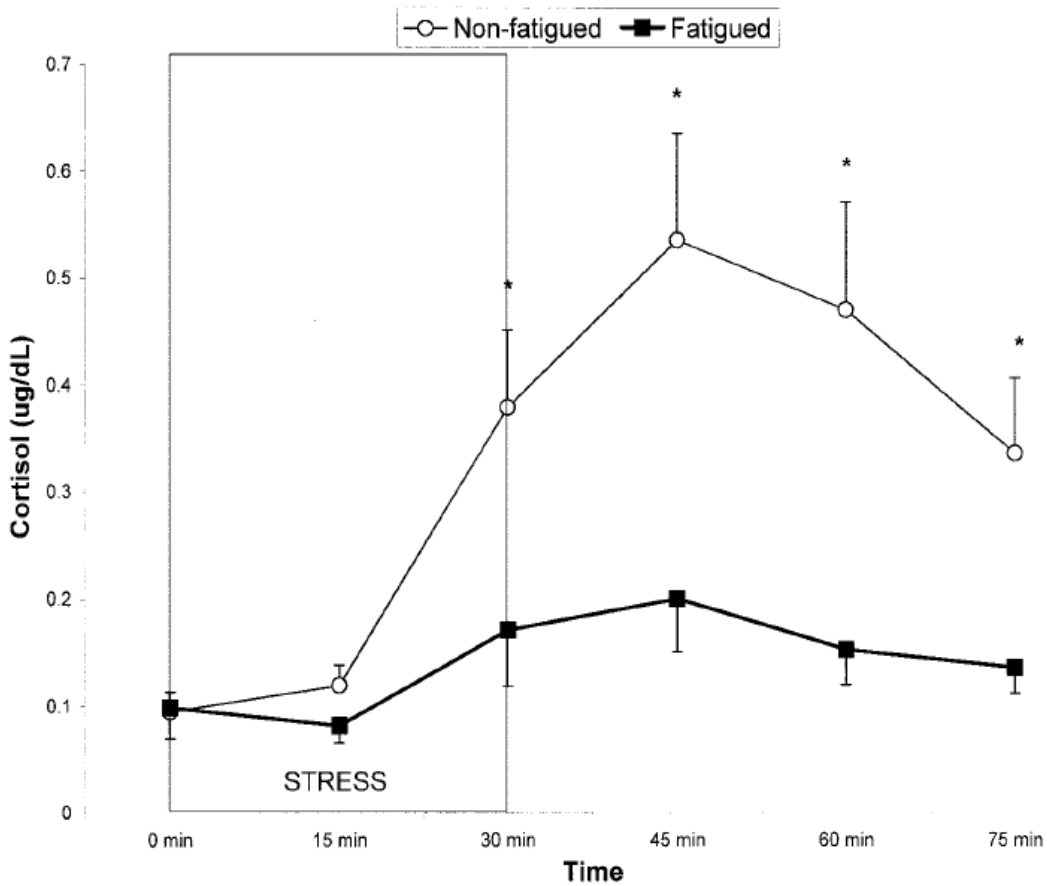
Symptom clusters



Potential mechanisms

- Proinflammatory cytokines
  - Correlation fatigue and inflammatory markers
- HPA axis dysfunction
  - Flattened cortisol slope fatigued breast cancer
- Circadian rhythm disruption
  - Less regular rhythm correlates with fatigue
- Serotonin dysregulation
  - Increased central 5HT in exercise-induced fatigue; also with TNFα
- Muscle metabolism dysregulation
  - ATP infusion improves fatigue; TNFα increases proteolysis

Ryan et al, The Oncologist 2007



Bower et al, Psychosomatic Medicine 2005

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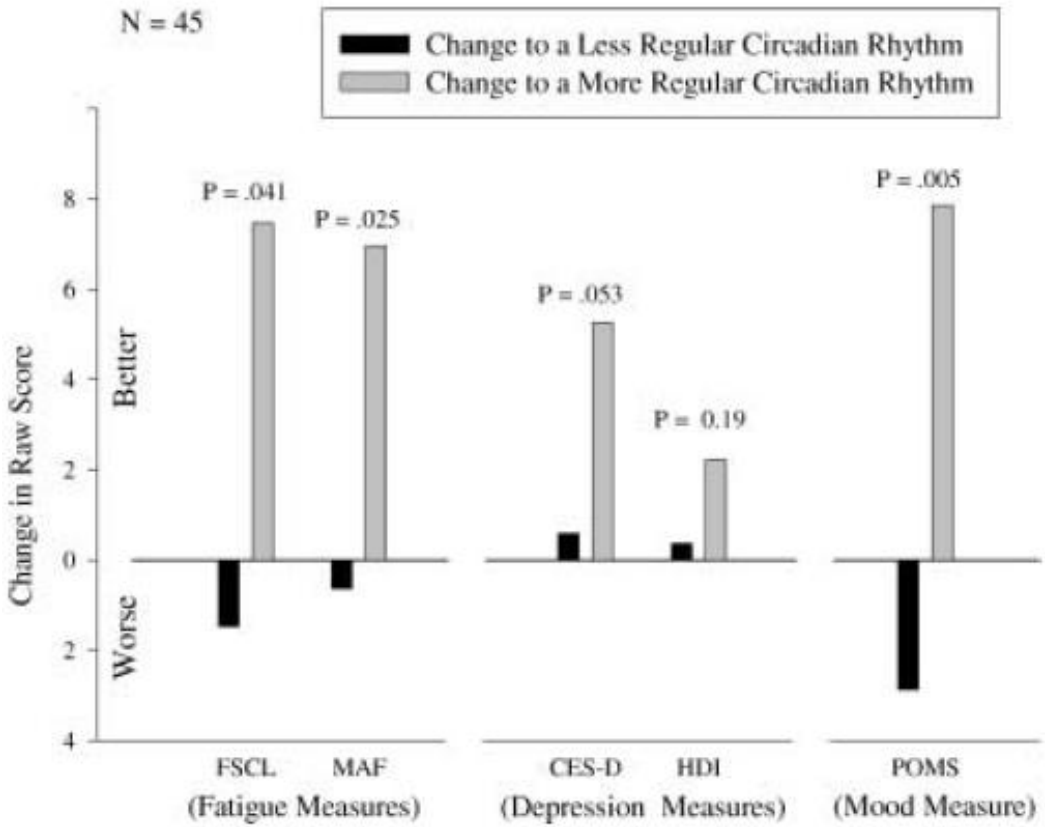

Roscoe et al, Support Care Cancer 2002

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Ryan et al, The Oncologist 2007

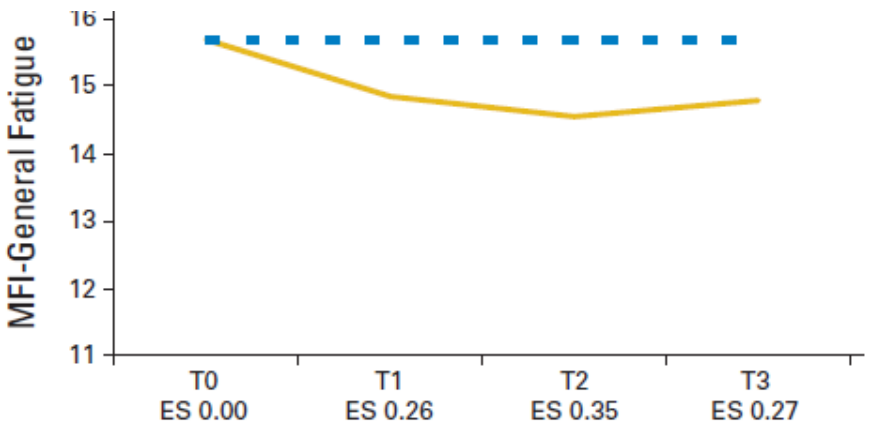
3. What can we do about it?

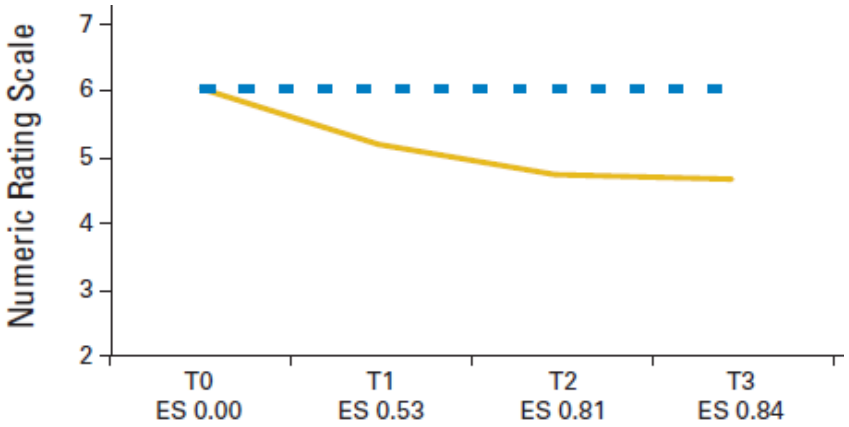
- Evidence from the adult literature
- Evidence from the TYA cancer literature
- Management in practice

Treat concurrent symptoms

De Raaf et al, J Clin Oncol 2013

- 152 fatigued patients advanced cancer
- Randomised to protocolized symptom control vs. usual care
- Significant improvements in fatigue at 2 months (p=0.005, effect size 0.35)





Drug treatment: meta-analysis

Drug	Std. mean difference	95% CI
Psychostimulants	-0.28	-0.48, -0.09
Erythropoetin	-0.28	-0.39, -0.17
Antidepressants	-0.08	-0.24, 0.07
Progestational steroids	-0.49	-1.74, 0.75

- Psychostimulants
  - FACT-F mean improvement of 2.21
- Erythropoetin
  - No longer recommended because safety concerns

Minton et al, Cochrane Database SR 2010

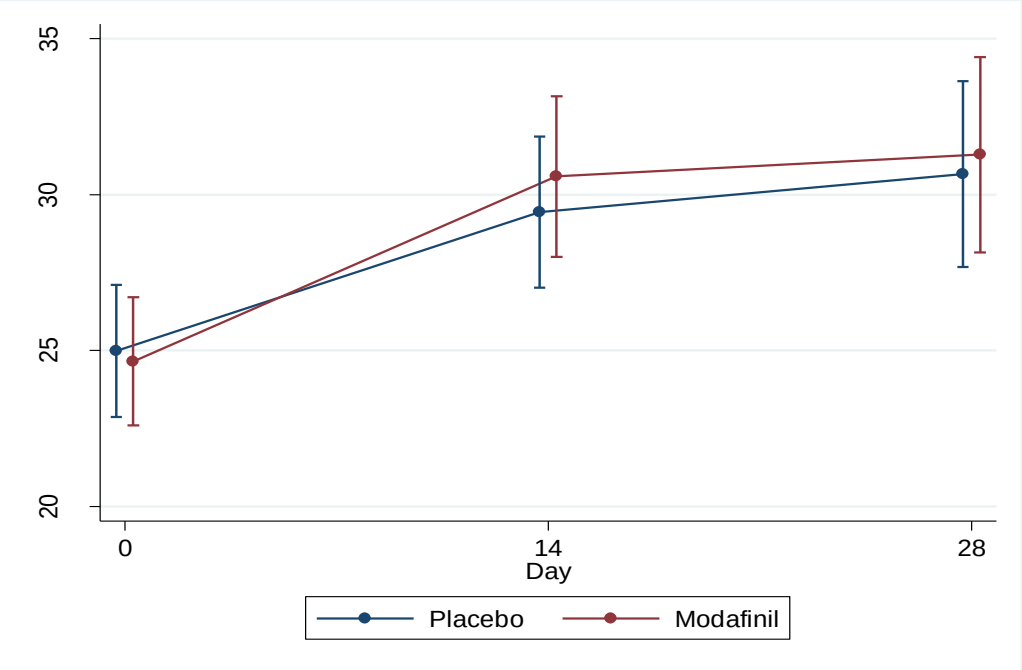
Drug treatment: psychostimulants

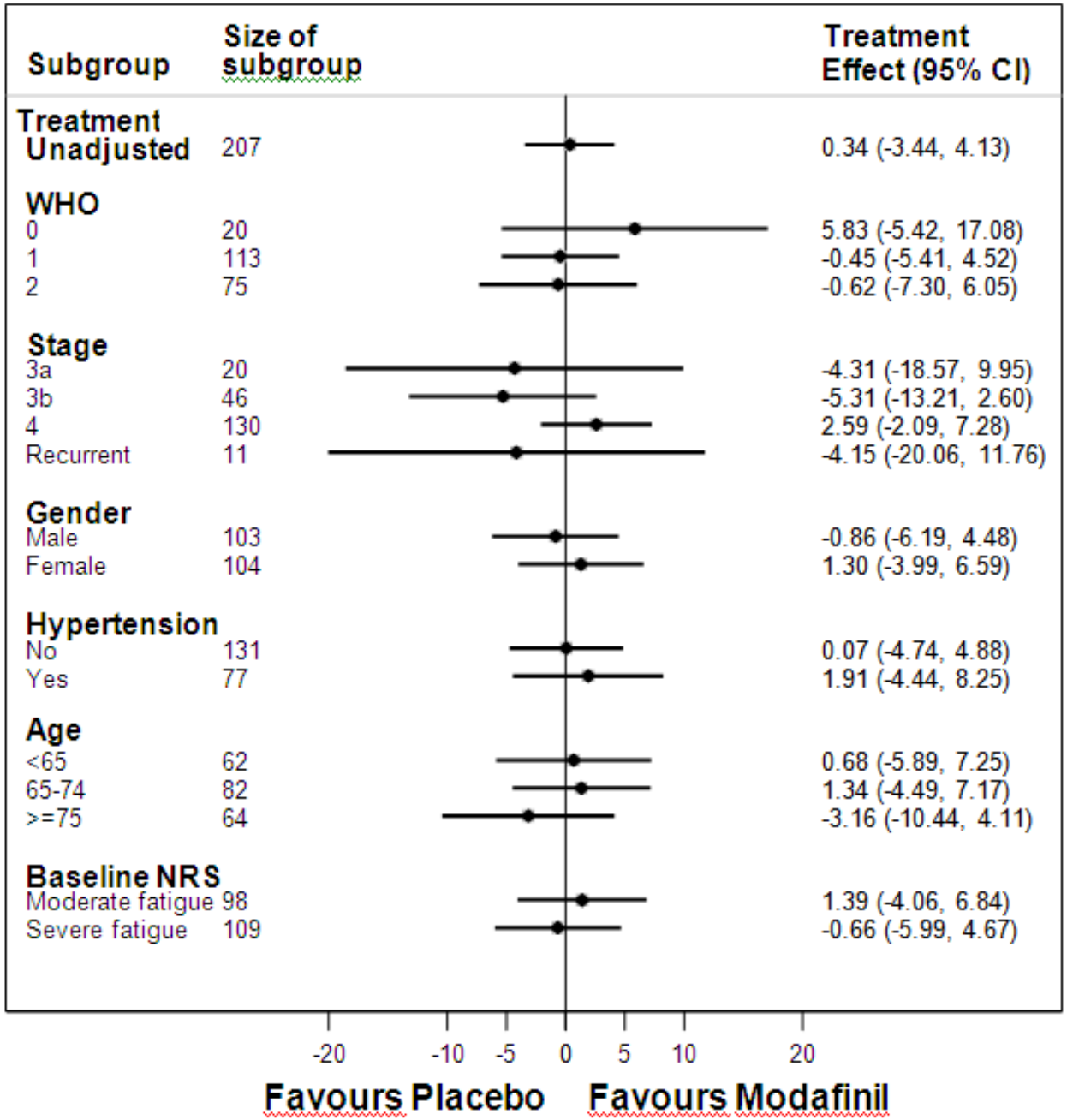
Jean-Pierre et al, Cancer 2010

- Marginal benefit subgroup with severe fatigue (0.4 in 10 point NRS)

Spathis et al, Journal of Clinical Oncology 2014

- Clinically significant placebo effect




Subgroup
Size of subgroup
Treatment Effect (95% CI)
Treatment
Unadjusted 207 0.34 (-3.44, 4.13)
WHO
0 20 5.83 (-5.42, 17.08)
1 113 -0.45 (-5.41, 4.52)
2 75 -0.62 (-7.30, 6.05)
Stage
3a 20 -4.31 (-18.57, 9.95)
3b 46 -5.31 (-13.21, 2.60)
4 130 2.59 (-2.09, 7.28)
Recurrent 11 -4.15 (-20.06, 11.76)
Gender
Male 103 -0.86 (-6.19, 4.48)
Female 104 1.30 (-3.99, 6.59)
Hypertension
No 131 0.07 (-4.74, 4.88)
Yes 77 1.91 (-4.44, 8.25)
Age
<65 62 0.68 (-5.89, 7.25)
65-74 82 1.34 (-4.49, 7.17)
>=75 64 -3.16 (-10.44, 4.11)
Baseline NRS
Moderate fatigue 98 1.39 (-4.06, 6.84)
Severe fatigue 109 -0.66 (-5.99, 4.67)
-20
-10
-5
0
5
10
20
Favours Placebo
Favours Modafinil

Drug treatment: steroids

Yennurajalingham et al, Journal of Clinical Oncology 2013

Dexamethasone for two weeks in adult cancer patients improves fatigue and quality of life (RCT)

BUT

Hinds et al, Cancer 2007

Dexamethasone increases fatigue and sleep disturbance in children and adolescents during continuation therapy for ALL (cross-over trial)

BMJ

BMJ 2013;347:f7141 doi: 10.1136/bmj.f7141 (Published 4 December 2013)

Choosing Wisely®

An initiative of the ABIM Foundation

EDITORIALS

Too Much Medicine: from evidence to action

Abstract submission open for 2014 Preventing Overdiagnosis conference

Ray Moynihan *senior research fellow*[1], Carl Heneghan *professor of evidence based medicine*[2], Fiona Godlee *editor in chief*[3]

TOO MUCH MEDICINE

In the past few years the individuals and groups calling for moderation and scepticism have begun to coalesce into a loose movement, to which the *BMJ* is now signing up. Impressed by the "Less is more" initiative at *JAMA Internal Medicine*, led by its editor Rita Redberg, and by the Choosing Wisely initiative set up by the American Board of Internal Medicine Foundation (doi:10.1136/bmj.f1266), we want to explore the causes and potential remedies of overinvestigation, overdiagnosis, and overtreatment.


Physical deconditioning
'I must be very ill'
'I am harming myself by doing things'
Functioning
Thinking
Fatigue
Reduced activity
More help from others
Fear, distress
Sleeping
'I can't get to sleep'
'I need to rest and sleep more'
Poor sleep hygiene

Non-drug treatments

1) Exercise

- *Cramp et al, Cochrane Database SR 2010*
  - 28 studies, 2083 participants (1172 breast cancer)
  - Exercise effective, SMD -0.23, 95% CI -0.33, -0.13

2) Psychosocial interventions

- *Geodendrop et al, Cochrane Database SR 2009*
  - During treatment: education, energy conservation
  - 4 of 5 fatigue focused studies positive (but only 3 of other 22)
- *Gielissen et al, J Clin Onc 2006, Br J Cancer 2007*
  - CBT improves fatigue in cancer survivors
  - Benefits maintained long term

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Study	N	Design	Intervention	Outcomes
Atkinson 2012	55	Uncontrolled	Structured exercise in gym, 2-3/week over 10 weeks	Improved fatigue and QOL
Hinds, 2000	78	RCT	Education to facilitate self-care	No benefit
Hinds, 2007	11	Pilot RCT	Structured exercise in hospital room, 30 mins twice daily for 2-4 days	No benefit
Keats, 2008	10	Uncontrolled feasibility	Structured exercise in gym, 90 mins/week 8 weeks, other activities 16 weeks	Improvement of fatigue, but not sustained
Rosenhagen 2011	13	Uncontrolled feasibility	Structured exercise in hospital room (stem cell transplant)	No benefit

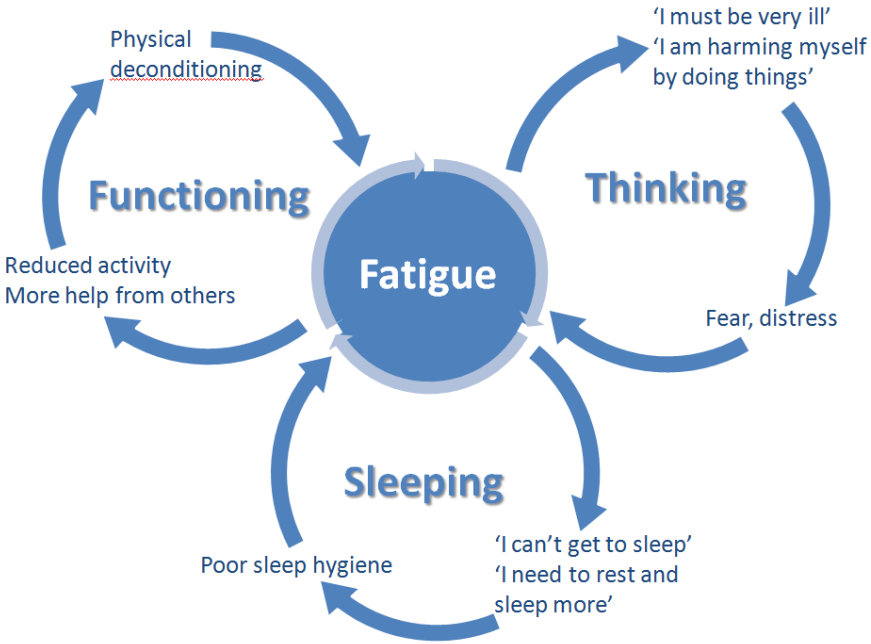
Management in practice

Precipitating factors

- Change the changeable eg anaemia, dexamethasone
- Manage concurrent symptoms eg pain, sleep disturbance

Perpetuating factors

- Education
- Exercise
- Energy conservation



Education about sleep hygiene

Improve the sleep environment

- Quiet, dark, 18°C bedroom
- Avoid light producing electronic devices
- Avoid using bedroom for activities unrelated to sleeping

Improve sleep-wake patterns

- Avoid naps (unless short and after lunch)
- Daylight and exercise in afternoon
- Hot bath ideally one hour before sleep
- Regular, relaxing pre-sleep routine
- Light snack or milky drink
- Relatively fixed bedtime and waking time

Optimise drug intake

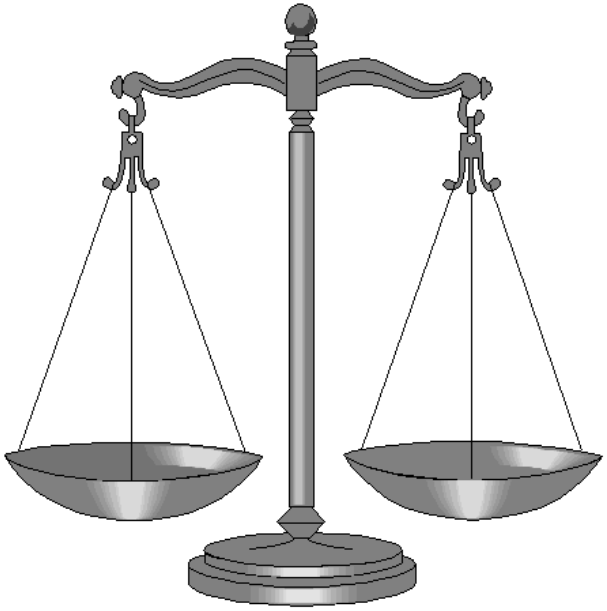
- Avoid caffeine and alcohol

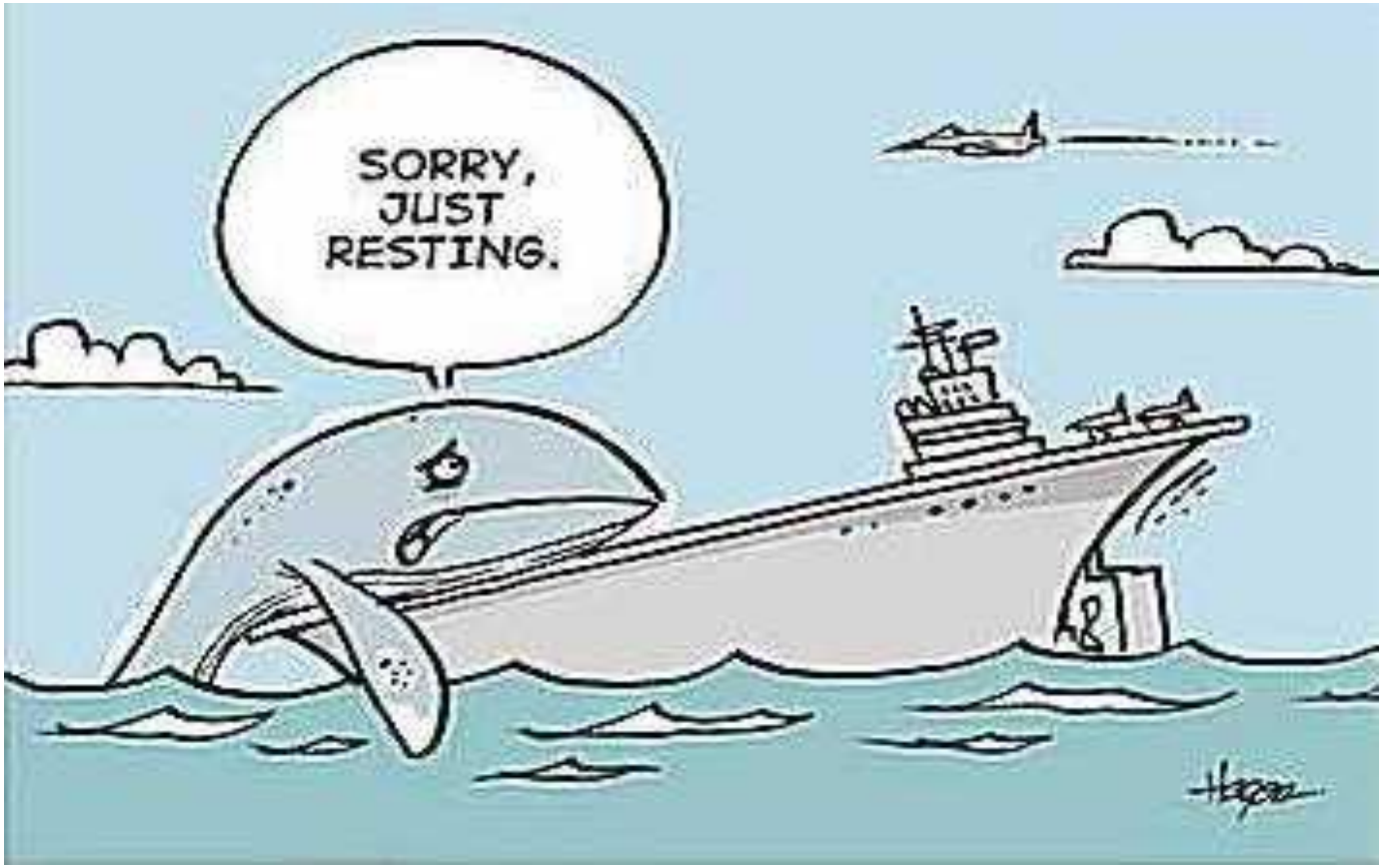
Exercise

- ‘Activity’ rather than ‘exercise’
- Understanding deconditioning vicious cycle
- Moderate activity helpful longer term, not harmful
- Weekly step-wise changes, 10%-20% each week
- Motivated by personally meaningful goal
- Consider activity diary, walking programme, pedometer

Energy conservation

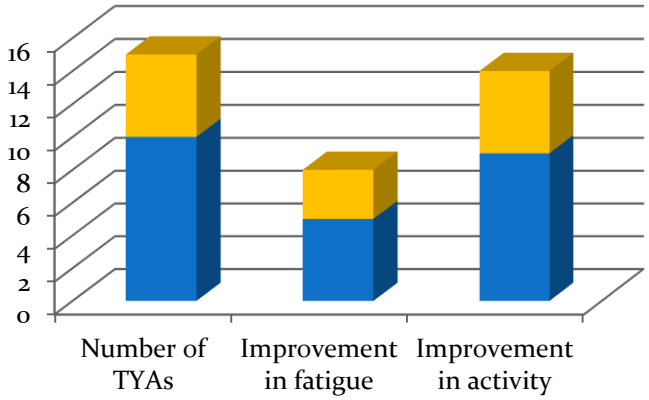
- Principles
  - Balance between activity and rest
  - Avoiding ‘all or nothing’
  - Models of energy
- Practice
  - Planning
  - Prioritising
  - Pacing




SORRY, JUST RESTING.

Clinical priorities

- Raise the profile of fatigue: ask proactively
- Include parents and/or peers
- Multidisciplinary approach, including AHPs
- Consider running fatigue workshops or groups
  - Dr Helen Hatcher, TYA service lead, Cambridge
  - Fatigue workshops with 15 young people and their carers
  - 66% carers underestimated fatigue severity



Research priorities

What is the prevalence and impact of fatigue?

- In non-malignant conditions
- In younger children

What is the experience of family and peers?

- Appreciation of fatigue severity
- Approach to fatigue, helpful or unhelpful

How effective are interventions, including length of impact?

- Non-pharmacological approaches
- Health coaching and behaviour change models

Research priorities

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Key points

- Fatigue is the most prevalent, distressing and neglected symptom in adults and TYAs with cancer.
- It can cause long-term adverse consequences; addressing maladaptive perpetuating factors can give long-term benefit.
- Fatigue is a barrier to activity, the intervention most likely to help; parent's well-meaning efforts to help can compound the problem.
- Research is needed, particularly evaluating non-cancer conditions, the experience of carers and non-drug interventions.

Ellie

- 26 year old, AML, GVHD, recurrent chest infections
- Dyspnoea, exercise tolerance 10 metres

- Key intervention with carer
- Free golf lessons

- After one year, regular golf
- After three years, ran marathon

Any questions?

Key references (1)

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