Addressing Fatigue, Sleep, and Cognitive Functioning As Part of Survivorship Care

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National Cancer Policy Forum
July 24, 2017

Scope of the Problem

Cancer-related symptom burden is substantial

- 27% of off-therapy patients have ≥ 3 moderate to severe symptoms[1]
- Most common symptoms: fatigue (27%) and disturbed sleep (22%)[1]

Poorly controlled symptoms contribute to:

- Poor quality of life including impaired physical and social functioning[2]
- Nonadherence with and discontinuation of oral therapies[3,4]
- Lower rates of return to work and impaired ability to work[5,6]

[1]Cleeland et al, Cancer 2013;119:4333-40 [2]Kim et al, J Pain Symptom Manage 2009;37:715-36
[3]Murphy et al, Breast Cancer Res Treat 2012;134:459-79 [4]Henry et al, J Clin Oncol 2012;30:936-42
[5]Sun et al, Supp Care Cancer; 2017:25:709-18 [6]Duijts et al, Psycho-Oncol 2014;23:481-92

Presentation of Fatigue, Sleep Problems, and Cognitive Problems in People with Cancer

- Pre-existing symptom
- Disease symptom
  - Initial disease symptom
  - Symptom of advancing disease
- Treatment side effect
- Persistent symptom after treatment completion
- New symptom after treatment completion

Assessment of Post-treatment Fatigue

- Patient-reported outcome measures (e.g., BFI)[1]
- Case definition interview[2]

[1]Mendoza et al, Cancer 1999;85:1186-96
[2]Donovan et al, Psycho-Oncol 2013;22:737-44

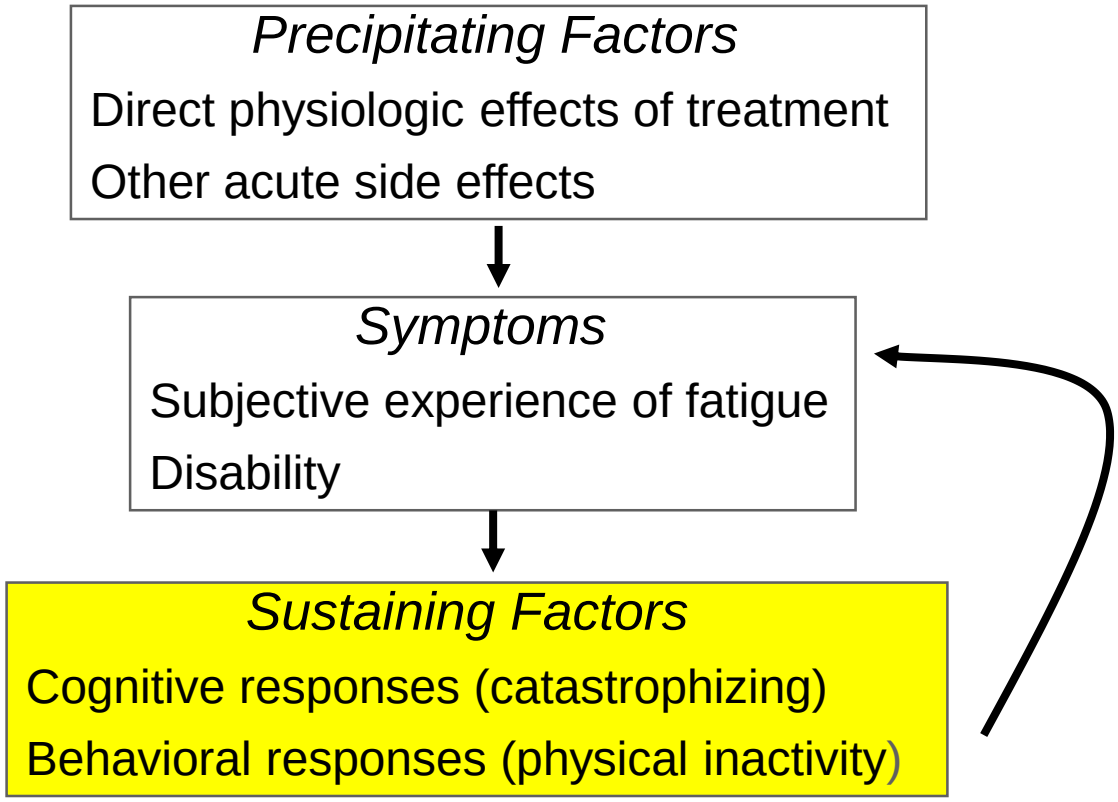
Risk Factors for Post-treatment Fatigue

- Pre-treatment fatigue[1]
- Type of cancer treatment[2]
- Body mass index[3]
- Polymorphisms in inflammation-related genes[4]
    - IL1B
    - IL6
    - TNFA

[1]Goedendorp et al, J Pain Symptom Manage 2013;45:213-22
[2]Donovan et al, J Pain Symptom Manage 2004;28:373-80
[3]Andrykowski et al, Cancer 2010;116:5740-48
[4]Bower, Nat Rev Clin Oncol 2014;11:597-609

Mechanisms for Post-treatment Fatigue

- Persisting inflammation (IL-1RA, CRP)[1]
- Cognitive and behavioral responses[2]



[1]Bower et al Brain Behave Immun 2013;30:S48-57 [2]Donovan et al, Health Psychol; 2007;26:464-72

Intervention Effects - Fatigue

- Meta-analysis of 113 RCTs[1]
- 11,525 patients (78% female)
- 45 studies of patients who completed treatment

Variable[a]	Overall WES (95% CI)	*P* Value	No. of Effect Sizes
After primary: exercise	0.26 (0.18 to 0.34)	<.001	29
After primary: psychological	0.42 (0.29 to 0.55)	<.001	13
After primary: exercise and psychological	0.32 (0.17 to 0.47)	<.001	7
After primary: pharmaceutical	0.08 (−0.17 to 0.32)	.55	4

[1]Mustian et al, JAMA Oncol, 2017;3:961-8

Interventions for Post-treatment Fatigue: ASCO[1] and Pan-Canadian Guidelines[2]

Recommended

- Exercise
- Cognitive-behavioral therapy
- Psychoeducation

Limited Evidence

- Mindfulness-based approaches
- Yoga
- Acupuncture

No Evidence

- Psychostimulant medications

[1]Bower et al, J Clin Oncol 2014;32:1840-50
[2]www.capo.ca/pdf/CRF_Guideline.pdf

Future Directions: Fatigue

Risk Factors and Mechanisms

- Expand findings on genetic risk factors
- Clarify underlying biological mechanisms

Treatment

- Identify recommended intensity of exercise
- Adapt effective interventions for more widespread dissemination and implementation
- Explore new intervention strategies

Assessment of Post-treatment Sleep Problems

- Patient-reported outcome measures (e.g., PSQI)[1]
- Polysomnography
- Actigraphy

[1]Buysse et al, Psychiatry Res 1989;28:193-213

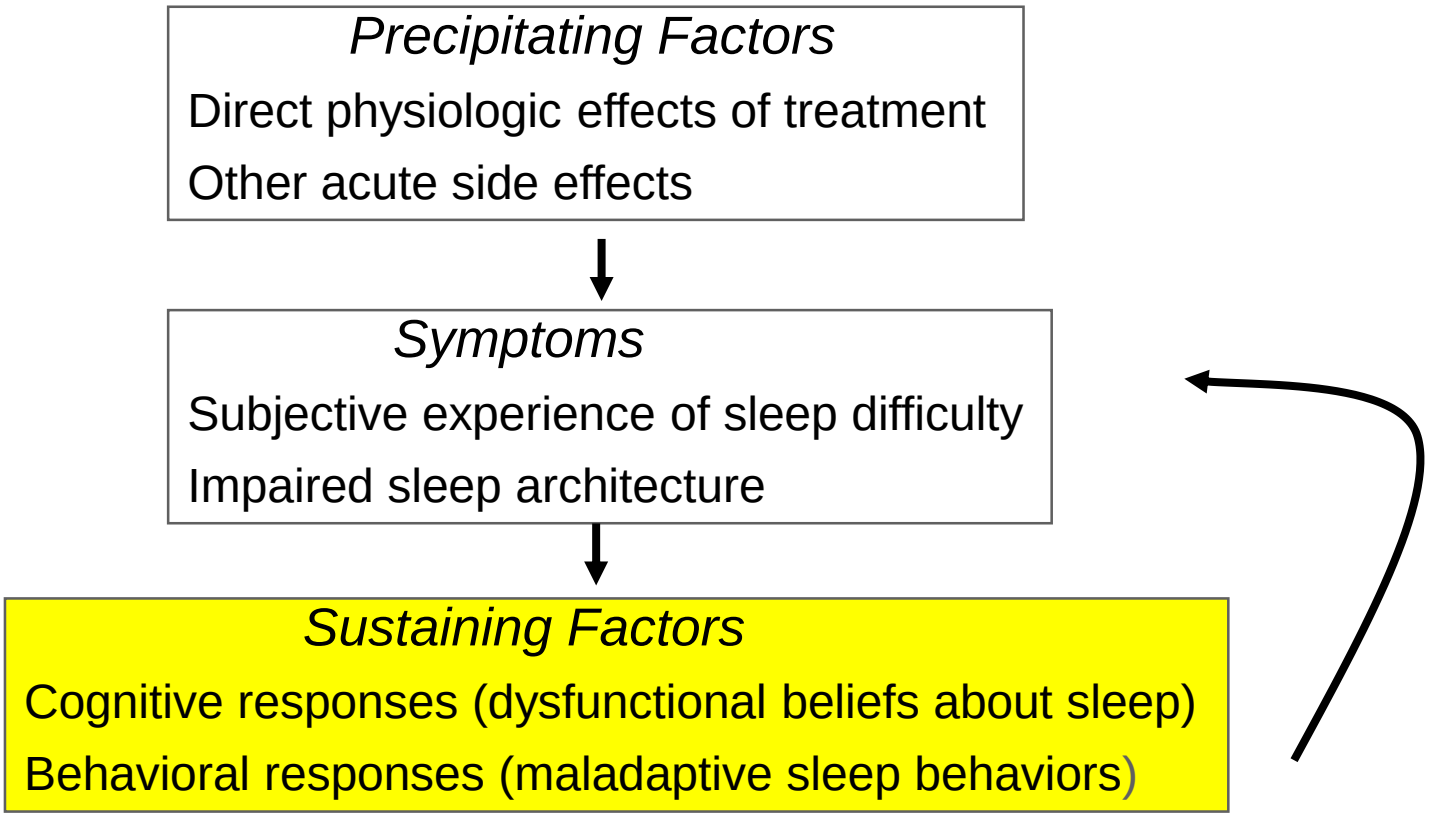
Risk Factors for Post-treatment Sleep Problems

- Pre-treatment sleep problems[1]
- Type of cancer treatment[1]
- Arousability[2]

[1]Savard et al, Sleep 2001; 24:583-90 [2]Savard et al J Clin Oncol 2009;27:5233-39

Mechanism for Post-treatment Sleep Problems

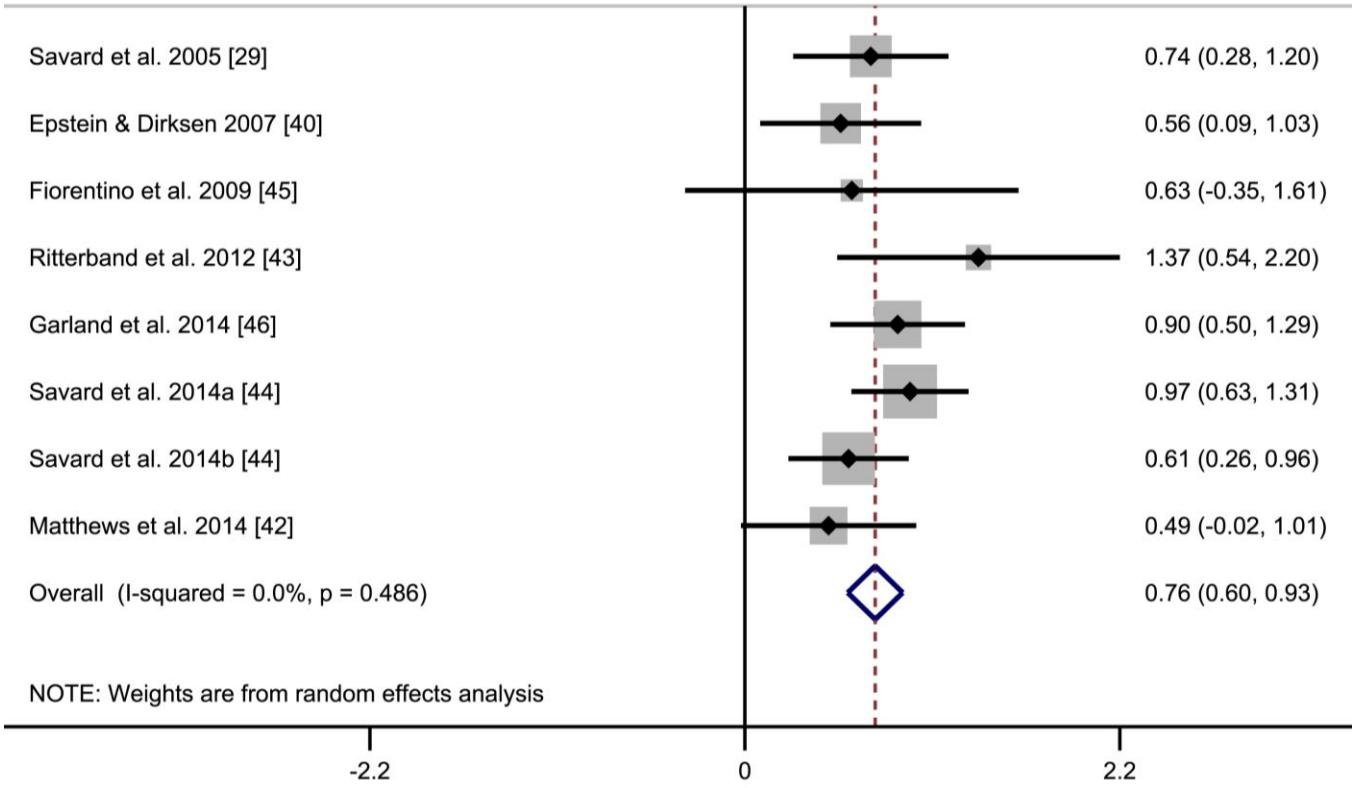
- Cognitive and behavioral responses[1]



[1]Savard et al, J Clin Oncol 2009:27:5233-5239

Intervention Effects - Sleep Problems

- Meta-analysis of 8 RCTs of cognitive-behavioral therapy for insomnia (CBT-I)[1]
- 752 patients (5 studies of breast cancer patients)



[1]Johnson et al, Sleep Med Rev 2016;27:20-8

Interventions for Post-treatment Insomnia: NCCN[1] and Pan-Canadian Guidelines[2]

Recommended

- Sleep hygiene measures
- Cognitive-behavioral therapy
- Hypnotic medications (short-term/intermittent)
- Psychoeducation

Suggested

- Exercise

[1]https://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf
[2]Howell et al, Support Care Cancer 2013;21:2695-706

Future Directions: Sleep Problems

Assessment

- Investigate apnea and other sleep disorders

Risk Factors and Mechanisms

- Identify agents interfering with sleep
- Clarify underlying biological mechanisms

Treatment

- Adapt effective interventions for more widespread dissemination and implementation
- Consider implications of symptom cluster concept

Post-treatment Cognitive Problems

The New York Times

Health

Chemotherapy Fog Is No Longer Ignored as Illusion

Sally Ryan for The New York Times

Debbie Kamplain of Peoria, Ill., hired a personal organizer to help her prepare to move her family to Indiana.

By JANE GROSS
Published: April 29, 2007

Assessment of Post-treatment Cognitive Problems

- Patient-reported outcome measures (e.g., FACT-Cog[1])
- Neuropsychological tests – Core measures[2]

Domains	Measures
Learning and memory	Hopkins Verbal Learning Test-Revised
Processing speed	Trail Making Test, Controlled Oral Word Association
Executive function	Trail Making Test Controlled Oral Word Association

- Functional imaging studies (fMRI, fPET)[3]
- Quantitative electroencephalography (qEEG)[4]

[1]Wagner et al, J Support Oncol 2009,7:W32-39 [2]Wefel et al, Lancet Oncol 2011;12:703-8
[3]Wefel et al, CA Cancer J Clin 2015;65:123-38 [4]Hunter et al, Psycho-Oncol 2014:23:713-5

Risk Factors for Post-treatment Cognitive Problems

- Age[1]
- Cognitive reserve[1]
- Genetic polymorphisms
  - APOE[2]
  - COMT[3]

[1]Ahles et al, J Clin Oncol 2010; 28:4434-40
[2]Ahles et al, Psycho-Oncol 2003;12;612-19
[3]Small et al, Cancer 2011;117:1369-76

Mechanisms for Post-treatment Cognitive Problems

Direct neurotoxic effects[1,2,3]

- Volume loss
- Reduced white matter integrity
- Altered neurochemistry and metabolism

Cytokine deregulation[1,2,3]

Hormonal changes[1]

[1]Janelsins et al, Intl Rev Psychiatry 2014;26:102-13
[2]Joly et al, J Pain Symptom Manage 2015;50:843-41
[3]Bray et al, Cancer Forum 2017;41:1

Interventions for Post-treatment Cognitive Problems

- Cognitive training[1]
- Memory and attention adaptation training[1]
- Cognitive rehabilitation[1]
- EEG neurofeedback[1]
- Exercise, yoga, Tai Chi, Qigong[2,3]
- Psychostimulant medications[3]
- Acetylcholinesterase inhibitors[3]

[1]Zeng et al, Integrative Cancer Ther 2016;15:424-34 [2]Zimmer et al, Biomed Res Intl 2016;1820954
[3]Wefel et al, CA Cancer J Clin 2015;65:123-38

Future Directions: Cognitive Problems

Assessment

- Integrate different assessment approaches

Risk Factors and Mechanisms

- Expand findings on genetic risk factors
- Clarify structural and functional brain changes

Treatment

- Conduct full-scale trials of promising interventions
- Explore possibility of preventing cognitive changes

Develop Evidence-based Treatment Guidelines

Moving Guideline Recommendations into Practice

Screening

↓

Assessment

Focused history
In-depth evaluation of presenting symptoms
Identification of contributing factors

↓

Management and Treatment

Education, support, and self-management strategies
Psychological and psychosocial interventions
Pharmacologic Interventions

↓

Follow-up and on-going re-assessment

Barriers to More Effective Symptom Control

Symptoms are not systematically assessed and reported

- Patient-reported outcomes (PROs) not used in many practice settings
- Even when collected, PRO data may not facilitate symptom control

Symptoms are not adequately managed

- Limited awareness of existing clinical practice guidelines
- Difficulty accessing resources for symptom management

Lack of systematic efforts to translate research into practice

- RCTs show benefits of integrated symptom assessment and reporting
- Implementation science approach yet to be applied

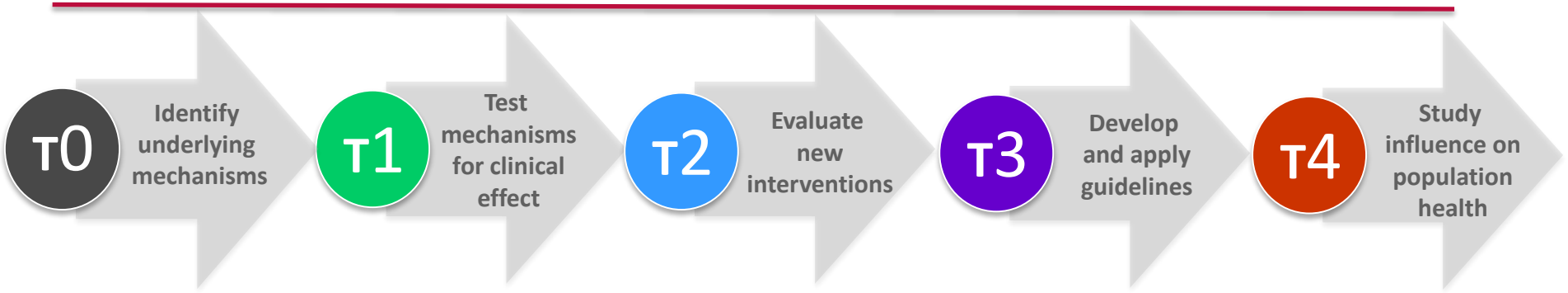
Cancer Moonshot℠
Blue Ribbon Panel Recommendation

Strategic research investment, based on implementation science, to accelerate clinical adoption of integrated systems to:

- Gather and monitor patient-reported symptoms
- Provide decision support and care using evidence-based symptom management guidelines

www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/funding/upcoming#impact

Conclusions



T0 Fill gaps in understanding biological basis of common symptoms

T1 Develop new intervention strategies based on mechanistic understanding

T2 Conduct full-scale trials of promising interventions

T3 Improve routine symptom management through implementation research

T4 Promote widespread use of PROs to be able to evaluate adequacy of symptom management at population level

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Triage and Stepped Care Models

No or mild symptoms
Active monitoring, education, support

Moderate symptoms
Evaluation
Low-intensity interventions (e.g., self-management)

Moderate symptoms, non-responsive
Additional evaluation
High-intensity interventions (e.g., individual therapy)
Consider combined modality treatment

Severe symptoms
Evaluation
High-intensity interventions (e.g., individual therapy)
Combined modality treatment