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

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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\(^5,6\)

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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)
- Cognitive and behavioral responses

**Precipitating Factors**
- Direct physiologic effects of treatment
- Other acute side effects

**Symptoms**
- Subjective experience of fatigue
- Disability

**Sustaining Factors**
- Cognitive responses (catastrophizing)
- Behavioral responses (physical inactivity)

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Intervention Effects - Fatigue

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

<table>
<thead>
<tr>
<th>Variable(^a)</th>
<th>Overall WES (95% CI)</th>
<th>P Value</th>
<th>No. of Effect Sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td>After primary: exercise</td>
<td>0.26 (0.18 to 0.34)</td>
<td>&lt;.001</td>
<td>29</td>
</tr>
<tr>
<td>After primary: psychological</td>
<td>0.42 (0.29 to 0.55)</td>
<td>&lt;.001</td>
<td>13</td>
</tr>
<tr>
<td>After primary: exercise and psychological</td>
<td>0.32 (0.17 to 0.47)</td>
<td>&lt;.001</td>
<td>7</td>
</tr>
<tr>
<td>After primary: pharmaceutical</td>
<td>0.08 (-0.17 to 0.32)</td>
<td>.55</td>
<td>4</td>
</tr>
</tbody>
</table>

\(^1\)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

Risk Factors for Post-treatment Sleep Problems

- Pre-treatment sleep problems\(^1\)
- Type of cancer treatment\(^1\)
- Arousability\(^2\)

Mechanism for Post-treatment Sleep Problems

- Cognitive and behavioral responses

  **Precipitating Factors**
  - Direct physiologic effects of treatment
  - Other acute side effects

  **Symptoms**
  - Subjective experience of sleep difficulty
  - Impaired sleep architecture

  **Sustaining Factors**
  - Cognitive responses (dysfunctional beliefs about sleep)
  - Behavioral responses (maladaptive sleep behaviors)

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1Savard 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: NCCN¹ and Pan-Canadian Guidelines²

**Recommended**

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

**Suggested**

- Exercise

²Howell 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

Chemotherapy Fog Is No Longer Ignored as Illusion

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\(^2\)

<table>
<thead>
<tr>
<th>Domains</th>
<th>Measures</th>
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<tbody>
<tr>
<td>Learning and memory</td>
<td>Hopkins Verbal Learning Test-Revised</td>
</tr>
<tr>
<td>Processing speed</td>
<td>Trail Making Test, Controlled Oral Word Association</td>
</tr>
<tr>
<td>Executive function</td>
<td>Trail Making Test, Controlled Oral Word Association</td>
</tr>
</tbody>
</table>

- 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\textsuperscript{1}
- Cognitive reserve\textsuperscript{1}
- Genetic polymorphisms
  - APOE\textsuperscript{2}
  - COMT\textsuperscript{3}

\textsuperscript{1}Ahles et al, J Clin Oncol 2010; 28:4434-40
\textsuperscript{2}Ahles et al, Psycho-Oncol 2003;12;612-19
\textsuperscript{3}Small et al, Cancer 2011;117:1369-76
Mechanisms for Post-treatment Cognitive Problems

Direct neurotoxic effects\textsuperscript{1,2,3}

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

Cytokine deregulation\textsuperscript{1,2,3}

Hormonal changes\textsuperscript{1}

\textsuperscript{1}Janelsins et al, Intl Rev Psychiatry 2014;26:102-13
\textsuperscript{2}Joly et al, J Pain Symptom Manage 2015;50:843-41
\textsuperscript{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\(^3\)

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
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