# Modeling Fatigue in Cancer
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FDA has not approved any product for the treatment of fatigue in cancer, despite the clear need for effective treatment of cancer-related fatigue. The reasons for this lack of fatigue treatments is a combined effect of lack of clear consensus on the clinical definition of fatigue, limited availability of new products that could treat fatigue, and challenges measuring fatigue for differential diagnosis and assessment of treatment effectiveness.

This document uses information from existing cancer fatigue measures and qualitative research to propose a model of fatigue in cancer – its manifestations, causes and consequences. We began by noting what would be required by FDA to secure approval of a product for the treatment of fatigue in cancer, then describe other concepts related to the diagnosis, severity rating, or causes of fatigue that would be important to consider in designing clinical trials and identifying study endpoint assessments.

An FDA approved product indication requires substantial evidence of clinical benefit. FDA defines 'clinical benefit' as improvement in survival, symptoms, and/or functioning (21 CFR Chapter 1 Section 314.510). Based on this, FDA approved fatigue indication (i.e., Rx for fatigue) would require substantial evidence of reduction in both symptoms (in yellow on the following figure) and functional impairment (in blue/purple). For symptoms to be considered evidence of clinically significant fatigue, they must be "unusual," different from muscle or stress induced fatigue that would be common even in normal functioning individuals. Symptoms that are not alleviated by rest, or that cause significant discomfort or functional impacts are required for diagnosis of cancer-related fatigue. Either the distress/significant discomfort or the functional impact make them unusual experiences of fatigue.

All concepts reflecting consequences of having cancer-related fatigue would be measures of the impact of fatigue. They help calibrate what is meaningful in terms of severity of symptoms or functional limitations but also what would be a meaningful improvement (green).

It is not clear how emotional symptoms (e.g., worry, anxiety, depressed mood, emotional exhaustion) fit in this model. They may be caused by the same factors that cause the fatigue (the cancer, the treatment, the experience of having cancer), but if so, are they evidence of clinical depression or of cancer-related fatigue.

There are several factors that are commonly attributed as causes of fatigue, including the cancer type and stage, current and past cancer treatment (orange).
Other factors determine the severity of the fatigue cancer patients experience, such as coping strategies and skills, the patient's expectations, and how much exertion the patient expends to function (pink). It is quite possible that an effective therapy could help patients feel enough better that they are willing and able to do more, but still become

severely fatigued.  Capturing this improvement could require a measure of the activity levels (such as monitoring the energy expended to accomplish tasks) to demonstrate an improvement in what could be accomplished at the expense of stable or worsening 'worst' symptom severity assessment.

The factors provide a context for fatigue symptoms to differentiate pathological fatigue from ordinary exertion, such as the amount of activity requiring exertion or amount of concentration or focused attention the patient is able to maintain (maroon).

It is not clear from existing research what feature or features of fatigue define the severity of fatigue.  For example, is it the intensity of fatigue symptom (worst fatigue) or the degree of functional impairment at a specified time point?  Or is it the length of time the fatigue symptoms lasts?  What role do time of day fatigue occurs or the variability of the symptom/functional impact over the course of the day play in characterizing cancer-related fatigue severity?  Where does predictability of the fatigue experience fit in patients' evaluation of severity (i.e., if fatigue can be anticipated, do coping or expectations alter the severity assessment)?

In addition to the concepts themselves, linkages between concepts is important to understand.  Most of the factors noted are correlated but it is not always clear what the causal linkages are among them. While many causal links are possible, characterizing the most common mechanisms that drive the fatigue experience is an important starting place for developing a conceptual model of fatigue.  A useful model requires parsimony; therefore the links noted focus on the most important and common pathways linking the concepts.  This should make the model more informative for designing effective treatments, study design, and analysis.

***Next step: link items and factors with references to the literature specifying what evidence we have for this linkage and its importance, and reference theories that explain the causal pathways that link the items.***

***Tricky bit is showing the 'dynamics' of the model in terms of what happens when things change.  Lots left to do…..***

**Causes of Cancer-Related Fatigue**

| Current Treatment | Cancer Type | Cancer Stage |
|---|---|---|
| Previous Treatments | | |

**Fatigue Symptoms**

| Tire easily | Lack of Energy | Tiredness never goes away |
|---|---|---|
| Tired but not | Listless | Lack of Motivation |
| Trouble Falling sleep | Sleep too much | Tired after rest |

**Functional Impairments**

**Severity Mediators**

| Exertion | Coping |
|---|---|
| Expectations | |

**Cognitive Functioning**

| Thinking Clearly | Decision Making |
|---|---|
| Mental tiredness | Reading comprehension |

**Physical Functioning**

| Lack of Appetite | Weakness /Strength |
|---|---|
| Stamina | Perform usual daily activity |

**Social Functioning**

**Fatigue Severity Characteristics**

| Variability | Perceived Trend (Improved /Worse) | Duration (how long it lasts) |
|---|---|---|
| Frequency (how often) | | Timing (when it happens) |
| Predictability | | |

**Emotional Well-being**

| Engagement (will & energy) | Drained (emotionally) | Accomplish Less |
|---|---|---|
| Anger | Worry | Frustration |

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