

# Treating Cancer-Related Fatigue: The Search for Interventions That Target Those Most in Need

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Fatigue is one of the most common and distressing adverse effects of cancer treatment. Up to 99% of patients experience some level of fatigue during treatment with radiation, chemotherapy, and biologic therapies.<sup>1</sup> Fatigue typically resolves in the year after treatment completion, but approximately 30% of patients experience more persistent fatigue that may endure for 10 years or more.<sup>2</sup> Fatigue is associated with decrements in all aspects of quality of life, and many patients report that they are unable to lead a normal life because of their fatigue.<sup>3</sup> Fatigue has also been associated with shorter recurrence-free and overall survival in patients with cancer.<sup>4</sup> Given its prevalence and impact, fatigue is an important target for identification and treatment.

What are effective treatments for cancer-related fatigue (CRF)? A diverse range of treatment strategies has been evaluated, including pharmacologic and nonpharmacologic approaches. Indeed, a recent review of the literature indicated that more than 170 intervention studies that have included fatigue as a primary or secondary outcome have been conducted in patients with cancer.<sup>5</sup> At this point, exercise has the strongest empirical support, with several recent meta-analyses concluding that physical activity has a moderate beneficial effect on CRF (effect sizes in the range of  $-0.30$  to  $-0.38$ ).<sup>6-11</sup> There is also some support for psychological interventions, with meta-analyses showing a small to moderate beneficial effect (effect sizes in the range of  $-0.10$  to  $-0.30$ ).<sup>10,12,13</sup> The more modest effect sizes that were seen in the psychological studies may be a result of the fact that many did not include a CRF-related aim or hypothesis<sup>13</sup>; the few trials that explicitly focused on fatigue, providing education about fatigue and instruction in self-care, coping techniques, and activity management, were more effective than nonspecific interventions.<sup>14</sup> There is more limited support for pharmacologic approaches to treating fatigue.<sup>15</sup> Although some trials have found beneficial effects for psychostimulants,<sup>16</sup> results are quite mixed, and a recent phase III, randomized, double-blind, placebo-controlled trial found no benefit for methylphenidate versus a placebo in treating CRF.<sup>17</sup>

On the basis of this literature, it would be reasonable to recommend physical activity to patients during and after cancer treatment (preferably under the supervision of a rehabilitation professional) and to provide them with targeted education about CRF. However, we do not know whether these strategies will be helpful for patients with more severe or persistent fatigue, given that very few intervention studies have specifically targeted these patients. This is particularly

true for nonpharmacologic treatments; although trials of such treatments are often described as interventions for cancer-related fatigue, the presence of fatigue is not a criterion for trial entry. Thus, it is unclear whether the interventions examined in these studies will be feasible and effective for those most in need. For example, fatigue was one of the primary barriers to adherence in an exercise trial that was conducted with survivors of prostate cancer.<sup>18</sup>

Only a handful of randomized controlled trials have targeted patients with moderate to severe fatigue and used presence of fatigue as a criterion for study entry. Results from these studies provide preliminary evidence that psychological (cognitive behavioral therapy<sup>19,20</sup>) and integrative medicine approaches (yoga, biofield therapy, mindfulness-based therapy<sup>21-24</sup>) may have beneficial effects on persistent post-treatment fatigue, but conclusions are limited by small sample sizes in several trials. There is a critical need for larger-scale studies that target patients with moderate to severe fatigue, particularly fatigue that does not remit after treatment completion.

The article by Molassiotis et al<sup>25</sup> that accompanies this editorial addresses this gap in the literature in its investigation of acupuncture for post-treatment fatigue in survivors of breast cancer. This was a large, multicenter trial that focused specifically on patients with moderate to severe fatigue. The authors enrolled 302 women who had been diagnosed with stage I to IIIA breast cancer, completed chemotherapy, and scored 5 or greater on a single-item 10-point fatigue scale. The mean duration of fatigue was 15 to 18 months, with a maximum duration of 69 months, indicating the chronic nature of the symptom in this sample. Results showed that 6 weeks of acupuncture, provided for 20 minutes per week, led to significant improvements in general fatigue as assessed by the Multidimensional Fatigue Inventory. The intervention also led to significant improvements in anxiety, depression, and quality of life. Patients in the control group received a detailed information booklet about coping with fatigue, which was likely comparable or superior to what typically would be provided in the post-treatment setting.

Findings from the study by Molassiotis et al,<sup>25</sup> together with earlier trials,<sup>24,26</sup> provide compelling evidence that acupuncture may be effective for reducing CRF, at least in the short term. It will be important to determine how enduring the effects of this treatment are, given that only the immediate post-treatment effects were described in this report, and to identify the frequency and duration of acupuncture that are necessary for improvement. In addition, it was unclear

whether fatigue levels in the acupuncture group decreased to pretreatment levels; if not, more intensive treatment may be indicated. Other treatments that have been developed for persistent CRF are more time consuming (eg, 6 months for cognitive behavioral therapy,<sup>19</sup> 3 months for yoga<sup>21</sup>), but these approaches also teach patients techniques that can be used after the intervention is completed, and both led to sustained improvements in fatigue.<sup>20,21</sup> Future trials should also compare acupuncture (and other promising treatments) with an active control arm as well as a no-treatment control arm to better evaluate treatment-specific effects.

Intervention trials with fatigued patients are challenging to conduct—as noted by Molassiotis et al,<sup>25</sup> they had to screen “many hundreds” of patients to accrue their desired sample size—but they are vital for identifying interventions that will work for those most in need. The study by Molassiotis et al represents an important advance in the literature and will hopefully motivate other investigators to undertake conceptually driven, methodologically rigorous trials that target patients with moderate to severe CRF. There is also a critical need for basic research on mechanisms underlying fatigue onset and persistence that will guide development of targeted therapies. In addition, determination of risk factors for persistent fatigue may allow us to intervene earlier with the most susceptible patients.

For now, what advice can we offer patients with persistent fatigue? Acupuncture may be helpful, particularly for women with non-metastatic breast cancer, although patients should be urged to follow the specific protocol that was found to be safe and effective in the study by Molassiotis et al.<sup>25</sup> In our trial of Iyengar yoga for persistent CRF, a number of our participants had attempted other types of yoga with no relief<sup>21</sup>; similarly, not all types of acupuncture are likely to be effective for reducing CRF. As more intervention studies specifically target patients with fatigue, the range of empirically supported treatment options for this group should expand, ultimately leading to enhanced quality of life for the growing population of survivors of cancer.

#### AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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