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Fatigue randomized controlled trials—how tired is "too tired" in patients undergoing glioma treatment?

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See the article by Lee et al, on pages 849–854.

The prevalence of fatigue in the primary brain tumor population ranges between 25% and 90% and occurs at all stages of care. Like sadness and major depressive disorder (MDD), frequency depends on the definition used. In MDD, there is a requirement for it to be pervasive, persistent, and interfering with the ability to work, sleep, study, eat, and enjoy life. For research purposes, fatigue has sometimes been defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (http://oralcancerfoundation.org/treatment/pdf/fatigue.pdf). Fatigue is one of the top 10 priority research areas identified by the brain tumor community.[1] High-quality research in this area is therefore very important, but challenging.

Theoretical models separate fatigue into primary fatigue, directly related to disease mechanisms, and secondary fatigue, related to non-disease-specific factors. Primary fatigue in any condition affecting the brain, whether it be brain tumor, irradiation, demyelination, stroke, or post–head injury, may be the result of centrally mediated processes: neuronal damage, inflammation, demyelination, or axonal loss leading to physical and cognitive impairment or disability. Suggested mechanisms in CNS diseases have been functional cortical reorganization that may result in a higher energy demand in certain brain areas, although mechanistic research is still in its infancy.[2] Secondary causes of fatigue may include psychological factors (anxiety or depression), co-occurring symptoms (sleep disturbance and pain), comorbid conditions (hormone dysfunction, infection, and malnutrition), or medication.[3]

In the current issue of *Neuro-Oncology*, Lee et al present an 8-week pilot randomized controlled trial (RCT) to prevent or ameliorate fatigue in patients with glioma who were undergoing radiotherapy or chemo-radiotherapy using a wakefulness-promoting medication, armodafinil.[4] Severity of fatigue was not a prerequisite of entry, and median fatigue was mild to moderate, examining the 4 fatigue scales used. Like most RCTs in fatigue in patients with brain tumors, accrual was slow, possibly because the patient/doctor focus was on cancer treatment. Also consistent with many primary brain tumor RCTs, retention was difficult (23% drop out) even over 8 weeks. At an early point in the treatment pathway such as this, it is uncertain whether the above definition of "fatigue" is fulfilled, and fatigue is often influenced by multiple factors, including distress, steroids, insomnia, and neurological impairment. In addition, enrollment of patients with no or mild fatigue gives little opportunity to demonstrate a significant improvement in Likert scales used to assess fatigue severity or impact on quality of life (QoL). While Lee et al did not find a statistically significant improvement in fatigue or QoL with armodafinil in patients undergoing radiotherapy, there was a trend toward improvement in the 42-day change in 3 measures of fatigue. They correctly state that it is possible that armodafinil does improve fatigue but that because of low statistical power to detect a difference due to small sample size or minimal effects, this was not seen. They also note the "unanswered questions" that should actually be known prior to any RCT: What is the most effective dose and duration of treatment required to see any benefit, if one were to be expected? Again this is similar to antidepressants in MDD: What is the effective dose? What is the effective duration? What are the side-effect profiles at these doses and duration? Only then can we ask: What is the size of the effect on fatigue and QoL against placebo? Did the patients think that the drug was worth taking for the amount of benefit received?

Management of fatigue will follow the same pathways irrespective of whether we consider this "neurological fatigue" or "cancer fatigue" and will include removal of drugs that may cause fatigue; advice about sleep, diet, and physical exercise; and, if present, management of anxiety or depression through talking therapies, cognitive behavioral therapy, mindfulness, or antidepressants.

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Previous RCTs of interventions for the management of fatigue in adults with primary brain tumor have been assessed in a Cochrane systematic review.[5] Only one RCT[6] included only patients with high levels of fatigue, while 8 others[7–14] included patients who may or may not have had fatigue at entry. All had very small sample size or had problems retaining patients. One study, although negative overall for fatigue, showed improved QoL and reduced fatigue with the use of armodafinil for patients with severe fatigue at study entry.[14]

Maybe we need to take a step back and agree on a standard working definition of major fatigue prior to trial entry using a structured clinical interview for fatigue. Major fatigue should have been present for a defined period and be severely affecting QoL before we consider drug therapy (eg, a major depressive episode has been characterized by the presence of a severely depressed mood that persists for at least 2 weeks [American Psychiatric Association]).

Patients should have tried simple nonpharmacological measures and have been resistant to these prior to entry. Management of fatigue will include advice regarding rest, diet, healthy living, physical exercise, and drugs that may cause fatigue; advice about sleep; and, where present, management of anxiety or depression through talking therapies, cognitive behavioral therapy, or mindfulness. If major fatigue is part of a major depressive episode, perhaps an antidepressant should be considered first, rather than drugs to promote wakefulness that may provoke psychiatric symptoms.

Drugs that provoke wakefulness (eg, modafinil/armodafinil) may be more appropriate where excessive sleepiness is a severe, persistent, and prominent symptom. Postmarketing adverse reactions associated with modafinil/armodafinil include mania, delusions, hallucinations, suicidal ideation, and aggression, some resulting in hospitalization. Where cognitive impairment is associated with excessive sleepiness, methylphenidate and other cognitive enhancers may be tried, but they have similar complications and may increase risk of seizures. Finally, a note of caution should be drawn about using these drugs in patients with brain tumors without fatigue or with mild or even moderate fatigue, without adequately assessing and informing them, prior to what may become a chronic prescription for fatigue.

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