Putting Methylphenidate for Cancer-Related Fatigue to Rest?

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Fatigue is the symptom most frequently experienced by patients with cancer and has a profound impact on their quality of life.[1,2] The National Comprehensive Cancer Network (NCCN) defines cancer-related fatigue (CRF) as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is disproportionate to recent activity and interferes with usual functioning.[1] Recent meta-analyses suggest that 4 to 7 out of 10 patients with cancer will experience CRF, with higher prevalence and severity in individuals receiving cancer treatments and in those with metastatic disease.[3,4] However, CRF is underreported and undertreated, in part because it is often considered unavoidable, and in part because of lack of effective treatments.[5]

CRF is a complex symptom with a multifactorial etiology that remains incompletely understood. Factors that may affect CRF include stage of cancer, cancer treatments (surgery, radiation, and systemic and/or targeted therapy), and whether these treatments are ongoing or completed.[6] Patients with advanced cancer are more likely to have comorbidities, physical deconditioning, polypharmacy, cachexia, anemia, opioid-related drowsiness, and cancer-related symptoms such as pain, insomnia, anxiety, depression, nausea, and dyspnea, all of which are associated with CRF.[5,6] Several interdependent mechanisms have been implicated in CRF, including dysregulations of inflammation, cellular immunity, circadian rhythms, and the hypothalamic-pituitary-adrenal axis, as well as alterations in ATP and muscle metabolism.[5,7,8] Studies have also suggested the role of genetic factors, focusing mainly on single-nucleotide polymorphisms in genes encoding proinflammatory cytokines.[9]

The approach to managing CRF involves screening with validated instruments, and identifying and addressing treatable contributing factors among those listed above. In addition, clinical practice guidelines for CRF emphasize the importance of patient and family/caregiver education, and counseling regarding self-monitoring of fatigue and energy-conservation strategies.[1,2] Exercise programs and psychosocial interventions (eg, cognitive behavioral therapy and psychoeducation) are recommended on the basis of evidence supporting their use, although they may be less feasible or effective in patients with advanced disease.[6] Short-term use of corticosteroids may be considered for patients with metastatic disease or those who are near the end of life. The NCCN suggests that psychostimulants (particularly methylphenidate) can be considered at all stages of disease if used cautiously after excluding or addressing potential contributing factors,[1] while European Society for Medical Oncology did not reach a consensus in this regard.[2]

Despite lack of overt endorsement from guidelines and scant evidence for their benefit, psychostimulants, and particularly methylphenidate, are widely used for CRF, especially in individuals with advanced cancer receiving palliative care.[10-13] Methylphenidate is a CNS stimulant that increases dopamine and norepinephrine levels via reuptake inhibition, mainly in the prefrontal cortex.[14] In its immediate-release formulation, peak serum concentrations are typically reached within 2 hours and the duration of action is 2-4 hours. Initially developed and approved by the US Food and Drug Administration for the treatment of attention-deficit hyperactivity disorder (ADHD), methylphenidate is also approved as a second-line therapy for narcolepsy and is used off-label for treatment of CRF, depression, and opioid-induced drowsiness.[14]

To date, 13 trials[15-27] have evaluated methylphenidate versus placebo for the treatment of CRF, of which only five enrolled 100 or more participants.[15,20,22,24,27] The characteristics of the participants in these 13 studies varied substantially with respect to disease stage, performance

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THE TAKEAWAY

In the article that accompanies this editorial, Stone et al[28] present a randomized, double-blind, placebo-controlled trial of individually dose-titrated methylphenidate for treatment of fatigue in patients with advanced cancer, finding that methylphenidate, although safe and well tolerated, was no more effective than placebo at relieving fatigue after 6 (±2) weeks. Future studies should consider the multifaceted nature of cancer-related fatigue, as well as the substantial placebo effects of psychostimulants, and may benefit from focusing on methylphenidate in combination with nonpharmacologic interventions, or for fatigue with a predominant emotional or cognitive component.

status, cancer treatments, primary outcomes, dose and duration of methylphenidate treatment, and severity of baseline fatigue. Acknowledging these differences, only 4 of the 13 studies found methylphenidate to be more effective than a placebo in improving CRF.[16,18,21,24] Among the five studies with at least 100 participants, the one study[24] that demonstrated a benefit enrolled patients with chemotherapy-related fatigue—mostly women with breast or ovarian cancer. The four remaining studies enrolled patients with advanced cancer and reported no difference between methylphenidate and placebo, although fatigue scores improved in both arms. Adverse events related to methylphenidate were rare, although increased nervousness and appetite loss were observed in one trial testing sustained-release methylphenidate,[22] and nausea, dry mouth, dizziness, and jitteriness in another trial that used higher doses.[24] Of note, recent meta-analyses using pooled data demonstrated a significant effect of methylphenidate for CRF compared with placebo, with moderate effect sizes.[12,13]

In the article that accompanies this editorial, Stone et al[28] present results from a phase III trial of methylphenidate for the treatment of CRF in patients with advanced, incurable cancer receiving palliative care from hospital, hospice, or community-based teams in the United Kingdom. Eligible participants reporting a fatigue score of ≥4/10 were randomly assigned to receive individually dose-titrated methylphenidate 5 mg tablets (starting at 5 mg twice a day and increasing, based on perceived efficacy and side effects, to a maximum of 20 mg three times a day over 6 weeks), or placebo tablets dosed in an identical manner. The primary outcome was the difference in the 13-item Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score at 6 (±2) weeks. The investigators met their target of 162 patients, of whom 147 were analyzed for the primary outcome. Both groups had improved FACIT-F fatigue scores, with a nonsignificant difference at 6 weeks. Although there were statistically significant differences in FACIT-F scores at most other weekly time points and across the 10-week study period, these did not meet the cutoff for clinical significance. Of the remaining 13 secondary symptom and quality-of-life outcomes, each measured at three time points, none were statistically significant except depression, which was less severe in the intervention group at 6 weeks. Adverse events were rare in both groups.

To our knowledge, the study by Stone et al[28] represents the largest trial of methylphenidate for CRF published to date with respect to the sample of participants evaluated. Slow accrual and high levels of dropout resulted in insufficient power for previous trials of methylphenidate for CRF.[15,18,23,25,26] By contrast, the study by Stone et al[28] achieved excellent recruitment and retention rates. Other methodologic strengths include the individualized dosing to a substantial maximum dose, and the relatively long period of follow-up.

Are we to conclude that no further trials of methylphenidate for CRF are warranted? One may also extend this question to all psychostimulants—randomized controlled trials for modafinil, dexamphetamine, and armodafinil have similarly been mostly negative.[10,12] Yet, there is a sound physiologic basis for their potential benefit. Before concluding that further study of methylphenidate should be put to rest, it is worth considering whether there are methodologic aspects that could be modified in future trials.

The choice of primary outcome is paramount and should take into consideration whether it is primarily the physical, emotional, or cognitive aspect of fatigue that is being targeted. The FACIT-F is the tool most commonly used in CRF studies and was also used in the study by Stone et al.[28] However, in a meta-analysis, the Piper Fatigue Scale was associated with the greatest reductions in CRF.[6] Of note, the Piper scale includes items that assess self-perceived concentration, memory, clarity of thinking, and depression, none of which are included in the FACIT-F. Given methylphenidate's cerebral localization of action in the prefrontal cortex, its effectiveness for improving concentration and attention in patients with ADHD (including children surviving cancer),[29] and preliminary findings from the study by Stone et al[28] and others[21,30] that methylphenidate may improve depression, the use of scales that include items evaluating emotional and cognitive fatigue should be considered for future trials.

Another important consideration for trials evaluating CRF in diverse cancer populations is the potential for heterogeneity of treatment effects.[31] In a negative trial, it is possible that some patients might have benefited but that the overall effect is diluted and therefore not significant.[32] Subgroup analyses can be useful to identify specific populations who

may benefit, although these analyses are prone to both low power and inflation of type 1 error, especially with relatively small subgroups.[31,32] In the trial by Stone et al,[28] there was a significant interaction between disease-modifying treatment (yes/no) and intervention (methylphenidate/placebo) on CRF, although there were no significant differences between methylphenidate and placebo within any subgroups; in other studies, patients with more severe fatigue or with depression experienced greater improvement from methylphenidate.[15,20,22] These results can inform future well-powered trials that could, for example, stratify according to these variables; plan for and replicate these subgroup analyses (including with newer predictive approaches)[33]; or specifically enroll patients with both fatigue and depression, or with more severe fatigue.

A consistent large placebo effect in trials of methylphenidate for CRF, including the study by Stone et al,[28] has raised the question of whether the placebo effect should be accounted for in the study design and analysis.[34] Part of this effect could be due to cointervention, and careful monitoring (or restriction) of concomitant interventions started during the trial is important, particularly for drugs known to improve CRF, such as dexamethasone.[35] However, several randomized controlled trials have documented the effectiveness of open-label placebo (ie, patients are informed that they are receiving the placebo), compared with usual care, for the treatment of CRF.[36-38] Various factors may play a role in the placebo effect, including expectation, hope of benefit, and the clinician-patient relationship.[39] Although use of open-label placebos to treat CRF is controversial, they may provide equivalent symptom relief to active drugs without associated side effects, and could be considered as a short-term stopgap treatment measure until reversible causes of CRF are identified and treated.[39]

In conclusion, Stone et al[28] present a methodologically rigorous placebo-controlled trial of methylphenidate for CRF in patients with advanced cancer receiving palliative care, finding it, in alignment with previous studies, to be safe but no more effective than placebo. However, we believe there remains room for further trials in this area, particularly in subpopulations that have demonstrated promise, using measures that are sensitive to the specific aspect of fatigue that is most likely to demonstrate a benefit. Considering the multifactorial nature of CRF, combination therapies of methylphenidate with other CRF treatments such as physical activity or cognitive behavioral therapy should also be considered.[40,41] In tandem, further inquiry into the pathophysiology and mechanisms of CRF may identify new pharmacologic therapies and lead to a more targeted, individualized approach to its assessment and treatment.

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