Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Long-Acting Methylphenidate for Cancer-Related Fatigue: North Central Cancer Treatment Group NCCTG-N05C7 Trial

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ABSTRACT

Purpose

Fatigue is one of the most common symptoms experienced by patients with cancer. This trial was developed to evaluate the efficacy of long-acting methylphenidate for improving cancer-related fatigue and to assess its toxicities.

Patients and Methods

Adults with cancer were randomly assigned in a double-blinded manner to receive methylphenidate (target dose, 54 mg/d) or placebo for 4 weeks. The Brief Fatigue Inventory was the primary outcome measure, while secondary outcome measures included a Symptom Experience Diary (SED), the Short Form-36 (SF-36) Vitality Subscale, a linear analog self-assessment, the Pittsburgh Sleep Quality Index, and the Subject Global Impression of Change.

Results

In total, 148 patients were enrolled. Using an area under the serum concentration-time curve analysis, there was no evidence that methylphenidate, as compared with placebo, improved the primary end point of cancer-related fatigue in this patient population ($P = .35$). Comparisons of secondary end points, including clinically significant changes in quality-of-life variables and cancer-related fatigue change from baseline, were similarly negative. However, a subset analysis suggested that patients with more severe fatigue and/or with more advanced disease did have some fatigue improvement with methylphenidate (eg, in patients with stage III or IV disease, the mean improvement in usual fatigue was 19.7 with methylphenidate v 2.1 with placebo; $P = .02$). There was a significant difference in self-reported toxicities (SED), with increased levels of nervousness and appetite loss in the methylphenidate arm.

Conclusion

This clinical trial was unable to support the primary prestudy hypothesis that the chosen long-acting methylphenidate product would decrease cancer-related fatigue.

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INTRODUCTION

Cancer-related fatigue, defined as a "persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning,"¹ is not relieved by sleep or rest,¹⁻³ and patients describe symptoms disproportionate to their level of physical activity.¹⁻⁴ It has a significant impact on overall quality of life (QOL).

In one study, fatigue adversely affected patient's daily lives more than did cancer-related pain (61% v 19%),⁵ while another study found that the

majority of patients (91%) self-reporting cancer-related fatigue felt they were unable to lead a normal life because of it.⁶ Therefore, it is not surprising that cancer-related fatigue is associated with substantial distress from disease symptoms and reduced performance status and is a prognostic factor for overall survival in patients with cancer.⁷

Fatigue is present in nearly all patients with advanced-stage tumors but also in long-term survivors, with a prevalence around 30%.⁸ It has been reported in higher proportions of patients receiving chemotherapy and radiotherapy, with prevalences

between 59% and 96% and between 65% and 100%, respectively.^{9,10} Despite the high prevalence of cancer-related fatigue, it remains undermanaged in the majority of patients, largely because of the lack of effective therapies for it.

Evidence-Based Interventions

Although a number of different nonpharmacologic and pharmacologic interventions have been explored as potential therapies for cancer-related fatigue, relatively few have been subjected to randomized, controlled trials. Of the nonpharmacologic options, exercise has the strongest evidence for effectively improving fatigue among patients with cancer.¹¹⁻¹⁷ In addition to exercise, a number of psychosocial interventions have been reported to be efficacious for the treatment of cancer-related fatigue, including group support,¹⁸ programs for coping strategies,¹⁹ stress management,²⁰ and tailored behavioral interventions.²¹ However, these interventions have not demonstrated even moderate effect sizes.

Finding effective pharmacologic therapies for cancer-related fatigue is difficult, because its mechanism is imprecisely understood. Limited data for breast cancer survivors support the hypothesis that fatigue is associated with a dysregulation in inflammatory processes and the hypothalamic-pituitary-adrenal axis.²² Further research is needed before it is understood how to target this physiology with respect to interventions for fatigue. However, published pilot data have suggested that psycho-stimulants may provide some benefit for patients with cancer-related fatigue.

Methylphenidate is a US Food and Drug Administration–approved CNS stimulant for the treatment of attention deficit hyperactivity disorder and narcolepsy. The mechanism of action for methylphenidate, although incompletely understood,²³ is predominantly to block uptake of dopamine by binding its transporter in the presynaptic cell membrane.^{24,25} The resulting increased synaptic dopamine particularly affects the striatum in the human brain.²⁶ The drug also has some ability to weakly block uptake of serotonin and norepinephrine.^{27,28}

Pharmacologic interventions with methylphenidate have suggested improvements in cancer-related fatigue, depressive symptoms, somnolence, and cognitive abnormalities in a number of nonrandomized studies.²⁹⁻³² In addition, several randomized, placebo-controlled trials have shown improvement in opioid-induced sedation with methylphenidate use among patients receiving strong narcotics for cancer-related pain.³³⁻³⁷

The largest pilot study that specifically examined cancer-related fatigue involved 31 patients with advanced cancer. They were given 5 mg methylphenidate every 2 hours as needed, up to a maximum of 20 mg, for 7 days.³⁸ Patients had significantly improved Brief Fatigue Inventory (BFI) scores after just 1 week of drug therapy, dropping from 7.2 ± 1.6 to 3.0 ± 1.9 . Patients in this study also reported improved anxiety, appetite, pain, nausea, depression, and drowsiness.

At least three other pilot studies reported similar findings. One such study³⁹ involving 30 patients reported improvements in fatigue, measured as increased stamina, while taking methylphenidate. Another nonrandomized study⁴⁰ claimed improved fatigue and functional ability in patients taking sustained-release methylphenidate along with exercise. Although the relative contributions of each of these components could not be separated, it was suggested that long-acting methylphenidate had at least some role in improving fatigue. In another nonrandomized study,⁴¹ nine of 11 patients reported im-

provements in fatigue symptoms from moderate/severe to mild with only 3 days of methylphenidate treatment.

In a follow-up study based on the promising results from their pilot trial,⁴² Bruera et al³⁸ tested methylphenidate for improving cancer-related fatigue in 112 patients. As in their pilot trial, patients were given 5 mg methylphenidate (or an identical-appearing placebo) every 2 hours as needed up to a maximum of 20 mg/d for 7 days. In this study, however, methylphenidate was not found to be any more effective for improving cancer-related fatigue than was the placebo.⁴³

Nonetheless, in another randomized, double-blind, placebo-controlled study⁴⁴ involving 152 cancer patients who were postchemotherapy, a different methylphenidate preparation was reported to be effective at improving cancer-related fatigue. In this study, patients received 27.7 mg/d of a sustained release preparation of the D-isomer Focalin. It was hypothesized that the D-isomer was the component that produced a clinically relevant decrease in cancer-related fatigue. If this was the case, it was proposed that the Bruera et al study⁴² dose of 20 mg/d administered only 10 mg/d of D-isomer, potentially a subtherapeutic level. Concerta (Ortho-McNeil-Janssen, Raritan, NJ) the drug of interest in this study is a racemic mixture of D- and L-isomers. Thus, a dose of 54 mg/d of Concerta was predicted to provide 27 mg/d of the D-isomer of methylphenidate, and it was hypothesized that this might produce the desired effect of improving cancer-related fatigue.

With the high prevalence of cancer-related fatigue and the limited number of therapeutic options, the purpose of this phase III, randomized, double-blind, placebo-controlled study of long-acting methylphenidate was to evaluate its efficacy for alleviating cancer-related fatigue, to assess its tolerability, and to study its effects on quality-of-life–related variables in patients with cancer-related fatigue.

PATIENTS AND METHODS

Patient Eligibility Criteria

Adults who were eligible for this trial had to have a history of cancer-related fatigue as defined by a score of 4 or more on a subjective fatigue level screening scale that ranged from zero (none) to 10 (as bad as it can be), for at least 1 month before registration. Patients were not eligible for this study if they had other causes of fatigue, including hypothyroidism, insomnia, uncontrolled pain, and/or anemia. Participants were required to have an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2 and a life expectancy of at least 6 months.

Contraindications to participation in the study included prior use of or hypersensitivity to methylphenidate; concomitant use of prescription stimulants or other medications/dietary supplements for fatigue; uncontrolled hypertension, brain malignancy/metastasis, psychiatric disorders (anxiety, bipolar syndrome, obsessive compulsive disorder, schizophrenia), acute/chronic progressive or unstable neurologic condition (dementia, delirium, or seizure disorder); hepatic, renal, cardiovascular, thyroid, or respiratory disease that would limit participation; major surgery within 1 month of registration; medical conditions for which methylphenidate is contraindicated (glaucoma, motor tics, family history or diagnosis of Tourette syndrome, history of drug or alcohol abuse, or intestinal obstruction); pregnant or nursing status; untreated hypothyroidism; or use of concurrent medications contraindicated with methylphenidate (eg, warfarin, anticonvulsants, tricyclic antidepressants, antipsychotics, monoamine oxidase inhibitors, clonidine, theophylline, and pseudoephedrine).

Random Assignment

Participants were stratified according to stage of disease (0, I, or II v III or IV), baseline fatigue score from eligibility screening (4 to 7 v 8 to 10), and

concurrent treatments (biologic therapy *v* not, chemotherapy *v* not, and radiation therapy *v* not). Patients were randomly assigned by computer using a dynamic allocation procedure⁴⁵ that balanced marginal distributions of stratification factors to one of two treatment groups for 4 weeks: long-acting methylphenidate or placebo. All participants and medical personnel providing care were blinded to treatment assignments. Informed consent was obtained from all participants through local institutional review boards, according to federal regulations.

Treatment Protocol

Participants took one tablet on days 1 through 7, two tablets on days 8 through 14, and three tablets on days 15 through 28. Each methylphenidate tablet was 18 mg, resulting in the goal dose of 54 mg/d for the final 2 weeks of the study. Tablets were to be taken in the morning. Doses were not to be increased if patients experienced adverse effects attributed to the study drug; rather, a dose-modification procedure was to be followed until the adverse event(s) no longer persisted. Weekly blood pressure and pulse rate checks were required of all participants to screen for study drug-induced hypertension and/or tachycardia.

Outcome Measures

The primary outcome measure was the BFI⁴⁶ to evaluate efficacy of methylphenidate at improving fatigue symptoms. Patients were to complete the BFI weekly on the same day, recording their fatigue 30 to 60 minutes after awakening, before taking their study drug for the day. The BFI also provided information about interference of fatigue on QOL measures. Secondary outcome measures included the weekly Short Form-36 (SF-36) Vitality Subscale,⁴⁷ the Linear Analog Self-Assessment items used in numerous North Central Cancer Treatment Group (NC-CTG) clinical trials⁴⁸⁻⁵⁰ for QOL measures, the Pittsburgh Sleep Quality Index (PSQI)⁵¹ completed at study entry and at the end of week 4, and the

Subject Global Impression of Change⁵² completed at the end of week 4 to evaluate patients' perceived improvements in overall quality of life, physical condition, and emotional state.

Adverse events and tolerability were assessed with Symptom Experience Diaries (SEDs), which were self-reported and completed at baseline and weekly throughout the study. These diaries assessed the severity of potential adverse effects on a scale of zero (not a problem) to 10 (as bad as it can be). Symptoms addressed in this diary included trouble sleeping, nervousness, shakiness/uncontrolled movements, headaches, abdominal pain, dizziness, loss of appetite, rapid/irregular heartbeats, vomiting, decreased sex drive, fatigue-related distress, and satisfaction with cancer-related fatigue control. The diary also allowed space to write in additional adverse effects noted by patients. Adverse event monitoring and reporting used the Common Terminology Criteria for Adverse Events (CTCAE) v3.0⁵³. Providers graded adverse events before the start of treatment and again at each weekly evaluation. Events included insomnia, mood alteration/anxiety, restlessness, tachycardia, skin rash, anorexia, involuntary movements, dizziness, headache, slurred speech, and abdominal pain.

Statistical Analysis

The primary end point was the prorated area under the [concentration-time] curve (AUC) of the Usual Fatigue question on the BFI for the baseline and for weeks 1 to 4, which was analyzed using the two-sample *t* test. With 140 patients enrolled, or 70 per treatment arm, and assuming approximately a 10% margin to account for patient cancellations and missing data, this study design provided 80% power to detect a difference of 50% times the standard deviation, with a two-sample *t* test. This is considered a moderate effect size.

Fig 1. CONSORT patient flow diagram. AE, adverse event; BFI, Brief Fatigue Inventory; AUC, area under the (concentration-time) curve.

All secondary end points were translated onto a zero- to 100-point scale, where zero is poor QOL or bad symptoms and 100 is best QOL or no symptoms, for comparability and ease of interpretation of clinical significance. Secondary analyses included confirmatory analyses of the primary end point using global evaluation of efficacy modeling and repeated analysis of variance (ANOVA) measures, comparisons of the AUCs of other QOL assessment scores via two-sample *t* tests, examination of change from baseline scores via two-sample *t* tests, examination of clinically significant^{54,55} changes of five and 10 points from baseline to the end of week 4 QOL variable scores using χ^2 methodology, and comparison of adverse event information using χ^2 or Fisher's exact methodology, as appropriate. Correlation analyses compared QOL scores during the 4 weeks of treatment. Finally, subgroup analyses were undertaken to evaluate whether benefit differed on the basis of baseline fatigue level and/or stage of disease.

RESULTS

Between February 29, 2008, and August 8, 2008, 148 patients were enrolled and randomly assigned on this trial. Patient participation and flow is depicted in a CONSORT diagram (Fig 1). Baseline patient characteristics are provided in Table 1, illustrating no statistically significant differences between the two study arms in the baseline-assessed variables.

The primary end point of prorated AUC for the usual fatigue question of the BFI did not show a statistically significant difference between the methylphenidate and placebo arms ($P = .32$; Table 2). The methylphenidate treatment arm demonstrated a 3.2% better fatigue score on average, which was 16% times the standard deviation of the fatigue scores (a small effect size) and not significantly different than that in the placebo arm. Figure 2 depicts mean usual fatigue scores over time and also illustrates no significant difference between the two arms.

The AUC comparison of the methylphenidate and placebo arms for all QOL variables assessed in this study failed to demonstrate any significant differences between the two groups. Variables included fatigue interference with general activity, mood, walking ability, normal work, relations with others, and enjoyment of life, as well as overall QOL. Mental, physical, spiritual, and emotional well-being, as well as social activity, overall sleep quality (PSQI), and measures from the vitality subscale were also compared between the two study arms and showed no significant difference in mean score using two-sample *t* tests. Specifically, there was no statistically significant improvement in sleep, as measured by the PSQI, or in mean scores for the SF-36 vitality subscale. In addition, there was no significant difference between the methylphenidate and placebo arms in changes from baseline for any of the QOL variables, including distress from fatigue or satisfaction with fatigue control.

Investigator-reported maximum toxicities, as measured by CTCAE v.3 were obtained by weekly phone calls to participants, and the overall toxicity incidence demonstrated no significant difference between the two study arms. Adverse effects relatively common in both groups included mild anxiety, dizziness, insomnia, and abdominal pain.

However, adverse events measured by the self-reported SEDs detected a significant increase in both nervousness and appetite loss in the methylphenidate arm compared with the placebo arm ($P = .003$ and $P = .034$, respectively; Table 3). Additionally, significantly more participants on the placebo arm (compared with the methylphenidate arm) reported 10-point improvements on the SED scores in the fol-

Table 1. Patient Baseline Characteristics

Characteristic	Methylphenidate Arm (n = 69)		Placebo Arm (n = 70)		P
	No.	%	No.	%	
Age, years					.263*
Mean	59.2		60.6		
SD	11.23		13.82		
Race					.605†
White	66	96	64	91	
Black or African American	3	4	5	7	
Unknown: patient unsure	0	0	1	1	
Sex					.425‡
Female	44	64	40	57	
Age group, years					.966‡
≥ 50	55	80	56	80	
Current chemotherapy	44	64	45	64	.949‡
Curative intent treatment	34	49	30	44	.545‡
Concurrent radiation	9	13	7	10	.574‡
Concurrent biological therapy	17	25	17	24	.962‡
Fatigue scale					.954‡
4-7	47	68	48	69	
8-10	22	32	22	31	
Stage					.954‡
0/I/II	22	32	22	31	
III/IV	47	68	48	69	
Type of cancer					.497†
Breast	26	38	20	29	
Colon	4	6	4	6	
Prostate	2	3	6	9	
Lung	10	15	8	11	
Combination/unknown/other	27	39	32	46	
Average fatigue over the last week (0-100, best)					.839*
Mean	33.6		34.0		
SD	15.43		17.23		
Median	30.0		30.0		
Average pain over the last 24 hours (0-100, best)					.399*
Mean	87		86		
SD	13.88		12.58		
Median	90		90		

Abbreviation: SD, standard deviation.

*Kruskal-Wallis exact test.

†Fisher's exact test.

‡ χ^2 test.

lowing symptoms: nervousness (38% v 19%), shakiness (18% v 7%), appetite loss (32% v 15%), abdominal pain (22% v 8%), and sex drive (17% v 5%).

Because the sample was heterogeneous, an exploratory analysis was done to evaluate whether there was any sign of benefit for any subgroup. Change in usual fatigue from baseline was evaluated on the basis of fatigue severity at baseline and stage of disease. In advanced-stage disease (III or IV), the mean improvement in usual fatigue was 19.7 with methylphenidate and 2.1 with placebo ($P = .02$). The early-stage participants (0, I, or II) actually had less of an improvement from baseline on usual fatigue with methylphenidate than did those with the placebo (17 v 29, respectively). Similar trends were seen in the vitality subscale of the SF-36. For those with the highest levels of worst fatigue (score of 8 to 10) at baseline, the mean change in usual fatigue

Table 2. BFI Fatigue Average AUC

BFI Question	Study Arm	No. of Patients	Mean Fatigue Score	95% CI	SD	Median Fatigue Score	P*
Fatigue right now	Methylphenidate	62	49.34	43.84 to 54.84	21.65	50.00	.684
	Placebo	63	47.90	42.93 to 52.87	19.73	47.50	
Usual fatigue (primary end point)	Methylphenidate	62	50.33	45.17 to 55.49	20.32	50.00	.317
	Placebo	63	47.15	42.86 to 51.43	17.00	48.75	
Worst fatigue	Methylphenidate	62	39.65	34.25 to 45.05	21.26	38.13	.167
	Placebo	63	34.60	29.84 to 39.36	18.88	32.50	

NOTE. Higher scores are better.

Abbreviations: BFI, Brief Fatigue Inventory; AUC, area under the concentration-time curve; SD, standard deviation.

*Wilcoxon rank sum test.

on methylphenidate was 26 versus 16 on placebo, although this was not statistically significant.

DISCUSSION

Despite a series of preliminary studies showing evidence supporting the efficacy of methylphenidate therapy for the management of cancer-related fatigue, the results of this trial did not show any statistically significant benefit for 54 mg/d doses of long-acting methylphenidate compared with placebo for alleviating cancer-related fatigue. Comparisons between the two treatment arms for secondary end points, including cancer-related fatigue change from baseline and percentage of patients experiencing a clinically significant change in QOL measures, were unable to demonstrate any significant benefit. These results support those reported in another placebo-controlled, double-blind, randomized trial.⁴²

These results, however, contrast with results from Lower et al,⁴⁴ which reported benefit for D-methylphenidate in a placebo-controlled trial. That trial differed from this current trial in several ways. First, the population for this current trial included a heterogeneous group of cancers with almost equal numbers of men and women and a slight majority of participants with later-stage disease. The population in the Lower et al study was almost all female and primarily had breast cancer, with a few

women having ovarian cancer. Stage of disease in the Lower et al sample is not specified. Furthermore, Lower et al claim that the scores had greater separations starting at 5 weeks, and their primary end point was at 8 weeks, while it was at 4 weeks in this study. Lower et al also used a 13-item fatigue scale, while this study used one usual fatigue question as the primary end point. It should be noted that the subjective perception of improvement between the methylphenidate and placebo groups in the Lower et al study was not statistically significant. Therefore, it is not clear whether the statistically significant difference in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores (methylphenidate, −10.5 and placebo, −6.8) is clinically important and for whom the treatment might have been more beneficial.

This current trial attempted to determine whether any groups of participants found methylphenidate to be helpful. There was clearly more benefit reported by those with stage III or IV disease using methylphenidate over placebo, while the early-stage participants receiving the active agent did not report more benefit. There also may have been more of a benefit in those with more severe fatigue. Therefore, these data support a hypothesis that could be tested in future research: Does D-methylphenidate provide benefit in patients with advanced disease with severe fatigue?

Fig 2. Mean usual fatigue scores over time by study arm for methylphenidate (solid gold line) and placebo (dotted blue line). Higher scores are better.

Table 3. Mean (SD) Scores From Symptom Experience Diary, Changes From Baseline

Symptom	Methylphenidate Arm (n = 49)		Placebo Arm (n = 56)		P
	Mean	SD	Mean	SD	
Nervousness	−2.7	20.08	9.5	17.15	.003
Appetite decrease	−5.2	21.04	6.6	28.87	.034
Sex drive	−0.9	22.63	9.8	37.17	.062
Abdominal pain	−3.5	21.85	3.6	19.49	.078
Dizziness	−2.2	15.58	2.1	17.76	.145
Shakiness	−0.6	11.97	1.4	18.82	.284
Heartbeat	−2.0	10.60	−1.6	16.60	.538
Vomiting	−0.8	9.19	0.4	18.29	.635
Headaches	−0.8	18.80	3.9	17.34	.718
Trouble sleeping	10.6	29.99	11.1	28.58	.858

NOTE. Higher numbers represent decreased symptoms over the baseline period.

Abbreviation: SD, standard deviation.

It is not surprising that participants in the methylphenidate treatment group reported increased adverse effects, including nervousness and appetite loss, compared with those in the placebo arm. Due to its psycho-stimulant properties, methylphenidate is associated with a variety of adverse effects, including some of those noted in this study. Nervousness is among the most common adverse effects noted with general methylphenidate use,^{23,56} while appetite loss and abdominal pain have been noted in many controlled clinical studies using this drug.⁵⁷ Decreased libido and shakiness have also been noted as adverse effects in a small percentage of participants in placebo-controlled methylphenidate studies. Because of the adverse effect profile seen in this study, as well as in the Lower et al trial, future evaluations of D-methylphenidate should take into account the risk-benefit ratio from the patient's perspective. Of note, it is recognized that a sustained-release methylphenidate preparation might not be as ideal for cancer fatigue as a more immediate release preparation.

In total, the results of this trial are unable to support the prestudy hypothesis that methylphenidate would be an effective therapy for the management of cancer-related fatigue, at least at a dose of 54 mg/d in this mixed sample.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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