Original Article

Efficacy of Dexmethylphenidate for the Treatment of Fatigue After Cancer Chemotherapy: A Randomized Clinical Trial

Elyse E. Lower, MD, Stewart Fleishman, MD, Alyse Cooper, MBA, Jerome Zeldis, MD, PhD, Herbert Faleck, DO, Zhinuan Yu, PhD, and Donald Manning, MD, PhD

University of Cincinnati Medical Center (E.E.L.), Cincinnati, Ohio; Continuum Cancer Centers of New York (S.F.), Beth Israel Medical Center & St. Luke's-Roosevelt Hospital Center, New York, New York; and Celgene Corporation (A.C., J.Z., H.F., Z.Y., D.M.), Summit, New Jersey, USA

Abstract

Cancer and its treatment can induce subjective and objective evidence of diminished functional capacity encompassing physical fatigue and cognitive impairment. Dexmethylphenidate (D-MPH; the D-isomer of methylphenidate) was evaluated for treatment of chemotherapy-related fatigue and cognitive impairment. A randomized, double-blind, placebo-controlled, parallel-group study evaluated the potential therapeutic effect and safety of D-MPH in the treatment of patients with chemotherapy-related fatigue. Change from baseline in the Functional Assessment of Chronic Illness Therapy-Fatigue Subscale (FACIT-F) total score at Week 8 was the primary outcome measure. One hundred fifty-four patients (predominantly with breast and ovarian cancers) were randomized and treated. Compared with placebo, D-MPH-treated subjects demonstrated a significant improvement in fatigue symptoms at Week 8 in the FACIT-F (P = 0.02) and the Clinical Global Impression-Severity scores (P = 0.02), without clinically relevant changes in hemoglobin levels. Cognitive function was not significantly improved. There was a higher rate of study drug-related adverse events (AEs) (48 of 76 [63%] vs. 22 of 78 [28%]) and a higher discontinuation rate because of AEs (8 of 76 [11%] vs. 1 of 78 [1.3%]) in D-MPH-treated subjects compared with placebo-treated subjects. The most commonly reported AEs independent of study drug relationship in D-MPH-treated subjects were headache, nausea, and dry mouth, and in placebo-treated subjects were headache, diarrhea, and insomnia. D-MPH produced significant improvement in fatigue in subjects previously treated with cytotoxic chemotherapy. Further studies with D-MPH or other agents to explore treatment response in chemotherapy-associated fatigue should be considered. J Pain Symptom Manage

This study was supported by investigator grants to E. E. L. and S. F. from the sponsor, Celgene Corporation. Novartis Corporation, East Hanover, NJ, supplied the study drug.

Presented as an abstract (No. 8000) at the 2005 American Society of Clinical Oncology Annual Meeting, and as a poster presentation (No. 5026) at the 2005 San Antonio Breast Cancer Symposium Annual Meeting.

Address correspondence to: Elyse E. Lower, MD, University of Cincinnati Medical Center, Albert Sabin Way, 1001 Holmes, Cincinnati, OH 45267-0565, USA. E-mail: elower@ohcmail.com

Accepted for publication: April 1, 2009.

0885-3924/09/$—see front matter
doi:10.1016/j.jpainsymman.2009.03.011

2009;38:650–662.

Key Words
Dexmethylphenidate, chemobrain, chemotherapy-related fatigue

Introduction

"Chemobrain" encompasses multiple symptoms, which can occur both during treatment and for a significant period of time after therapy completion. A frequently reported component of this syndrome includes chemotherapy-induced fatigue. National Comprehensive Cancer Network Guidelines define cancer-related fatigue as a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning.[1] Surveys of cancer patients suggest that cancer-related fatigue is common and results in substantial adverse physical, psychosocial, and economic consequences for patients and caregivers.[2–5] This fatigue may be accompanied by cognitive impairment,[6] another component of "chemobrain."[7] It is now appreciated, however, that many symptoms may occur before the initiation of chemotherapy and have an etiology in the cancer itself.[4]

Pilot studies have demonstrated that use of methylphenidate alone,[8] or in combination with aerobic exercise,[9] may lessen cancer-related fatigue in adult cancer survivors. Additionally, cognitive and social functioning were improved in survivors of childhood acute lymphoblastic anemia and brain tumors who were treated with methylphenidate (20 mg/day).[10] Patients with malignant glioma treated with methylphenidate (10–30 mg/day) reported an improvement in cognitive function.[11]

Dexmethylphenidate HCl (D-MPH, Focalin®, Celgene Corp., Summit, NJ, the D-isomer of D,L-threo-methylphenidate [D,L-MPH]), the product used in this study, has been approved in the United States for the treatment of attention-deficit hyperactivity disorder (ADHD) in children and adolescents, and a once-a-day formulation of D-MPH (Focalin XR®) has been approved in the United States for the treatment of ADHD in children, adolescents, and adults. Both the pharmacological properties[12–15] and the clinical efficacy[16] of D,L-MPH reside in both the D and L enantiomers and, therefore, D-MPH is efficacious at roughly half the dose of D,L-MPH.[17] No adverse events (AEs) unique to chirally pure D-MPH have been reported.[18]

We conducted a multicenter, randomized, placebo-controlled, parallel-group study to test the hypothesis that D-MPH would produce a significant reduction in fatigue compared with placebo after cytotoxic chemotherapy in patients with cancer. Recruitment occurred after completion of chemotherapy to identify the largest number of subjects with fatigue symptoms.

Methods

Subjects

This study was conducted from September 2002 through December 2003 at 24 academic and community-based cancer centers. Detailed training was provided to facilitate uniform administration of efficacy outcome measures. All subjects provided written informed consent, which, along with the protocol, was approved by each center's institutional review board. This study was registered with http://ClinicalTrials.gov (number NCT00047476).

One hundred sixty-eight subjects were enrolled; of these, 154 were randomized to double-blind treatment (see Fig. 1 for additional information on the 14 subjects who were not randomized). Subjects were males or nonpregnant, nonlactating females aged 18–70 years with diagnoses of cancer, excluding primary or metastatic brain tumors, previously treated with ≥4 cycles of cytotoxic chemotherapy completed ≥2 months before study entry. Subjects were required to have a life expectancy of >6 months, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, and a physical examination without focal neurological deficit.

Before study enrollment, subjects needed to meet the proposed International Classification

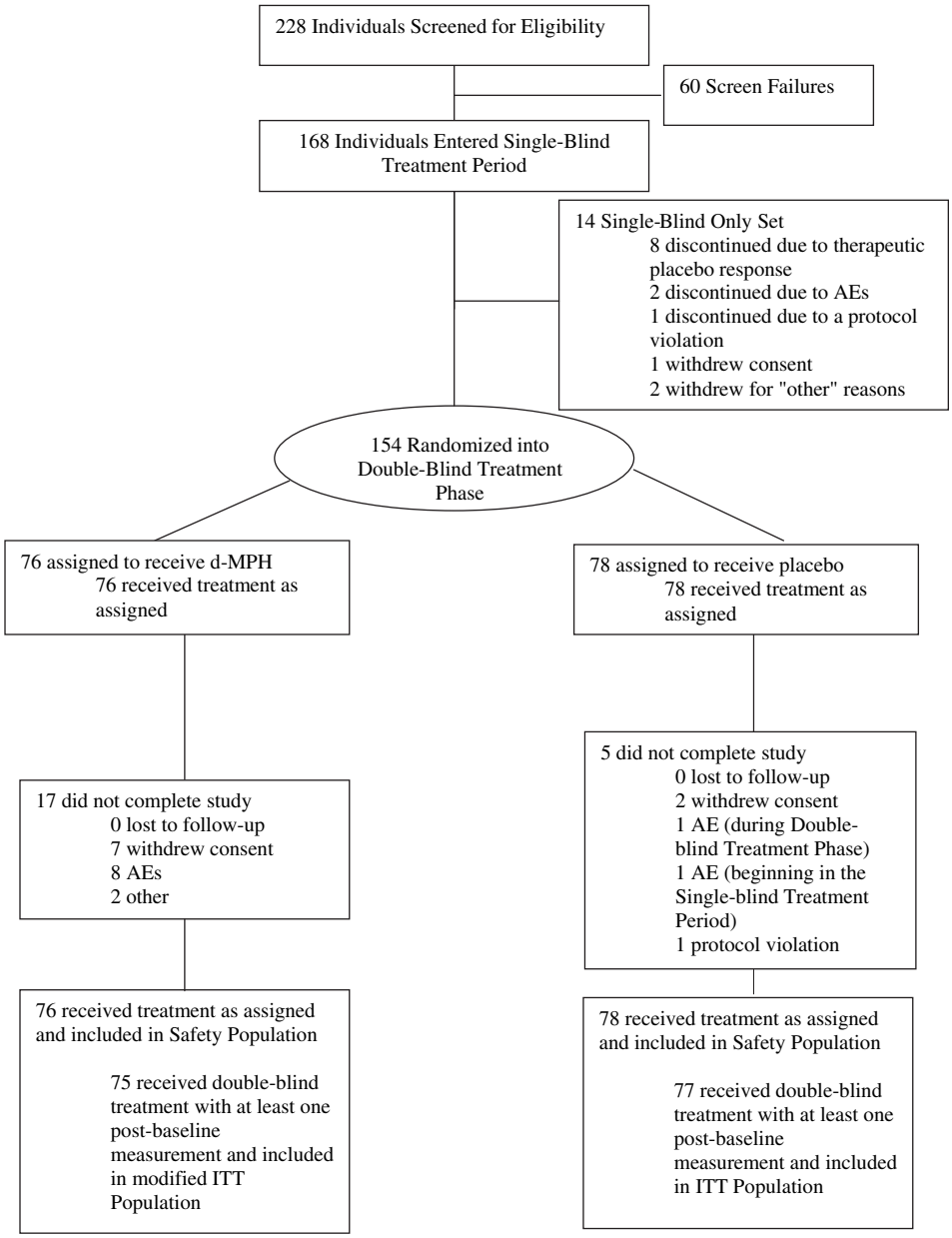

Fig. 1. Trial flow diagram.

of Disease, Tenth Revision (ICD-10) criteria for cancer-related fatigue (Table 1)[19] and achieve a Mini-Mental State Exam (MMSE) score of ≥20 (the minimum requirement for High Sensitivity Cognitive Screen [HSCS] validity[20]), a Beck Depression Inventory-II (BDI-II) score of <18 (no greater than moderate depression[21]), and a Clinical Global Impression-Severity (CGI-S) score ≥3 (mildly impaired[22]). Race determination was self-reported and used to compare the composition of treatment groups at baseline. There was no a priori hypothesis about race and treatment effect.

Subjects were excluded from entry for concurrent treatment with anticancer therapies (biological and/or radiation therapy), history of major psychiatric illness, attention-deficit disorder (ADD), learning disabilities or special educational support, prior treatment with methylphenidate or D-MPH, or an inability to

Table 1
Proposed ICD-10 Criteria for Cancer-Related Fatigue

A1	Significant fatigue, diminished energy, or increased need to rest disproportionate to any recent change in activity level
A2	Complaints of generalized weakness or limb heaviness
A3	Diminished concentration or attention
A4	Decreased motivation or interest to engage in usual activities
A5	Insomnia or hypersomnia
A6	Experience of sleep as unrefreshing or nonrestorative
A7	Perceived need to struggle to overcome inactivity
A8	Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued
A9	Difficulty completing daily tasks attributed to feeling fatigued
A10	Perceived problems with short-term memory
A11	Postexertional malaise lasting several hours
B	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C	There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer therapy.
D	The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium.

Subjects were required to have B impairment and at least six (or more) of the A symptoms present every day or nearly every day during the same two-week period in the past month before screening; additionally, at least two of those symptoms were required to be A1 and A3 (diminished concentration or attention) or A10 (perceived problems with short-term memory).
Reprinted with permission from Cella et al. [19]

maintain a stable dose regimen of opioids or other centrally-acting drugs for at least seven days before the study (to eliminate confounding fatigue and/or cognitive impairment based on variable, intermittent opioid usage in nonopioid-tolerant subjects). Subjects were also excluded from entry if, in the opinion of the investigator, their symptoms of fatigue and/or cognitive impairment were felt to be attributable to current, naturally occurring menopause. Additional exclusion criteria included other medical or psychiatric conditions or laboratory abnormalities that may have increased risk associated with study drug administration or study participation or may have interfered with the interpretation of study results, use of monoamine oxidase inhibitors within 30 days, or a history of seizure disorder or drug/alcohol abuse.

Procedures

The randomization scheme was generated by a statistician not involved with the study and was provided to the site's unblinded investigational pharmacist. D-MPH and identically appearing placebo tablets were provided in bulk supply to the pharmacy at the investigator's site. Packaging and labeling of study drug containers was completed by the pharmacists on site. Eligible subjects were randomized by the investigator to double-blind treatment of either 5 mg D-MPH twice a day (10 mg/day) or identically appearing placebo twice a day in a 1:1 ratio within each site in a centrally determined block size of four. Site personnel responsible for the administration of interventions and assessment of outcomes were blinded to subjects' treatment group assignments. Poststudy assessments of blinding were not performed with either subjects or investigators.

The information relative to the primary and secondary efficacy measures that were assessed in this study is shown in Table 2. At the baseline/randomization visit (Week 0), after a seven-day, single-blind, placebo run-in period, the investigator assessed the severity of symptoms and therapeutic placebo response using the CGI-S and the Clinical Global Impression-Improvement (CGI-I) Scales, respectively. Subjects eligible for randomization were those who maintained or worsened in their severity of symptoms (CGI-S) and had confirmation of worsening or no improvement during single-blind placebo treatment (CGI-I). Other exploratory efficacy assessments performed at this time included the Functional Assessment of Chronic Illness Therapy-Fatigue Subscale (FACIT-F), modified Swanson, Nelson and Pelham Attention Deficit/Hyperactivity Scale (SNAP), and the HSCS.

During the double-blind treatment phase, subjects were seen weekly for efficacy and safety assessments. Efficacy assessments, including the FACIT-F total score and CGI-I and modified SNAP total scores, were obtained

Table 2
Assessment of Primary and Secondary Efficacy Measures

Measure	No. of Items	Scaling	Scoring	Validity	Reliability
FACIT-F (primary)	13	0 = not at all to 4 = very much	FACIT-F total score = [(sum of questions 7 and 8) + (sum of Q's 1−6 and 9−13 each deducted from 4)] multiplied by 13 divided by the number of questions answered). Question 14 was analyzed separately	0.66	Cronbach's alpha initial/retest = 0.93/0.95 Test-retest reliability = 0.90
SNAP	18	1 = not at all to 4 = very much	Total score = sum of scores for questions 1−18. If in the event a subject is missing the answer to any of the questions, then the sum for questions 1−18 will be equal to the mean of the answered questions multiplied by 18	Yes[a]	Yes[a]
HSCS	26	Numeric item scoring; overall classification of level of improvement = mild, moderate, or severe	Total HSCS score = sum of subscale scores: Memory Subscale total score = (39 − sum of 3 sentence scores) + (18 − sum of 3 word pair trial scores) + (13 − sentence recall score) + (6 − word pair recall. Language Subtest Subscale score = repetition score + fluency score + (30 − response naming score) + reading score + (sum of writing to dictation scores). Visual-motor score = total visual-motor score Spatial score = (8 − spatial total score). Attention and concentration score = Alternating numbers score (number of false starts + errors) + signaling to numbers score. Self-regulation and planning score = conflicting stimuli score + sentence construction score.	Yes[a]	Inter-rater reliability for overall score = 0.98 Test-retest correlation = 0.95 for overall screen
CGI-I	1	1 = very much improved to 7 = very much worse	Recorded directly onto case report form as an overall score	Yes[a]	Yes[a]
CGI-S	1	1 = normal, not at all impaired to 7 = among the most extremely impaired subjects	Recorded directly onto case report form as an overall score	Yes[a]	Yes[a]

[a] Scale reported as reliable and valid in numerous indications; however, no specific information regarding the reliability/validity of the scale in this indication is available.

weekly and at the end of the double-blind treatment phase. The CGI-S and HSCS also were evaluated at the end of the double-blind treatment phase. Safety assessments included physical examinations, electrocardiographs, AEs, vital signs, and laboratory testing.

Over the eight-week double-blind treatment phase, weekly dose modifications were allowed at the investigator's discretion based on the magnitude and the duration of the therapeutic response, as assessed by weekly CGI-I scores. Optimal magnitude of therapeutic response was achieved through weekly dose escalations up to 10 mg/day (2.5, 5, or 10 mg tablets), and optimal duration of response was achieved by adjustment of the dose frequency. Maximum allowed total daily dosage was 50 mg/day; dosing frequency could be twice or three times per day.

The primary efficacy measure was the sustainability of effect from baseline for the FACIT-F total score at completion of the eight-week double-blind treatment phase using last observation carried forward (LOCF) analysis.[23]

Secondary exploratory efficacy measures included CGI-S,[22] CGI-I,[22] HSCS overall total and subscale scores,[20] and SNAP total scores.[15] The HSCS questionnaire tested six cognitive domains (memory, language, visual-motor, spatial, attention/concentration, and self-regulation and planning) and has been used for cognitive assessment (short- and long-term) before and after chemotherapy in breast cancer patients. The HSCS is sensitive for detecting subtle cognitive impairment, has been validated for use in subjects aged 16–65 years, and has high inter-rater and test-retest reliability.[5,20,24,25] The modified SNAP scale, initially designed to assess ADD in children, was modified to assess behavioral symptoms in adults and has been used to assess D-MPH efficacy in the treatment of ADD.

Statistical Analysis

Sample size estimates based on the study of Yellen et al.[23] required 60 evaluable subjects per group to detect a 15% relative difference with 80% power, using a two-tailed *t*-test at the 0.05 level. Factoring in a 10% placebo run-in responder rate and 15% dropout rate, 80 randomized subjects per group (160 total subjects) were required to obtain 120 evaluable subjects.

The intent-to-treat (ITT) population, as defined by the protocol, consisted of all randomized subjects who received at least one dose of double-blind study drug and had at least one post-baseline measurement for CGI-I, CGI-S, modified SNAP, FACIT-F, or HSCS. The safety population consisted of all subjects who received at least one dose of double-blind treatment (D-MPH or placebo).

Time since prior cytotoxic chemotherapy and type of prior cytotoxic chemotherapy were compared between treatment groups using *t*-tests. Screening scores for ICD-10 criteria, BDI-II total score, MMSE, CGI-S, and age were summarized using summary statistics (*n*, mean, standard deviation [SD], median, minimum, maximum), whereas ECOG performance status, gender, race, education level, and employment status were summarized with frequency tabulations for each treatment group separately and pooled over both arms. Homogeneity of these variables was assessed by *t*-test for continuous variables (ICD-10 criteria, BDI-II total score, MMSE, and age) and Fisher's exact tests for categorical measures (gender, race, education level, and employment status). Ordered categorical variables (ECOG performance status, CGI-S) were assessed by the Cochran-Mantel-Haenszel test.

For the change from baseline endpoints, the primary analysis used an analysis of covariance (ANCOVA) model to test for differences between treatment groups. For the primary endpoint, the change from baseline scores on the total scores of the FACIT-F, the distribution assumption of normality was checked using the Shapiro-Wilk test on the standardized residuals from the ANCOVA model at the 0.05 level of significance. No substantial departure from normality was detected. The ANCOVA model incorporated terms for treatment, center, baseline score, and treatment × baseline interaction using a LOCF analysis approach. By using LOCF, missing FACIT-F total scores at a specific week were replaced with the last post-baseline value obtained. If a subject was missing all values post-baseline, the baseline value was not brought forward. For scores that did not involve calculation of change from baseline and could be considered ordinal data (e.g., CGI-S, CGI-I), a nonparametric ANCOVA was used.[26] This method is based on ranked data, and the treatment effect is

assessed by adjusting for baseline and using center as a stratification variable. SAS® version 8.2 statistical software (SAS Institute, Inc., Cary, NC) was used for all analyses; $P < 0.05$ (two-tailed) was considered significant.

Results

The safety population consisted of 154 subjects who were randomized in a 1:1 ratio to either D-MPH ($n = 76$) or placebo ($n = 78$) (14 subjects were not randomized; see Fig. 1 for additional information). The ITT population consisted of 75 subjects who received D-MPH and 77 subjects who received placebo. Breast cancer was the most prevalent cancer diagnosis (D-MPH: 78%, placebo: 73%), followed by ovarian cancer (D-MPH: 13%, placebo: 17%). The treatment groups were well matched at screening and baseline for demographic characteristics, MMSE, BDI-II, FACIT-F total score, CGI-S, CGI-I (after the single-blind placebo treatment period), number of ICD-10 cancer fatigue criteria, type of prior cytotoxic chemotherapy (Table 3), and time since last chemotherapy (Table 4). A between-group comparison, however, revealed that D-MPH-treated subjects had lower screening ECOG performance status scores, indicating better performance than that of the placebo-treated subjects ($P = 0.03$).

Table 3
Baseline Characteristics of the Subjects (ITT Population)

Characteristics	D-MPH ($n = 75$)[a]	Placebo ($n = 77$)[a]	Total ($n = 152$)[a]
Demographics			
Age, mean (SD), years	52.5 (10.2)	53.2 (8.4)	52.8 (9.3)
Women, *n* (%)	71 (94.7)	72 (93.5)	143 (94.1)
White, *n* (%)	62 (82.7)	59 (76.6)	121 (79.6)
ECOG Performance Status Scale, *n* (%)[b]			
0	43 (57.3)	33 (42.9)	76 (50.0)
1	30 (40.0)	36 (46.8)	66 (43.4)
2	2 (2.7)	8 (10.4)	10 (6.6)
3 or 4	0	0	0
Number of ICD-10 criteria selected, mean (SD)[c]	11.0 (1.9)	10.9 (2.0)	10.9 (2.0)
BDI-II total score, mean (SD)	10.8 (4.6)	10.9 (4.6)	10.8 (4.6)
MMSE, mean (SD)	28.7 (1.7)	28.8 (1.5)	28.7 (1.6)
FACIT-F total score, mean (SD)	30.9 (10.2)	30.0 (10.1)	30.5 (10.1)
CGI-S, *n* (%)[d]			
1 or 2	0	0	0
3	20 (27.0)	19 (25.0)	39 (26.0)
4	36 (48.6)	35 (46.1)	71 (47.3)
5	16 (21.6)	18 (23.7)	34 (22.7)
6	1 (1.4)	2 (2.6)	3 (2.0)
7	1 (1.4)	2 (2.6)	3 (2.0)
CGI-I, *n* (%)[e]			
1 or 2	0	0	0
3	2 (2.7)	0	2 (1.3)
4	68 (90.7)	73 (94.8)	141 (92.8)
5	4 (5.3)	3 (3.9)	7 (4.6)
6	1 (1.3)	1 (1.3)	2 (1.3)
7	0	0	0
Modified SNAP, mean (SD)	34.9 (8.8)	36.2 (9.1)	35.5 (9.0)
HSCS total score, mean (SD)	35.9 (17.0)	37.1 (18.1)	36.5 (17.5)
Time since last chemotherapy, mean (SD) (weeks)	123.8 (116.5)	107.0 (95.8)	115.3 (106.5)

[a] Subject 11007 (randomized to D-MPH) discontinued from study after randomization due to an AE before recording any post-baseline assessments; Subject 15004 (randomized to placebo) withdrew consent after one post-baseline CGI-I assessment. These two subjects were excluded from the ITT analysis set but are included in the safety analysis set (demographics and ECOG performance status).
[b] ECOG: 0 = fully active, able to carry out all predisease performance without restriction (Karnofsky 90–100); 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work (Karnofsky 70–80); 2 = ambulatory and capable of all self-care but unable to carry out work activities; up and about more than 50% of waking hours (Karnofsky 50–60); 3 = capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30–40); and 4 = completely disabled, cannot carry on any self-care, totally confined to bed or chair (Karnofsky 10–20).
[c] ICD-10: subjects must have met the proposed ICD-10 criteria for cancer-related fatigue. Subjects must have had "B" criteria and at least a total of six "A" criteria, two of which must have been A1 and A3 or A10.
[d] CGI-S: 1 = normal, not at all impaired; 2 = borderline mentally impaired; 3 = mildly impaired; 4 = moderately impaired; 5 = markedly impaired; 6 = severely impaired; 7 = among the most extremely impaired subjects.
[e] CGI-I: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse. Assessment of CGI-I followed one week of single-blind placebo treatment to assess for therapeutic placebo response.

Table 4
Prior Cytotoxic Chemotherapy

Cytotoxic Chemotherapy	D-MPH ($n = 75$)	Placebo ($n = 77$)
Cyclophosphamide	55 (73.3)	60 (77.9)
Doxorubicin	49 (65.3)	40 (51.9)
Paclitaxel	27 (36.0)	33 (42.9)
Fluorouracil	25 (33.3)	32 (41.6)
Methotrexate	18 (24.0)	21 (27.3)
Carboplatin	12 (16.0)	17 (22.1)
Docetaxel	11 (14.7)	10 (13.0)
Vincristine	7 (9.3)	2 (2.6)
Cisplatin	3 (4.0)	5 (6.5)
Dacarbazine	4 (5.3)	3 (3.9)
Etoposide	3 (4.0)	4 (5.2)
Rituximab	5 (6.7)	2 (2.6)
Vinblastine	2 (2.7)	4 (5.2)
Bleomycin	1 (1.3)	4 (5.2)
Folinic acid	3 (4.0)	2 (2.6)
Ifosfamide	4 (5.3)	1 (1.3)
Mesna	4 (5.3)	1 (1.3)
Prednisone	4 (5.3)	1 (1.3)
Cytarabine	1 (1.3)	2 (2.6)
Melphalan	1 (1.3)	2 (2.6)
Thiotepa	0 (0.0)	3 (3.9)
Epirubicin	0 (0.0)	2 (2.6)
Topotecan	2 (2.7)	0 (0.0)
Trastuzumab	0 (0.0)	2 (2.6)

The mean highest dose achieved was 27.7 mg/day (range 10–70 mg/day) in D-MPH-treated subjects and 39.3 mg/day (range 10–70 mg/day) in placebo-treated subjects. The mean final doses were 25.5 mg/day (D-MPH) and 38.5 mg/day (placebo). One (1.3%) D-MPH-treated subject and two placebo-treated subjects (2.6%) had major violations involving proper study drug administration. Analyses, both including (ITT analysis) and excluding (per protocol analysis) the data from these subjects, did not significantly influence the primary efficacy results.

Analyses of primary and secondary efficacy variables measured during the eight-week double-blind treatment phase using the LOCF approach are listed in Table 5. A significantly greater improvement in mean change from baseline FACIT-F total score was observed for the D-MPH group compared with placebo at Week 8, which was the primary endpoint ($P = 0.02$). The adjusted mean change from baseline score at Week 8 was −10.5 and −6.8 for D-MPH and placebo subjects, respectively. A repeated measure analysis using a mixed model as an exploratory analysis showed that treatment effect changed over time. As shown in Table 5, as well as in Fig. 2, a greater improvement in the D-MPH group's total FACIT-F scores as compared with the placebo group's total FACIT-F scores was seen at Weeks 1, 5, 6, and 7, with greater separation in total scores noted at later visits, particularly starting at Week 5. Given the baseline differences in ECOG scores, further exploratory analyses were performed to assess the potential impact of this difference on the primary efficacy variable; significant results were maintained ($P = 0.03$).

In a post hoc analysis (data not shown), FACIT-F data for subjects (regardless of treatment) were compared with their CGI-I scores. For the purpose of this analysis, CGI-I scores were categorized into two groups: Group 1 combined subjects with CGI scores of "1" and "2" (very much improved and much improved, respectively) and Group 2 combined subjects with CGI-I scores of "3" through" 7" (minimally improved, no change, minimally worse, much worse, and very much worse, respectively). Those subjects reporting a clinically meaningful improvement (very much or much improved) on the CGI-I averaged a 13.2 point reduction in total FACIT-F scores compared with baseline. Group 2 subjects averaged a 3.7 point reduction in total FACIT-F scores compared with baseline.

The reduction in fatigue as measured by the FACIT-F also was reflected in a decreased severity of symptoms measured by CGI-S scores. In exploratory secondary analyses, nearly all D-MPH- and placebo-treated subjects had decreased CGI-S scores, indicating decreased severity of symptoms from baseline to Week 8. At baseline, 56 of 75 (74.7%) D-MPH-treated subjects were scored "3 = mildly impaired" or "4 = moderately impaired" and 18 (24.0%) were scored "5 = markedly impaired," "6 = severely impaired," or "7 = among the most extremely impaired subjects." In the placebo treatment group, baseline CGI-S scores were similarly distributed, with 54 of 77 (70.1%) placebo-treated subjects scoring 3 or 4, and 22 (28.6%) scoring 5, 6, or 7. At the end of the double-blind treatment phase, 54 of 75 (72.0%) D-MPH-treated subjects scored 1, 2, or 3, as compared with 45 of 77 (58.4%) placebo-treated subjects ($P = 0.02$).

Change in cognitive function was assessed using the HSCS overall score and subscale scores. There was little to no significant change in either treatment group for the overall or subscale scores.

Table 5
Analyses of Primary and Secondary Efficacy Outcomes (ITT Population)

Efficacy Outcomes	D-MPH ($n = 75$)[a]	D-MPH Observed Cases	Placebo ($n = 77$)[a]	Placebo Observed Cases	*P* Value
Primary outcome					
FACIT-F total score: adjusted mean (SEM) for change from baseline					
Week 1	−4.7 (0.8)	74	−2.6 (0.8)	75	
Week 2	−6.2 (0.9)	67	−3.8 (0.9)	75	
Week 3	−6.4 (1.0)	65	−4.3 (1.0)	75	
Week 4	−8.7 (1.0)	63	−6.0 (1.0)	74	
Week 5	−9.3 (1.1)	62	−5.0 (1.1)	74	
Week 6	−9.2 (1.1)	63	−6.2 (1.1)	74	
Week 7	−9.7 (1.1)	60	−6.2 (1.1)	72	
Week 8	−10.5 (1.2)	54	−6.8 (1.2)	69	0.02
Secondary outcomes					
CGI-S score at Week 8, *n* (%)					0.02
1	21 (28.0)		8 (10.4)		
2	14 (18.7)		16 (20.8)		
3	19 (25.3)		21 (27.3)		
4	7 (9.3)		14 (18.2)		
5	3 (4.0)		7 (9.1)		
6	0		0		
7	1 (1.3)		2 (2.6)		
Missing	10 (13.3)		9 (11.7)		
Total	75 (100.0)		77 (100.0)		
CGI-I score at Week 8, *n* (%)					0.06[b]
1	17 (22.7)		9 (11.7)		
2	25 (33.3)		21 (27.3)		
3	16 (21.3)		22 (28.6)		
4	11 (14.7)		19 (24.7)		
5	6 (8.0)		6 (7.8)		
6 or 7	0		0		
Total	75 (100.0)		77 (100.0)		
HSCS overall score: adjusted mean (SEM) for change from baseline to Week 8	12.2 (1.8)		9.0 (1.7)		0.18[c]
Modified SNAP score: adjusted mean (SEM) for change from baseline to Week 8	8.7 (0.9)		8.4 (0.9)		0.81[c]

[a]All efficacy assessments were performed for the ITT population, which consisted of all randomized subjects who received at least one dose of double-blind study drug and had at least one post-baseline measurement for CGI-I, CGI-S, modified SNAP, FACIT-F, or HSCS. Analyses were based on LOCF. Exploratory analyses uncorrected for multiple comparisons suggested significant differences at Weeks 1, 5, 6, and 7 of study.
[b]*P* value from nonparametric ANCOVA procedure[21] and including center as a stratification.
[c]*P* value for overall comparison of treatment groups from the final ANCOVA model. The final ANCOVA model contained terms for treatment, center, baseline score, and treatment × baseline score.

Because of the possible contribution of anemia to subjects' fatigue, hemoglobin levels were monitored during the study. At baseline, mean hemoglobin levels were similar between treatment groups (D-MPH: 13.2 g/dL, placebo: 13.4 g/dL); 60 of 76 (79%) D-MPH-treated subjects and 62 of 78 (80%) placebo-treated subjects had normal hemoglobin levels at screening. There were no clinically relevant changes in mean hemoglobin values in either treatment group over the course of the study; few subjects shifted from low to normal hemoglobin levels.

AEs occurring in ≥10% of subjects in either treatment group are presented in Table 6; the most commonly reported AEs independent of study drug relationship in the D-MPH treatment group were headache, nausea, and dry mouth, and in the placebo treatment group were headache, diarrhea, and insomnia. There was a higher rate of AEs in the D-MPH treatment group. Of all subjects reporting AEs, 48 of 76 (63%) D-MPH-treated subjects and 22 of 78 (28%) placebo-treated subjects had AEs with a suspected relationship to study drug. Dry mouth, headache, nausea, and feeling jittery were the most common AEs suspected to be related to D-MPH treatment. Two serious adverse events (SAEs) occurred in placebo-treated subjects: pneumonia that resolved with treatment and elective surgery for incisional hernia. During the double-blind treatment phase, more (8 of 76 [11%]) D-MPH-treated subjects compared with placebo-treated

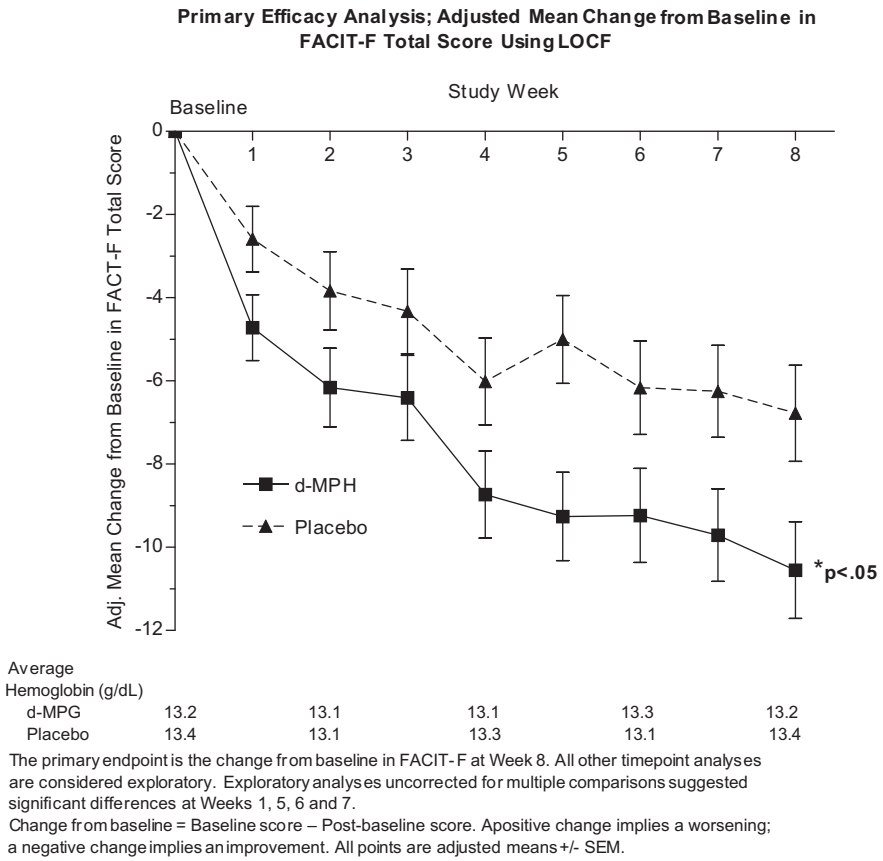

Fig. 2. Primary efficacy analysis; adjusted mean change from baseline in FACIT-F total score using LOCF.

subjects (1 of 78 [1.3%]) had AEs that led to study discontinuation ($P = 0.02$). The AEs leading to discontinuation in the D-MPH treatment group were nausea, vomiting, feeling jittery, and abnormal electrocardiogram; in the placebo group, cardiac flutter led to discontinuation. Most AEs were mild or moderate in severity; 7 of 76 (9%) D-MPH-treated subjects and eight of 78 (10%) placebo-treated subjects reported AEs with a highest intensity of severity.

Safety and efficacy results were confirmed by an independent statistician.

Discussion

In this study, D-MPH treatment in an individualized dosing regimen based on therapeutic response and side effects was associated with significant reduction of fatigue in adult cancer subjects after chemotherapy, as demonstrated by greater decreases in the FACIT-F total score. In two pilot studies, reductions in fatigue have been observed in advanced cancer patients treated with methylphenidate alone[8] and in melanoma patients treated with a combination of methylphenidate and an exercise regimen.[9] Data from our study demonstrated a 10.5 point FACIT-F reduction from baseline for D-MPH-treated subjects. In a post hoc analysis (data not shown), subjects, regardless of treatment, who reported a clinically meaningful improvement (very much or much improved) on the CGI-I also reported an average reduction of 13.2 points in FACIT-F scores compared with baseline. This change from baseline is consistent with reported clinically meaningful changes of 10 points[27] and 17 points[28] in FACIT-F scores.

In the present study, reductions in fatigue were achieved in D-MPH-treated subjects at a mean dose of 27.7 mg/day, well below the 50 mg/day maximum allowed per protocol, whereas mean daily dosage in placebo-treated subjects reached a high of 39.3 mg/day. This is consistent with findings in a pilot study by

Table 6
AEs Reported by At Least 10% of the Subjects in Either Treatment Group (Safety Population)

MedDRA[b] Body System and Preferred Term	D-MPH ($n = 76$)[a] *n* (%)	Placebo ($n = 78$)[a] *n* (%)
Gastrointestinal disorders		
Nausea	21 (27.6)	6 (7.7)
Dry mouth	20 (26.3)	7 (9.0)
Diarrhea	11 (14.5)	10 (12.8)
Nervous system disorders		
Headache	31 (40.8)	26 (33.3)
Dizziness	15 (19.7)	6 (7.7)
Psychiatric disorders		
Insomnia	14 (18.4)	8 (10.3)
Anxiety	10 (13.2)	5 (6.4)
Nervousness	10 (13.2)	4 (5.1)
General disorders and administration site conditions		
Feeling jittery	10 (13.2)	1 (1.3)
Infections and infestations		
Nasopharyngitis	8 (10.5)	5 (6.4)

[a]All safety analyses were performed for the safety analysis population, which included subjects who received at least one dose of double-blind treatment (D-MPH or placebo).
[b]Standard dictionary for adverse event coding for clinical trials.

Bruera et al.[8] who found that with self-administration of methylphenidate up to 20 mg/day over a four-week period, most subjects had continued symptomatic response without significant dose increase. A subsequent short-duration (seven days) double-blind, placebo-controlled study of methylphenidate, the racemic compound, failed to find a significant benefit.[29] Low baseline fatigue, low dose, a short observation period, and daily nurse telephone contact may have contributed to the observed high placebo response and lack of an active drug benefit.

The results of this study do not support a D-MPH-mediated reduction in cognitive impairment experienced by adult cancer patients after cytotoxic chemotherapy; however, this study was not powered for this endpoint and the data should be regarded as exploratory. It is also possible that any cognitive dysfunction predated chemotherapy and could be due to the cancer itself. This study did not assess prechemotherapy cognitive function. The HSCS is known to be susceptible to practice effects and, therefore, may be underestimating the level of cognitive dysfunction (or improvement) in these subjects. The low number of randomized men and the dominance of breast and ovarian cancers limit the applicability of this study to the broad range of post-treatment cancer patients who experience fatigue and cognitive impairment.

Future studies should address a broader range of cancers and chemotherapy regimens to fully assess the potential of D-MPH treatment. Larger studies that stratify for type of cancer and treatment could help discern which types of cancers and/or families of chemotherapeutic agents may be most associated with fatigue. Other factors such as concomitant medications and level of activity, for example, exercise, could also be evaluated.

In conclusion, our results support that D-MPH can be of benefit in the treatment of fatigue in a select group of patients after the completion of cytotoxic chemotherapy. Further studies to explore treatment response to D-MPH or other agents for the treatment of chemotherapy-related fatigue should be considered

Acknowledgments

The Focalin Study Group

Participating Site Staff Members. Veena Charu, MD (Pacific Cancer Medical, Inc.); James Cleary, MD and Renae Quale, RN (University of Wisconsin Hospital and Clinics); Susan Ferguson, MD (Cooper Green Hospital); Filiz Gokce, MD, CCRP (Cancer Research Network, Inc.); Stewart Fleishman, MD (Continuum Cancer Centers of New York, Beth Israel Medical Center & St Luke's-Roosevelt Hospital Center); Julie Gralow, MD (Seattle Cancer Care Alliance); Elyse Lower, MD (University of Cincinnati Medical Center); Manuel Modiano, MD (Arizona Clinical Research Center); Steven Passik, PhD (Markey Cancer Center); Larry Puls, MD (Gynecologic Oncology Research & Development LLC); Donald Royall, MD (University of Texas Health Science Center, San Antonio); Jack Salah, MD (Jacksonville Center for Clinical Research); John Thropay, MD, and Maribelle Sunga, BS, CCRP (Clinical Trials and Research Associates); Rodney Tucker, MD (University of AL Palliative Care Institute); Michael Weitzner, MD (H.L. Moffitt Cancer & Research Institute); Stephen Yandel, DO, and Wendy Beckner (Osler Medical); Lorrin Kwoek-Chong Yee, MD (Northwest Medical Specialties (PPLC).

Clinical Operations Support. R. Mennie (sponsor)

Medical Writing Support. A. Allred, PhD (Lineberry Associates)

Statistical Consultant. R. Buncher, PhD (University of Cincinnati)

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