Effects of Methylphenidate on Fatigue and Depression: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Context. Fatigue is highly prevalent in populations with advanced illness and is often associated with depressed mood. The role of psychostimulant therapy in the treatment of these conditions remains ill defined.

Objectives. To evaluate the response of fatigue and depression in patients with advanced illness to titrated doses of methylphenidate (MP) as compared with placebo.

Methods. In a randomized, double-blind, placebo-controlled trial, 30 hospice patients, both inpatients and outpatients, who had fatigue scores of at least four on a scale of zero to 10 (0 = no fatigue and 10 = worst fatigue), were randomly assigned to receive either 5 mg of MP at 8 AM and 1 PM or placebo. Doses of MP were titrated every three days according to response and adverse effects. Home care patients were monitored daily by telephone and visited by a research nurse on Study Days 0 (baseline), 3, 7, and 14. Fatigue was assessed using the Piper Fatigue Scale as the primary outcome measure and validated by the Visual Analogue Scale for Fatigue and the Edmonton Symptom Assessment Scale (ESAS) fatigue score. Subjects in inpatient facilities were interviewed or assessed by staff on an identical schedule. Depressive symptoms were assessed by the Beck Depression Inventory-II, Center for Epidemiologic Studies Depression Scale, and the ESAS depression score. Primary statistical analysis was conducted using repeated-measures multivariate analysis of the variance.

Results. Both MP- and placebo-treated groups had similar measures of fatigue at baseline. Patients taking MP were found to have significantly lower fatigue scores (Piper Fatigue Scale, Visual Analogue Scale for Fatigue, and ESAS) at Day 14 compared with baseline. The improvement in fatigue with MP treatment was dose-dependent; the mean average effective dose was 10 mg on Day 3 and 20 mg on Day 14 (dose range of 10–40 mg). Placebo-treated individuals showed no
significant improvement in fatigue. For patients with clinically significant depression on Day 0, treatment with MP was associated with a significant reduction in all test indices for depressed mood. For the placebo group, the changes in measures of depression were less than observed in the treatment group but were inconsistent between assessment tools. No significant toxicities were observed.

**Conclusion.** MP reduced symptoms of fatigue and depression when compared with placebo. The effect of MP on fatigue was dose-dependent and sustained over the duration of the study. J Pain Symptom Manage 2012;43:68–77. © 2012 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

**Key Words**
Methylphenidate, hospice, placebo controlled, fatigue, depression

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**Introduction**

Clinically significant fatigue is a near ubiquitous symptom in palliative care, occurring in more than 75% of patients with cancer.1,2 Fatigue is multidimensional and impairs patients’ sense of well-being, activities of daily living, relationships with others, and compliance with treatment.3,4 Despite enormous clinical importance, fatigue is often under-recognized and undertreated.1

The U.S. National Cancer Institute guidelines on cancer-related fatigue recommend the use of psychostimulants for fatigue, based on “limited experience,”5 a position supported by a 2008 Cochrane Database review, which found that methylphenidate (MP) showed a small but significant improvement in cancer-related fatigue when compared with placebo.6 Published data are conflicted, however, regarding psychostimulant effectiveness in the treatment of fatigue in noncancer vs. cancer patients and within cancer populations. In the noncancer population, two randomized controlled trials (RCTs) have demonstrated a reduction in fatigue with psychostimulant treatment.7,8 In the cancer population, case series and nonrandomized studies have shown a reduction in fatigue with psychostimulant treatment, but three RCTs showed no evidence that psychostimulants improved cancer-related fatigue compared with placebo.9–14 Discrepancies between studies may reflect variability in psychostimulant dosing and titration, as well as heterogeneity within the study population. In fact, subset analysis of the RCT data did suggest that cancer patients with more advanced illness or fatigue appeared to benefit from receiving MP treatment as opposed to placebo.12,14 This observation is consistent with the concept of fatigue as a complex multidimensional syndrome in which variables, such as fatigue severity or degree of debility, may influence responsiveness to psychostimulant treatment.

A number of open-label studies and case series demonstrate that psychostimulant treatment may improve other quality-of-life indicators, such as depressed mood, in patients with debilitating illness.15–17 The symptom complex of fatigue overlaps with the constructs of mood disorders, and, therefore, it is unclear whether the effects of psychostimulants on fatigue are related to or distinct from its mood-enhancing properties.18 It is possible that psychostimulants are particularly effective for patients in whom depression is a major contributor to fatigue. Conversely, improvement in mood may depend on amelioration of somatic complaints, such as fatigue. Despite some evidence that mood responds favorably to MP treatment, there is a paucity of data that measure the effect of psychostimulants on fatigue and mood concurrently.

The present study was designed as a double-blind placebo-controlled trial to evaluate MP therapy in hospice patients. Its primary objective was to determine the response of fatigue to titrated doses of MP; to clarify the treatment response, fatigue was stratified based on severity and assessed as a multidimensional syndrome. A second objective was to assess the treatment of fatigue relative to symptoms of depression.
Methods

Patients

Study patients were recruited from individuals receiving either inpatient or outpatient hospice care at The Center for Hospice & Palliative Care in Buffalo, New York. Patients were identified and invited to participate by their attending physicians based on the evaluation of inclusion and exclusion criteria. Inclusion criteria were 1) diagnosis of terminal illness, including cancer and noncancer diseases, 2) absence of significant cognitive impairment, defined as a Mini-Mental State (MMS) examination \( \leq 22 \), and 3) presence of fatigue for at least two weeks, assessed by scoring four or greater on the 11-point scale included in the Edmonton Symptom Assessment Scale (ESAS). Exclusion criteria included 1) history of seizure disorder or cardiac arrhythmias; 2) diagnosis of dementia; 3) diagnosis of psychosis according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, criteria; 4) severe hepatic or renal dysfunction (i.e., creatinine levels or hepatic function tests greater than twice the normal limit); 5) concurrent treatment with selective serotonin reuptake inhibitors, sympathomimetics, tricyclic antidepressants, or monoamine oxidase inhibitors; and 6) hypersensitivity to MP. The experimental protocol was approved by the institutional review boards of The Center for Hospice & Palliative Care in Buffalo, New York, and the University at Buffalo.

Design and Procedures

The study was designed as a double-blind placebo-controlled trial, with patients randomized to one of the two arms, receiving either placebo or MP administered as identical capsules. After providing informed consent, patients were randomized to treatment or placebo via a random number table in which odd numbers were assigned to the treatment group and even numbers to the placebo group. Randomization and blinding procedures were implemented and supervised by the hospice Director of Quality Improvement and Corporate Compliance. Baseline data included patient weight, blood pressure and heart rate, clinical laboratory testing (complete blood count, comprehensive metabolic panel, and thyroid stimulating hormone), and MMS examination. Functional status was rated according to the Karnofsky Performance Status (KPS) scale. Multiple symptoms were assessed using the ESAS, a multidimensional questionnaire with domains in pain, tiredness, nausea, depression, anxiousness, drowsiness, appetite, sense of well-being, and shortness of breath. Each domain in the ESAS is scored from zero to 10, with higher scores representing increased disability or severity. The ESAS has been validated for assessment of quality of life in palliative care.

On Study Days 0 (baseline), 3, 7, and 14, patients were visited by a study nurse, who conducted a physical examination that included a check of vital signs and review of systems. She also obtained all patient self-report measures during these visits. MP dosing began at 5 mg given at approximately 8:00 AM and 1:00 PM. Patients were monitored by telephone daily to ensure that the maximum tolerated dose of MP (up to 40 mg/day) was titrated as quickly as possible (dosage increases by 10 mg/day every three days) and to monitor any adverse events or intolerable side effects. Placebo group patients received 350 mg starch capsules up to a maximum of eight capsules, which was the same maximum capsule count as the MP group. All patients were given a 10-day supply of 36 capsules to accommodate twice daily dosing with an increase of one capsule every three days. The study physician recommended dosage reductions to a maximum tolerated dosage if side effects were reported or observed, including anxiety, irregular heartbeat, fever, hot and dry skin, or any uncontrolled head, mouth, neck, arm, or leg movements. The study physician remained blinded to patient groups throughout the study.

In addition to daily telephone assessments by the study nurse, patients were asked to record any adverse drug effects in a daily symptom diary. A Data Safety Monitoring Board convened by the hospice medical director met weekly to review all clinical data and provide oversight for adverse reactions.

Fatigue Assessment

In addition to the KPS and ESAS, patients were administered a series of self-reported and observer-rated measures on Days 0 (baseline), 3, 7, and 14. The primary outcome measure was the influence of MP on the symptom of fatigue from Days 0–14 according to the Piper Fatigue Scale (PFS). Fatigue assessment
was designed to measure fatigue as a single symptom and as a symptom cluster with multiple dimensions. The PFS consists of four subscales to comprehensively assess the symptom of fatigue; fatigue was further validated by two additional measurements, the ESAS fatigue score and the Visual Analogue Scale for Fatigue (VAS-F). The VAS-F is a self-administered 18-item scale (0–100 mm) to assess fatigue and energy. The severity of fatigue is calculated as a mean of 13 items in the fatigue subscale (higher number = greater severity).

**Depression Assessment**

Depressive symptoms were measured by the revised Beck Depression Inventory-II (BDI-II), which has been validated for use in a variety of clinical settings. The BDI-II comprises 21 items rated on a four-point scale and summed for a total score (0–63). Suggested cutoff scores for depression are 0–13 for minimal to no symptoms of depression, 14–19 for mild symptoms of depression, 20–28 for moderate symptoms, and 29–63 for severe symptoms. In the present study, depression was defined as a score of 14 or greater. In addition to the BDI-II, psychological well-being was assessed by the ESAS depression score and the Center for Epidemiologic Studies Depression Scale (CES-D).

**Statistical Analysis**

The primary outcome was fatigue as measured by the PFS. Secondary endpoints included the additional self-reports of fatigue and depression. The sample size was determined by power analysis of possible scenarios using moderate effect sizes defined as change in PFS total score of 33%–50% from the baseline value. The resulting power estimates ranged from 0.70 to 0.95, with corresponding sample sizes ranging from six to 23. The final sample target of 15 per group was estimated to be sufficient to detect a change from baseline of 40% with power = 0.80.

The PFS, ESAS, and all fatigue and depression scores were analyzed using multivariate analysis of variance (MANOVA), with the individual scores as the dependent variables and the treatment as the independent variable. Complete data were obtained from all participants with the exception of one measure (CES-D) on Day 14 for one of the patients in the active drug arm. Therefore, the analysis was conducted with complete cases with the exception of the CES-D analysis in which the participant with the missing data point was excluded.

Given the multiple scores being tested in the MANOVA analysis, post hoc tests were used, where significant effects were observed to assess the specific differences among treatment and controls. The Scheffé test was used in the post hoc analyses. Repeated-measure analysis was used to assess the significance of changes in scores across Study Days 0, 3, 7, and 14. Again, the Scheffé test was used in post hoc analysis of scores between time points.

**Results**

Forty patients gave formal consent to participate in the study. Of the 40 patients, 30 patients completed the study to enable statistical analysis (six died before the initiation of the treatment, one died after two placebo doses, two died within the first week, and one withdrew because of nausea). The flow of patients through the study phases is shown in Figure 1.

Table 1 presents the demographic and medical characteristics of the subjects enrolled in the study. Placebo and treatment groups were comparable. All patients had hemoglobin greater than or equal to 11.0 g. Overall performance status was comparable between the drug-treated and placebo groups at baseline (Day 0 mean KPS score was 57 in both groups, respectively) and essentially unchanged by Day 14 (Day 14 mean KPS score also was 57 in both groups, respectively). MMS examination scores were 29 for both the control and treated groups. Fatigue was the most distressing symptom identified by participants (Table 2). Both the treatment and the control subjects began the study with similar levels of fatigue identified as moderate to severe according to three separate measures (Fig. 2). There were no significant changes in fatigue reported in the placebo group over the 14 days, as evaluated by all three tools. With MP treatment, MANOVA analysis showed that fatigue was significantly reduced as assessed by all test measures (P = 0.023).
The PFS was considered the most comprehensive measure of fatigue, and the primary outcome measure was the influence of MP on the PFS from Day 0 to Day 14. In those patients treated with MP, the total PFS score showed a marked reduction from a mean intensity of 6.2 on Day 0 to 2.1/2.5 on Day 14 (66% reduction from baseline). As shown in Figure 3, the improvement in fatigue with MP was multidimensional, as score reduction was noted for all four subscales of the PFS. The VAS-F scale also yielded a comparable 55% reduction of fatigue in patients taking MP (Day 0 = 4.9/2.7 and Day 14 = 2.2/3.1), although significance was not noted until Day 7 (P = 0.05) and Day 14 (P = 0.0007). A similar reduction (64% from baseline) was demonstrated by the ESAS index of fatigue for those subjects taking MP (Day 0 = 7.4 ± 2.0 and Day 14 = 2.7 ± 1.3).

Depression scores indicated that 86.6% of the MP-treated and 60% of the placebo-treated patients were considered depressed as measured by the CES-D score of 16 or higher (mean [standard deviation]: 25.0 [6.7] for MP and 19.5 [7.8] for the placebo group) at Day 0. Using the BDI-II, 60% and 66.6% of the MP and placebo groups, respectively, were considered clinically depressed as measured by a value of 14 or higher. There were no statistically significant differences in the three measurements for depression as a function of time for patients in the placebo group (Fig. 4). MP treatment resulted in a significant improvement from Day 0 to Day 14 using the BDI-II and CES-D indices and statistically relevant improvement compared with placebo at Days 7 and 14 using the ESAS scale. Specifically, in the study population, the CES-D depression mean decreased from 25.0 (Day 0) to 16.7 ± 9.5 on Day 14 (33% reduction, P = 0.002); the average BDI-II score decreased from 15.1 to 11.8 ± 9.1 (22% reduction, P = 0.028); and the ESAS depression score of 2.9 on Day 0 decreased to 1.92 ± 2.0 (35% reduction, P = 0.05).
Table 2 presents the findings from the ESAS domains of pain, tiredness, nausea, depression, anxiousness, drowsiness, appetite, sense of well-being, and shortness of breath. The symptom of anxiety was of interest given its reported prevalence in advanced illness and theoretical potentiation by MP. Anxiety was scored as more distressing than pain at the onset of the study (ESAS anxiety score = 3.1/C6 2.3 for the MP group and 2.6/C6 2.2 for the placebo group). By Day 14, anxiety scores increased by 31% for the control group yet decreased for the MP group by 46% compared with baseline. MP also improved subjective evaluation of overall well-being, with ESAS mean score reduction from 6.0 ± 2.0 (Day 0) to 3.7 ± 2.0 (Day 14), a 39% improvement (P = 0.04), whereas the placebo group’s mean score of well-being decreased from 5.0 ± 1.8 to 4.8 ± 2.1 during the 14-day trial, a 5% improvement.

In the present study, pain was given the same initial mean score (ESAS pain score = 2.1) by both treated and untreated patients. Pain was reduced by 48% by Day 14 for the MP-treated population vs. 15% for the control group. Also, MP was not shown to significantly increase appetite, whereas the placebo group did record improvement in appetite. The MP treatment group also suffered a substantial increase in nausea as measured by the ESAS (Day 0 = 0.9/C6 1.0 to Day 14 = 1.5/C6 3.4), whereas the control group did not (Day 0 = 1.7/C6 2.8 to Day 14 = 1.7/C6 2.1).

The response of fatigue to MP treatment was dose-dependent, with a mean effective dose of 10 mg on Day 3 and 20 mg on Day 14 (dose range of 10–40 mg). The mean placebo dose was 40 mg on Day 14. MP was not discontinued by any patient because of toxicity, despite dosing levels as high as 40 mg/day. With the exception of nausea, side effects associated with the use of MP were negligible. Vital sign measurements also were unaffected by treatment with MP and did not differ significantly from the placebo group.

Discussion
Fatigue is an almost universal symptom complex for patients with advanced illness. Although

### Table 2
Comparison of Mean ESAS Scores for Placebo- and MP-Treated Groups at Baseline (Day 0) and Day 14

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>MP Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 14</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.93 ± 2.37</td>
<td>6.58 ± 2.31</td>
</tr>
<tr>
<td>Depression</td>
<td>3.93 ± 3.06</td>
<td>3.58 ± 2.57</td>
</tr>
<tr>
<td>Well-Being</td>
<td>5.07 ± 1.77</td>
<td>4.82 ± 2.09</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2.60 ± 2.20</td>
<td>3.42 ± 2.87</td>
</tr>
<tr>
<td>Pain</td>
<td>2.07 ± 1.44</td>
<td>1.75 ± 1.86</td>
</tr>
<tr>
<td>Appetite</td>
<td>3.13 ± 2.26</td>
<td>2.25 ± 2.34</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.73 ± 2.81</td>
<td>1.67 ± 2.06</td>
</tr>
</tbody>
</table>

SD = standard deviation. Scores: 0 = best; 10 = worst.
several factors contributing to fatigue can be addressed, debilitating fatigue is often complex and makes definitive treatment difficult. In such instances, management should focus on symptomatic relief.5

In the present double-blind study, both MP and placebo groups rated fatigue as moderate to severely distressing. MP was found to reduce fatigue by 50% or more from baseline. Validation of these results by three independent fatigue instruments is noteworthy, as there is no standard definition or measure of fatigue. The reduction in fatigue was comprehensive, as all measured dimensions of fatigue improved with MP treatment (PFS subscales: cognition, affective, sensory, and behavioral). Placebo-treated individuals showed no significant improvement in fatigue.

These findings are in agreement with several uncontrolled nonrandomized studies7–11 assessing psychostimulant efficacy, yet differ from the results from three recent RCTs.12–14 The outcome discrepancies may reflect differences in study design and study populations. Within a heterogeneous study population, certain subgroups of patients may benefit from psychostimulant treatment more than others.23 For example, MP has been shown to be effective in reducing somnolence in patients receiving opioids26 and in the management of depression.15–17 Patients with severe fatigue or advanced disease also appear to gain a greater reduction in fatigue from MP.12,14 Furthermore, in contrast to the present study, most published data used fixed doses of a psychostimulant, with the exception of the study by Bruera et al.12 in which titration was dose limited and patient directed. Prior studies also have demonstrated that MP may act as a coanalgesic in the reduction of pain.10,15,27 Also, in contrast to the findings of others,10 in our study, MP was not shown to significantly increase appetite.

In part, establishing a management strategy for fatigue is complicated by the causality relationships among fatigue, physical illness, and depression/anxiety. The conceptual distinction between cause and consequence has treatment implications because medications, such as benzodiazepines, used for the treatment of anxiety may increase the patient’s perception of fatigue. Conversely, interventions that reduce fatigue may improve distressed mood, as shown in the present study. MP treatment was associated with a reduction in anxiety scores, whereas anxiety worsened in the control group, a trend shown by others.12,28 MP-treated patients also demonstrated improvement in depressed mood, although the response was less robust when compared with fatigue or anxiety reduction. Baseline measures of depressed mood were less distressing than fatigue or anxiety in the MP treatment group; thus, it is not unexpected that there would be relatively less change
The diagnosis and treatment of fatigue may depend on the recognition of fatigue as more than a consequence of a comorbid mood disorder. In the present study, the observed decrease in fatigue with MP treatment is likely more than a consequence of enhanced mood, as fatigue improved in patients whose depressive symptoms were stratified as minimal and increases in energy were disproportionate to changes in mood. In fact, concomitant depression does not appear to be a significant predictive factor for the efficacy of MP in the reduction of fatigue. The clinical usefulness of MP also is difficult to explain based solely on its actions as a stimulant, given the drug’s demonstrated ability to reduce anxiety. Others have suggested that cancer patients may become depressed or anxious as a consequence of disease-related fatigue.29,30

Fatigue is multidimensional in expression. Therefore, interventions that reduce fatigue may improve multiple symptoms in medically ill patients. In the present study, treatment with MP appears to benefit symptoms as diverse as pain and cognition (as measured by the PFS subscale). It is unclear whether MP acts directly to mediate these symptoms or indirectly as a consequence of altering the experience of illness by improving less tangible outcomes, such as restoration of energy, sense of well-being, and ability to concentrate. For example, MP may not directly reduce pain, but instead may alter one’s ability to cope with, and thereby experience pain. Similarly, MP may not exert its effect as a primary antidepressant but may restore coping modalities compromised in advanced illness.

Several published reports have demonstrated that the response to MP is rapid.7–11 In the present study, the efficacy of MP was noted as early as Day 3. For patients with limited life expectancy, rapid reduction in fatigue is crucial, as treatment improves a constellation of symptoms that dramatically interfere with quality of life. The trend in the reduction of fatigue and distressed mood continued from Day 3 until study completion on Day 14. Unlike most prior studies, MP was titrated and a clear relationship between dose and fatigue reduction was demonstrated. Dose escalation of MP to effect may reflect drug tolerance or possibly be expected as fatigue progresses with disease advancement. One goal of dose titration was to determine the optimal dose at which fatigue was improved without causing excessive side effects. However, global optimal dosing cannot be determined because adverse effects were insignificant, and clinical outcomes continued to improve at study end. It is possible, therefore, that further increases of MP dose may sustain or improve distressing symptoms, although the side effects would need to

Fig. 3. Comparison of Piper Fatigue subscale scores for placebo- and MP-treated groups. Results reported as percent change from baseline at Days 3, 7, and 14. Key: a = significantly different between Days 0 and 14 with $P < 0.05$; b = significantly different between placebo and control with $P < 0.05$. 
dependent, with the mean average effective dose of 20 mg a day on Day 14. Placebo-treated individuals showed no significant improvement in fatigue. For patients with clinically significant depression on Day 0, treatment with MP was associated with a significant reduction in all test indices for depressed mood. For the placebo group, the changes in measure of depression were less than observed in the treatment group but inconsistent between assessment tools.

**Disclosures and Acknowledgments**

The authors declare no conflicts of interest.

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