JOURNAL WATCH

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**Full reference**: Kerr CW, Drake J, Milch RA, et al. Effects of methylphenidate on fatigue and depression: a randomized, double-blind, placebo-controlled trial. J Pain Symptom Manage 2012;43:68–77.

## **ABSTRACT**

**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 dosedependent; the mean average effective dose was 10 mg on Day 3 and 20 mg onDay 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.

## **EVALUATION**

**Strengths:**This is a double-blind randomized placebo-controlled study using validated scales (including ESAS) and the first to examine dose titration. The population studied (hospice, non-cancer and cancer patients) is fairly generalizable to our cohort.

**Weaknesses**:The sample size was small (n=30) and duration of study was limited (14 days). While methylphenidate was demonstrated to be effective, there is no information about the long-term use of a stimulant.

**Relevance to Palliative care:**Fatigue is highly prevalent in this population and can be associated with depressed mood. Psychostimulants may be appropriate for individuals with moderate to significant fatigue (ESAS>4) and low mood. It is well tolerated with good effect when appropriately titrated and also confers a better overall sense of wellbeing.

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

| Variable   | Plac            | rebo            | MP Tre          | eatment         |
|------------|-----------------|-----------------|-----------------|-----------------|
|            | $Mean \pm SD$   |                 |                 |                 |
|            | Day 0           | Day 14          | Day 0           | Day 14          |
| Fatigue    | $6.93 \pm 2.37$ | $6.58 \pm 2.31$ | $7.40 \pm 2.03$ | $2.69 \pm 1.32$ |
| Depression | $3.93 \pm 3.06$ | $3.58 \pm 2.57$ | $2.93 \pm 3.12$ | $1.92 \pm 1.98$ |
| Well-Being | $5.07 \pm 1.77$ | $4.82 \pm 2.09$ | $6.00 \pm 2.04$ | $3.67 \pm 2.06$ |
| Anxiety    | $2.60 \pm 2.20$ | $3.42 \pm 2.87$ | $3.13 \pm 2.33$ | $1.69 \pm 2.21$ |
| Pain       | $2.07 \pm 1.44$ | $1.75 \pm 1.86$ | $2.07 \pm 2.15$ | $1.08 \pm 1.50$ |
| Appetite   | $3.13 \pm 2.26$ | $2.25 \pm 2.34$ | $4.13 \pm 2.70$ | $4.08 \pm 3.40$ |
| Nausca     | $1.73 \pm 2.81$ | $1.67 \pm 2.06$ | $0.87 \pm 0.99$ | $1.54 \pm 3.36$ |

SD = standard deviation. Scores: 0 = best; 10 = worst.

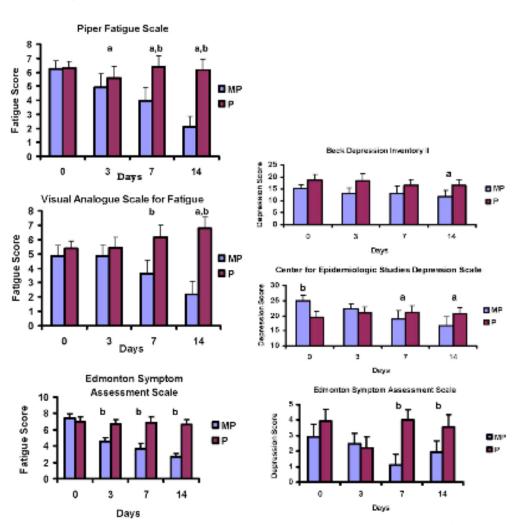


Fig. 2. Comparison of mean fatigue scores for placebo- and MP-treated groups according to three cebo and control with P < 0.05.

Fig. 4. Comparison of mean scores for placebo- and MP-treated groups according to three indices of deindices of fatigue. Results reported as mean fatigue pression. Results reported are mean average depresscores at baseline (Day 0), Days 3, 7, and 14. Key: sion scores at baseline (Day 0), Days 3, 7, and 14. a = significantly different between Days 0 and 14 Key: a = significantly different between Days 0 and with P < 0.05; b = significantly different between pla- 14 with P < 0.05; b = significantly different between 14placebo and control with P < 0.05.