

## Methylphenidate for Management of Fatigue in the Palliative Care Setting

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### Clinical Question

Does methylphenidate (Ritalin) improve fatigue in the palliative care setting?

### Evidence-Based Answer

No recent evidence demonstrates that methylphenidate improves fatigue in patients receiving palliative care. Methylphenidate can be used to minimally improve fatigue symptom scores in patients with cancer-related fatigue. (Strength of Recommendation [SOR]: C, based on a meta-analysis of multiple randomized controlled trials [RCTs] with heterogeneous results.) Methylphenidate can also be used to modestly improve fatigue scores in patients with human immunodeficiency virus infection, Parkinson disease, and sarcoidosis. (SOR: C, based on a single small RCT for each condition.) Approximately 5% to 30% of medically ill older adults receiving methylphenidate experience adverse effects (e.g., agitation, tachycardia, insomnia). Methylphenidate rarely produces non-life-threatening cardiovascular and central nervous system-activating adverse effects.

### Evidence Summary

Fatigue is associated with diverse illnesses and is common in palliative care settings. No recent studies have evaluated methylphenidate in the treatment of fatigue in general palliative care settings.<sup>1</sup> One small double-blind crossover trial (n = 61) found that methylphenidate given for four days improved lethargy, fatigue, and depression in chronically ill older patients in care facilities.<sup>2</sup> However, this study was performed in 1958, before palliative care was defined, and the authors did not describe how fatigue was assessed.

A Cochrane review of five RCTs (N = 426) evaluating the use of psychostimulants for the management of cancer-related fatigue (i.e., a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with normal functioning and is not relieved by rest<sup>3</sup>) found that methylphenidate slightly improved symptom scores.<sup>4</sup> Four of the included studies evaluated methylphenidate, and one evaluated dexamphetamine.<sup>3,5-8</sup> All of the studies used standardized survey instruments to measure fatigue symptoms. Although only one study demonstrated a significant difference (3.7-point improvement vs. placebo out of 52 possible points for fatigue symptom scores on the non-disease-specific Functional Assessment of Chronic Illness Therapy–Fatigue [FACIT-F] Scale), the meta-analysis favored methylphenidate over placebo. There was a reduction in fatigue scores of  $-0.28$  standard deviations (95% confidence interval,  $-0.48$  to  $-0.09$ ). The methylphenidate group had a two-point reduction in fatigue symptom scores on the FACIT-F; this was the minimum clinically significant difference that was detectable.<sup>4</sup>

High-quality but small RCTs demonstrated that methylphenidate modestly reduced fatigue symptom scores in ambulatory adult patients with human immunodeficiency virus infection,<sup>9</sup> older patients with Parkinson disease,<sup>10</sup> and adults with sarcoidosis.<sup>11</sup> Patients with human immunodeficiency virus who were treated with methylphenidate had a 1.3-point improvement (out of 10 possible points) on the Piper Fatigue Scale. Those with Parkinson disease had a 4.6-point improvement (out of 54 possible points) on the Fatigue Severity Scale and a 5.2-point improvement (out of ►

80 possible points) on the Multidimensional Fatigue Inventory. Patients with sarcoidosis who were treated with dexamethylphenidate (Focalin) in a crossover trial had a five-point improvement (out of 52 possible points) on the FACIT-F.

A systematic review of the use of methylphenidate in medically ill older adults (44 studies, 1,355 patients) found that adverse effects were reported in 5% to 30% of patients.<sup>12</sup> However, controlled studies found no significant differences in rates of adverse effects compared with placebo. The most common adverse effects were agitation or restlessness, sinus tachycardia or palpitations, delirium or confusion, and insomnia. One serious but uncommon adverse effect was arrhythmia, which was reversible with discontinuation.

### Recommendations from Others

Guidelines from the National Comprehensive Cancer Network state that treatment with methylphenidate or modafinil (Provigil) may be considered in select patients with terminal cancer and fatigue.<sup>13</sup> A statement from the British Columbia Medical Services Commission states that psychostimulants such as methylphenidate, dextroamphetamine, and modafinil may be beneficial in managing fatigue when no correctable underlying cause can be found.<sup>14</sup> The European Association for Palliative Care guidelines state that methylphenidate may have a role in the management of opioid-induced sedation and cognitive failure in patients for whom opioid dose reduction or dose rotation is impractical or inappropriate.<sup>15</sup>

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