Psychostimulants for Fatigue in HIV Patients: How Useful?

Breitbart W, Rosenfeld B, Kaim M, Funesti-Esch J. A randomized, double-blind, placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus disease. Arch Intern Med 2001;161:411–20.

Study Overview

Objective. To determine the efficacy of methylphenidate hydrochloride and pemoline for treating fatigue in patients with HIV.

Design. Randomized, double-blind, placebo-controlled trial. Analysis was based on patients who completed at least 3 of 7 assessments.

Setting and participants. Ambulatory patients with HIV were recruited via posters from a variety of health care settings in New York City. Advertisements did not indicate the exact nature of the study. Participants had to be older than 18 years, fluent English speakers, and able to swallow oral medications. Researchers screened 213 eligible patients who experienced fatigue lasting 2 or more weeks and had a fatigue score of 5 or more on a 1 to 10 scale. Of these, 69 patients were excluded for 1 or more of the following reasons: active substance abuse, urine toxicology screen positive for a nonprescription controlled substance, diagnosis of major depressive or psychotic disorder, cognitive impairment precluding informed consent or data collection, medical contraindications (severe renal or hepatic disease, history of cardiac disease, seizure disorder), or taking contraindicated medications (monoamine oxidase inhibitors, bupropion, guanethidine, or other sympathomimetic agents).

Intervention. At the beginning of the study, all subjects received identical-appearing capsules twice daily: either methylphenidate 7.5 mg, pemoline 18.75 mg, or placebo. Patients were rapidly tapered up to a maximum daily dose of 60 mg of methylphenidate, 150 mg of pemoline, or 8 placebo capsules. Patients were seen weekly for 6 weeks and received frequent calls between visits from nurses who monitored response and side effects.

Main outcome measures. Fatigue was measured using the Piper Fatigue Scale (PFS) and the Visual Analog Scale for Fatigue Severity (VASF). Both change scores (a decrease of 5 or more points on PFS or 50 mm on VASF was considered clinically significant), and regression slopes of decreased fatigue were analyzed.

Main results. Among the study population, 57% were men; about half were African American, 19% were white, and 22% were Hispanic. Risk factors for HIV were varied: 22% homosexual, 39% heterosexual, and 34% injection drug use. According to the Centers for Disease Control classification criteria, 21% of patients were in category A for HIV disease, 39% were in category B, and 40% were in category C. Almost 80% of patients were taking antiretroviral medication, and almost 60% received combination therapy including protease inhibitors.

About 8% of randomized patients (7 in the methylphenidate group, 4 in the pemoline group, and 1 in the placebo group) never started the study medication, and 16% (9 in the methylphenidate group, 8 in the pemoline group, and 6 in the placebo group) did not complete the study. Two patients in each active group and 1 control patient withdrew because of side effects. At the end of the study, doses of methylphenidate and pemoline averaged 51 mg/day and 96.0 mg/day. 41% of methylphenidate patients and 36% of pemoline patients enjoyed a clinically significant improvement compared with 15% of controls ($P = 0.04$). Total PFS scores decreased by 4.2 points, 3.8 points, and 2.9 points for methylphenidate, pemoline, and placebo patients, respectively ($P = 0.04$), while total VASF scores showed similar though nonsignificant changes (26.2 for methylphenidate patients, 25.5 for pemoline patients, and 16.9 for placebo patients; $P = 0.21$). Side effects were fairly uncommon in both treatment groups, and only jitteriness and hyperactivity combined occurred significantly more often in patients receiving active medication ($P = 0.04$).

Conclusion. Methylphenidate and pemoline may benefit some patients with HIV-related fatigue.

Commentary

This study by Breitbart et al had a good general design, although the decision not to use an intention-to-treat analysis may have introduced a type I error into study results. A more conservative and better analysis would have included

an intention-to-treat analysis using no change or a control-group mean as an estimate for patients without data. Given that treatment effect was not significant for VASF scores and that overall effect size was modest, such an analysis may have substantially tempered Breitbart and colleagues' conclusions. Should these results prove valid, the number needed to treat is reasonable: 4 for methylphenidate and 5 for pemoline. Further studies are needed to confirm efficacy of these medications for fatigue in HIV patients.

Applications for Clinical Practice

This study does not provide strong enough evidence to change routine care for patients with HIV disease. However, for carefully selected patients in whom fatigue is debilitating or otherwise substantially affects quality of life, 1 of the 2 study medications may be considered. Patients should be made aware of the weakness of evidence supporting this treatment and the relatively low likelihood for benefit.