

### LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital (MGH) sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. Such consultations require the integration of medical and psychiatric knowledge. During their thrice-weekly rounds, Dr. Huffman and Dr. Stern discuss the diagnosis and management of conditions confronted. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

Dr. Huffman is Chief Resident at MGH and a Clinical Fellow in Psychiatry at Harvard Medical School. Dr. Stern is Chief of the Psychiatric Consultation Service at MGH and an Associate Professor of Psychiatry at Harvard Medical School.

Corresponding author:  
Jeff C. Huffman, M.D.  
(e-mail: Jhuffman@partners.org).

## Using Psychostimulants to Treat Depression in the Medically Ill

Jeff C. Huffman, M.D., and Theodore A. Stern, M.D.

**H**ave you ever wondered if there is a class of antidepressants that works within days instead of weeks or months? Have you considered using psychostimulants in the medically ill but weren't sure if it would be safe? These issues are framed by the following case presentation of an elderly man with symptoms of major depressive disorder that complicated his recovery from respiratory failure. A discussion of the use of psychostimulants in medically ill patients follows the case presentation; a brief annotated bibliography is also included.

### Case Presentation

Mr. A, a 71-year-old man with a history of chronic obstructive pulmonary disease (COPD), hypertension, and hypercholesterolemia was admitted to the hospital for the treatment of a COPD exacerbation. When his symptoms of COPD worsened on the third day of hospitalization, he was transferred to the intensive care unit and intubated. He remained intubated for 6 days, and his respiratory function improved enough to allow for extubation. Mr. A slowly recovered, but by the fifth day of hospitalization, he appeared withdrawn, apathetic, and dysphoric. His appetite had waned, as had his participation in his daily regimen of chest physical therapy. Psychiatric consultation was requested for evaluation of depression. Finding symptoms of major depressive disorder, poor oral intake, and limited participation in his medical and rehabilitative care, the consultant psychiatrist considered prescribing a psychostimulant.

### Why Are Psychostimulants Used in the Treatment of Depression?

Psychostimulants effectively treat acute depression. These agents are rapidly acting (frequently having a therapeutic effect within 48 hours) and have been well tolerated in a variety of settings and patient populations. Stimulants should be considered in the treatment of any patient with depression. This class of medications may be particularly useful, however, in situations in which rapid recovery is essential. Psychostimulant treatment may be especially warranted when depression has led to poor nutritional intake in medically fragile patients, limited participation in crucial rehabilitation activities (e.g., poststroke physical therapy and occupational therapy), and impaired decision-making capacity during times when key medical decisions need to be made.

### What Populations Have Benefited From the Use of Psychostimulants?

A wide variety of patient populations have benefited from the use of psychostimulants. Dextroamphetamine and methylphenidate, the 2 most frequently used stimulants, have been studied in a number of prospective and retrospective trials. Among medically healthy patients, stimulants have been used to treat children and adolescents with attention-

deficit/hyperactivity disorder, to augment the treatment of major depressive disorder in adults, and to treat depression in the elderly.

Stimulants have also been used safely and effectively for those with poststroke depression, for those with human immunodeficiency virus (HIV)-associated depression, and for those who have difficulty weaning from mechanical ventilation. Furthermore, numerous studies of patients with cancer and depression have found that stimulants improve mood and other symptoms associated with major depressive disorder; a retrospective chart review by Olin and Masand<sup>1</sup> found that more than 80% of cancer patients responded favorably to use of methylphenidate. Stimulants have also effectively treated cognitive disturbances in patients with HIV infection and in cancer patients undergoing cranial radiation.

Among acutely depressed medical inpatients, psychostimulants are also safe and effective. Woods and coworkers<sup>2</sup> completed a retrospective study of 66 medical and surgical inpatients at Massachusetts General Hospital (MGH) treated with psychostimulants (mean age of 72 years). The authors found that 48% of the stimulant trials resulted in marked or moderate improvement and that 73% of the trials resulted in at least some improvement of depressive symptoms. Only 7% of the trials were discontinued because of side effects, none of which were life-threatening. Notably, the effects of stimulants upon heart rate and blood pressure were minimal, and appetite in these patients actually increased (in conjunction with the treatment of their depression).

Despite these favorable data on the use of psychostimulants in the treatment of depression, larger double-blind, placebo-controlled trials are still needed to confirm their efficacy, to delineate their side effect profiles, and to determine their optimal dosing regimens.

### What Are Contraindications to the Use of Psychostimulants?

There are few absolute contraindications to the use of psychostimulants in the treatment of depression. Several conditions should be considered, however, as relative contraindications. Some relatively contraindicated conditions center around the potential of psychostimulants to raise blood pressure and heart rate. Although elevation of blood pressure and heart rate has, in general, been minimal at MGH, the presence of several conditions (e.g., recent myocardial infarction, ongoing congestive heart failure, low ejection fraction, uncontrolled hypertension or tachycardia, or a history of ventricular arrhythmia) may place an individual at risk for adverse events when even small changes in these parameters develop. In addition, it is prudent to avoid the use of stimulants in hyperdynamic states, such as hyperthyroidism. In these cases, one may consider the administration of a stimulant to be a small

“cardiac stress test.” When using stimulants in patients with any of these conditions, one should dose stimulants more cautiously and check vital signs more frequently.

Furthermore, the administration of stimulants should be avoided in patients who have been treated with monoamine oxidase inhibitors within the previous 2 weeks, who are pregnant (since there are no data in humans regarding the safety of stimulants in pregnancy), who have a history of adverse reaction to stimulants, or who have a history of stimulant abuse.

### How Are Stimulants Dosed, and How Are Side Effects Monitored in Depressed Populations?

Dosing of psychostimulants can begin with a single 5-mg dose of dextroamphetamine or methylphenidate, given orally in the morning. If the patient is medically fragile or is at some elevated risk of having an adverse reaction, one can begin with a 2.5-mg dose. The peak effect of these medications occurs in 2 to 4 hours. Therefore, mood and vital signs should be evaluated 2 to 4 hours after the dose to assess the effect of the stimulant on these parameters. If there is no response, the next morning's dose can be doubled. The dose may be increased by 5 mg/day until a response is achieved, intolerable side effects occur, or a dose of 20 mg is reached. Most practitioners would consider no response after a dose of 20 mg to be a failed trial.

If depressive symptoms improve, and this improvement lasts throughout the day, once-daily administration should be continued. If there is initial improvement of mood and energy that wanes in the afternoon, the same dose used in the morning can be repeated in the early afternoon. Late afternoon or evening administration should be avoided because use of stimulants may interfere with sleep.

The appropriate duration of psychostimulant therapy remains open to debate. In the MGH study,<sup>2</sup> most patients received stimulants only until their hospital discharge. A small subset of those studied remained on the medication for 2 to 3 weeks after discharge, while a few remained on the medication for more than a year.

### Should Psychostimulants Be Used for Mr. A?

Mr. A would be considered a good candidate for psychostimulant treatment of his depressive symptoms on the basis of the information presented here. He had no obvious contraindication to the use of stimulants, and he would most likely have benefited from their rapid onset of action. This rapid effect would have been particularly important for him because his poor appetite and inability to participate in his care were contributing to a suboptimal medical outcome. He could have been started at either 2.5 or 5 mg of dextroamphetamine or methylphenidate. His vital signs should have been monitored closely (especially

during the first few hours following a dose), given his medical fragility. Both the literature on psychostimulants and our experience suggest that he would have tolerated this treatment well and had an excellent chance of responding rapidly to treatment.

*Drug names:* dextroamphetamine (Dexedrine and others), methylphenidate (Ritalin, Concerta, and others), pemoline (Cylert).

REFERENCES

1. Olin J, Masand P. Psychostimulants for depression in hospitalized cancer patients. *Psychosomatics* 1996;37:57–62
2. Woods SW, Tesar GE, Murray GB, et al. Psychostimulant treatment of depressive disorders secondary to medical illness. *J Clin Psychiatry* 1986;47:12–17

ANNOTATED BIBLIOGRAPHY

Review Articles

Rozans M, Dreisbach A, Lertora JL, et al. Palliative uses of methylphenidate in patients with cancer: a review. *J Clin Oncology* 2002;20:335–339  
 –A comprehensive overview of the use of methylphenidate in 49 patients with terminal cancer. The use of methylphenidate for treatment of depression, cognitive dysfunction, and opioid-induced somnolence in cancer patients is discussed. In addition, the authors describe the use of methylphenidate as an analgesic augmentation strategy in patients with cancer.

Masand PS, Tesar GE. Use of stimulants in the medically ill. *Psychiatr Clin North Am* 1996;19:515–547  
 –A comprehensive review of the clinical uses of psychostimulants in the medically ill, including those with cancer and HIV infection. The pharmacology, side effects, and abuse potential of stimulants are discussed.

Emptage RE, Semla TP. Depression in the medically ill elderly: a focus on methylphenidate. *Ann Pharmacother* 1996;30:151–157  
 –A review of the clinical studies using methylphenidate to treat depression in medically ill elderly patients. The authors conclude that methylphenidate is an effective and safe treatment for depression in this patient population. They recommend that stimulants be used in medically ill elderly individuals when depression interferes with function and/or rehabilitative efforts.

Satel SL, Nelson JC. Stimulants in the treatment of depression: a critical overview. *J Clin Psychiatry* 1989;50:241–249  
 –An older but comprehensive review of the safety and efficacy of psychostimulants for the treatment of depression. The authors found that stimulants appeared less effective than standard antidepressants in the treatment of primary depression; however, geriatric patients and those with comorbid medical illness appeared to have a better response to stimulants. In the studies reviewed, stimulants were well tolerated and safe, and the authors conclude that these agents may be safer than tricyclic antidepressants in elderly or medically ill patients.

Original Articles

Breitbart W, Rosenfeld B, Kaim M, et al. 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;161:411–420  
 –A well-designed study that compared the efficacy of methylphenidate, pemoline, and placebo for the treatment of fatigue in 144 ambulatory HIV patients. Patients receiving either of the psychostimulants had

significantly greater improvements in fatigue than did those receiving placebo; improvement in fatigue was significantly associated with improvement in depressive symptoms and quality of life. Both psychostimulants were well tolerated, with hyperactivity and jitteriness the only side effects occurring more frequently with stimulants than with placebo.

Hinkin CH, Castellon SA, Hardy DJ, et al. Methylphenidate improves HIV-1-associated cognitive slowing. *J Neuropsychiatr Clin Neurosci* 2001;13:248–254  
 –A single-blind, placebo-controlled, crossover study of methylphenidate (30 mg/day) in the treatment of cognitive slowing in 16 patients with HIV infection. Patients improved on information-processing tasks with methylphenidate compared with placebo; subjects with the greatest cognitive slowing or depressive symptomatology at baseline had the most improvement, while patients without baseline cognitive slowing did not improve. Depressive symptomatology was not significantly affected by methylphenidate in this cohort. Methylphenidate was well tolerated.

Macleod AD. Methylphenidate in terminal depression. *J Pain Symptom Manage* 1998;16:193–198  
 –A prospective trial of methylphenidate in 26 hospice inpatients with major depression. Forty-six percent of the subjects had a significant response to methylphenidate; however, in the subset of patients who died of their illness within 6 weeks, only 7% had a significant response to stimulant treatment. This article suggests that patients who are near death may require higher doses of stimulants or may be more refractory to treatment.

Wagner GJ, Rabkin JG, Rabkin R. Dextroamphetamine as a treatment for depression and low energy in AIDS patients: a pilot study. *J Psychosom Res* 1997;42:407–411  
 –An open trial that used dextroamphetamine (median dose, 10 mg/day) to treat depression and low energy in 24 acquired immunodeficiency syndrome patients with CD4 counts of less than 200 cells per mm<sup>3</sup>. Seventy-five percent of all subjects (and 95% who completed at least 6 weeks of the study) had significant improvement of both mood and energy with dextroamphetamine treatment. Dextroamphetamine was well tolerated in this study.

Olin J, Masand P. Psychostimulants for depression in hospitalized cancer patients. *Psychosomatics* 1996;37:57–62  
 –A retrospective analysis of 59 hospitalized cancer patients treated with psychostimulants for depression. The authors found that 73% of patients showed marked or moderate improvement of depressive symptoms and that improvement usually began within the first 2 days of treatment. They also note that side effects uncommonly led to drug discontinuation (10%) and that appetite improved in more than half of the patients.

Wallace AE, Kofoed LL, West AN. Double-blind, placebo-controlled trial of methylphenidate in older, depressed, medically ill patients. *Am J Psychiatry* 1995;152:929–931  
 –A prospective, double-blind, placebo-controlled crossover trial of methylphenidate in 16 elderly, medically ill patients with depression. Patients had statistically significant improvement of their depressive symptoms when taking methylphenidate as compared with the phase when they received placebo. Improvements associated with methylphenidate appeared rapidly, and the majority of subjects tolerated the medication without significant adverse effects.

Woods SW, Tesar GE, Murray GB, et al. Psychostimulant treatment of depressive disorders secondary to medical illness. *J Clin Psychiatry* 1986;47:12–17  
 –A 5-year retrospective investigation of 66 medically ill inpatients at MGH who received psychostimulant treatment for depression. The authors found stimulants to be safe, well tolerated, and efficacious. Approximately 50% of patients had a moderate or marked response to treatment, while three fourths had at least some beneficial response. Nearly all of the patients had their peak response within the first 2 days of treatment.