schizophrenia by Joseph Levine, M.D., et al. (1). We would like to point to a finding not mentioned by the authors that may be clinically significant. The authors reported that the significant difference in mean homocysteine levels was entirely in male patients younger than 50. However, it appears from Table 1 that female patients ages 50 to 59 had a significantly higher mean homocysteine level than the female comparison subjects of the same age (mean=16.1 μM, SD=1.5, versus mean=11.3 μM, SD=2.3) ($t=3.65$, $df=59$, $p<0.001$, two-tailed). This finding might be related to the postmenopausal status of these women. Menopause is associated with increased homocysteine levels (2), and hormone replacement therapy decreases homocysteine levels in postmenopausal women (3). Women with schizophrenia may have poor nutritional status, which may modulate homocysteine levels, and/or be less likely to take hormone replacement therapy, which may explain the difference between the women with schizophrenia and the comparison subjects. Therefore, women's hormonal status should be taken into account in the design of future randomized controlled trials on the effect of folic acid, cobalamin, and pyridoxine supplementation.

In addition, the finding of no differences in homocysteine levels in the groups older than 60 (1, 4) is compatible with an association that has been found between a mutation in the methylenetetrahydrofolate reductase gene and good therapeutic response to conventional neuroleptics (5). Subjects with neuroleptic nonresponse may be overrepresented in older hospitalized patients with schizophrenia.

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Drs. Belmaker and Levine Reply

TO THE EDITOR: We thank Dr. de Haan and colleagues for bringing to our attention this additional level of complexity in our data. Clearly, homocysteine levels reflect numerous hormonal, nutritional, and lifestyle factors, and the relationships with schizophrenia should be seen within a multivariate model.

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On Chronic Fatigue Syndrome

TO THE EDITOR: We read with interest the recent review by Niloofar Afari, Ph.D., and Dedra Buchwald, M.D., concerning chronic fatigue syndrome (1), a ubiquitous symptom illness that is characteristically resistant to pharmacological and nonpharmacological interventions. We report the case of a patient whose core chronic fatigue syndrome symptoms responded rapidly and dramatically to a trial of add-on modafinil.

Ms. A was a 50-year-old female health care practitioner with a history of well-controlled major depression, hypertension, asthma, and hyperlipidemia. She began to experience insidious and disabling fatigue, a sore throat, myalgias, subjectively nonrestorative sleep, cognitive problems, migratory joint pain, right-sided carotidynia, and severe postexertional malaise. Her symptoms were initially believed to be due to a mild infectious illness; however, her symptoms progressed unremittingly. Further questioning about her symptoms revealed an absence of episodic "sleep attacks," cataplexy, hypnagogic or hypnopompic activity, sleep paralysis, lightheadedness, and loss of consciousness.

Despite extensive medical workups by internal medicine primary and subspecialty care services, no organic basis for her symptoms could be discovered. Neuropsychological testing showed normal intelligence and some problems with working memory and learning new information. Polysomnography failed to document any abnormalities, including those that would have suggested narcolepsy. Two cranial magnetic resonance imaging studies had findings that were clinically insignificant. Functionally, Ms. A complained of social withdrawal and an inability to work because of her symptoms, especially cognitive dulling and fatigue. She adamantly denied feeling depressed or being unable to experience pleasure.

Ms. A's concurrent medication list included venlafaxine, bupropion, propranolol, fluticasone, and albuterol. Bupropion was discontinued because of its presumed ill effects on sleep. Judicious use of clonazepam at bedtime was unhelpful in restoring sleep, while switching her antihypertensive medication to ramipril did not reduce fatigue. A brief trial of low-dose amitriptyline provided only modest relief of carotidynia before being discontinued because of bothersome side effects. She refused to participate in subsequent antidepressant trials, including a monoamine oxidase inhibitor after venlafaxine washout, other augmenting strategies, and nonpharmacological interventions, believing that they would not be helpful in ameliorating a "physical" process. She did, however, consent to a trial of modafinil, 200 mg/day, after discussion of off-label use.

Within 48 hours, Ms. A reported "dramatic" improvements in subjective alertness and a resolution of disabling fatigue. She began exercising daily without postexertional malaise and had resumed limited work duties at the 8-week follow-up. Close monitoring of her blood pressure and serum lipid levels showed no change. Clinical im-