Letters to the Editor

Treatment of Acute Mania With Topiramate

TO THE EDITOR: Several antiepileptic agents have been found to be effective in the treatment of mania and the prophylaxis of affective episodes in bipolar disorder (1). Whereas carbamazepine and valproate have been widely used in those patients, several studies support a role for the newer antiepileptic drugs, such as lamotrigine (2) and gabapentin (3).

Topiramate is a chemically novel antiepileptic drug that is available in a number of countries for the treatment of partial seizures. Although the mechanism of action of this substance is not yet fully understood, preclinical evidence suggests that it interferes with sodium conductance, augments the effect of γ-aminobutyric acid, blocks glutamate receptors, and has weak carbonic anhydrase inhibiting properties (4). Topiramate has a favorable pharmacokinetic profile and is generally well tolerated in patients with epilepsy (5). Psychotropic side effects (such as abnormal thinking) can usually be controlled by slow escalation of the dose. Unlike most other psychopharmacological drugs, the substance is associated with substantial weight loss. Here we report the efficacy of topiramate in a patient with acute mania by using an on-off-on study design.

Ms. A was a 36-year-old nurse with a 10-year history of bipolar disorder that resulted in at least 15 hospitalizations, predominantly for episodes of psychotic mania. She was admitted to our closed ward for acute mania that was characterized by a euphoric mood, logorrhea, psychomotor agitation, insomnia, and religious delusions. Previous treatment with carbamazepine was stopped because of inefficacy. Ms. A started treatment with a loading dose of valproate, 1800 mg/day, and haloperidol, 6 mg/day. Topiramate was added to this standard regimen in a dose of 25 mg on day 1 and 50 mg on day 2. Ms. A improved rapidly, as shown by a decrease in her Young Mania Rating Scale score from 41 on day 1 to 13 on day 15. Sedation and extrapyramidal dyskinesia were recorded as side effects. On day 15, her topiramate therapy was discontinued, whereas her valproate and haloperidol therapy was continued with an unchanged dose. Ms. A experienced a serious relapse of her manic symptoms that resulted in a Young Mania Rating Scale score of 33 on day 19. Her topiramate therapy was restarted on day 19. Her Young Mania Rating Scale score decreased to 20 on day 23 and 11 on day 30. Her haloperidol treatment was discontinued on day 35 without any further recurrence of her manic or psychotic symptoms. Her plasma levels of valproate were 41.6 mg/liter on day 1, 64.5 mg/liter on day 13, 66.6 mg/liter on day 18, and 60.0 mg/liter on day 25. Her haloperidol plasma levels were reported to be below 2 mg/liter on days 3 and 13.

This case report suggests the antimanic properties of topiramate. Whereas this patient's initial improvement could have been caused by combination therapy and thus cannot unequivocally be attributed to topiramate alone, the interruption of topiramate administration clearly provoked a severe and reversible manic relapse. The reinstitution of topiramate, however, again led to rapid improvement. The drug has been effective in a lower dose than is used for the treatment of epilepsy (target dose=200 to 400 mg/day) and was well tolerated. Valproate and haloperidol plasma levels remained unchanged after the addition of topiramate.

Although preliminary results on the use of topiramate therapy in treating bipolar disorder have been presented (6, 7), further double-blind studies to elucidate the antimanic and mood stabilizing effects of topiramate are warranted.

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Tiagabine and the Treatment of Refractory Bipolar Disorder

TO THE EDITOR: Gabapentin and lamotrigine have been recently introduced as add-on medications for the treatment of partial seizures. Several case reports and open studies in the psychiatric literature indicate that these two newer anticonvulsant drugs show promise in the treatment of bipolar disorder (1). Another anticonvulsant used for the treatment of partial seizures, tiagabine, was recently approved by the U.S. Food and Drug Administration (2). We report a positive response to tiagabine as an add-on agent in two patients with refractory bipolar disorder. Both patients gave written informed consent to take tiagabine for a non-FDA-approved indication.

Ms. A was a 46-year-old woman with a 23-year history of bipolar disorder type I with rapid cycling. Her illness had been difficult to manage. She had used the following medications in varying combinations and doses: lithium carbonate, imipramine, fluoxetine, divalproex, sertraline, gabapentin, clonazepam, alprazolam, thioridazine, risperidone, olanzapine, thiothixene, lamotrigine, and quetiapine.

Ms. A was taking a combination of quetiapine, lamotrigine, and alprazolam. This combination was initially effective; however, about 6 months later, she began to experience an increasing recurrence of mixed and manic symptoms. We elected to begin a trial of tiagabine. Her quetiapine therapy was discontinued and replaced with tiagabine, beginning at 1 mg/day (one-fourth of a 4-mg tablet) because she had a history of marked sensitivity to psychiatric medications. Lamotrigine and alprazolam treatment was continued. In response to the tiagabine, Ms. A commented that her mood was better than it had been in years. Her sleep was consistent, she was cognitively sharp, her energy and motivation were markedly improved, her dysphoria and anhedonia were resolved, and she could experience happiness. After 2 months of taking an average of 3 mg/day of tiagabine, she began to experience a manic episode. Restabilization was finally accomplished by increasing the tiagabine to 4 mg/day. She continued to experience benefit from tiagabine after 5 months. Her other psychiatric medications were lamotrigine (6.25 mg/day) and alprazolam (0.75 mg at bedtime) for insomnia.

Ms. B was a 42-year-old woman with a 6-year history of bipolar disorder type I. Her treatment course was initially turbulent. She was treated with the following medications in varying combinations and doses: lithium, temazepam, trazodone, amitriptyline, diazepam, sertraline, bupropion, paroxetine, fluoxetine, nortriptyline, divalproex, carbamazepine, flurazepam, and gabapentin. She was stabilized with a combination of lithium, venlafaxine, and flurazepam. Although she continued this combination therapy for several years, repeated occurrences of manic symptoms required adjunctive treatment. The following adjunctive medications were used without success: clonazepam, risperidone, haloperidol, lamotrigine, thioridazine, olanzapine, primidone, and quetiapine.

When Ms. B continued to experience marked recurrences of manic symptoms, we began a trial of tiagabine. Like Ms. A, Ms. B was sensitive to psychotropic drugs and was therefore started on the same low initial dose of 1 mg at bedtime. She gradually increased the dose to 4 mg at bedtime. She experienced no side effects and was able to lower her dose of flurazepam. Mood response was quite good; there was a marked reduction of manic symptoms. She took tiagabine for at least 3 months and was satisfied with the improved control of her manic symptoms. In addition to tiagabine, her other psychiatric medicines were venlafaxine (25 mg/day), lithium (300 mg/day), and flurazepam (7.5 mg at bedtime) for treatment of insomnia.

To our knowledge, these are the first case reports of the successful use of tiagabine as an augmenting agent for bipolar disorder. Tiagabine is a γ-aminobutyric acid uptake inhibitor that is metabolized by the liver. Most studies of the use of tiagabine for epileptic patients indicate that it is usually well tolerated (3). One report emphasized that a group of patients with epilepsy and psychiatric disorders (including depression) tolerated tiagabine as well as a group of patients with epilepsy without a history of psychiatric disorders (4).

The therapeutic range for tiagabine plasma concentrations has yet to be established. Our patients responded to a low dose of tiagabine compared to the doses required for seizure control in patients with epilepsy, according to the neurological literature. In our experience, psychiatric patients tend to respond to lower doses of anticonvulsants than patients with epilepsy. It is hoped that this encouraging response to tiagabine in two patients can be duplicated in other patients with refractory bipolar disorder.

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Lamotrigine-Induced Rash After Sun Exposure

TO THE EDITOR: Lamotrigine is an antiglutamatergic agent that promises treatment of bipolar disorder (1), especially in cases of bipolar depression (2). The main adverse effect of lamotrigine is skin eruption, which occurs in about 5% of treated patients and can in rare instances be severe (3). There are sparse reports in the literature of the occurrence of Stevens-Johnson syndrome (3) and toxic epidermal necrolysis (4). We present two cases of rashes appearing some time after the onset of lamotrigine administration.

Mr. A, a 42-year-old man with a diagnosis of schizoaffective disorder, bipolar type, was hospitalized in our clinic after a recurrence of his disorder that was induced by discontinuing his drug therapy. He received lamotrigine, 25 mg t.i.d., coadministrated with haloperidol, 20 mg b.i.d. His dose of lamotrigine was titrated gradually within a month. One year later, during Mr. A's last hospitalization, his dose of lamotrigine was raised to 100 mg b.i.d., whereas his dose of haloperidol stayed the same. He showed a marked regulation of his mood fluctuations after his discharge, and he also experienced a relatively satisfying vocational and social adjustment. Three months later, an acute maculopapular rash with itching appeared, which subsided after his lamotrigine treatment was interrupted. The day before the rash appeared, he had been exposed to sunlight while doing agricultural work.

Ms. B, a 30-year-old woman with a diagnosis of bipolar disorder type I (her most recent episode was manic), received lamotrigine as a prophylactic therapy. Her lamotrigine dose was titrated gradually within 1 month up to 100 mg b.i.d.. Six months later, while her mood had a normal fluctuation, she developed an acute maculopapular rash with itching. The day before the rash appeared, she had been exposed to the light of a solarium. The rash subsided after her treatment with lamotrigine was discontinued.

In these cases, the absence of a history of skin disease and the subsidence of the rash after the discontinuation of lamotrigine lead to the conclusion that the rash was a side effect of the drug. In the first case, we presume that it was probably related to insolation because of Mr. A's vocational activities. (He was a farmer.) In the second case, we conclude that it was related to exposure to the intense light of a solarium. The appearance of the rash, therefore, could be considered a delayed reaction to lamotrigine therapy, in combination with a stimulating factor (insolation). These findings lead us to propose that patients who receive lamotrigine should avoid prolonged exposure to sunlight.

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Reduction of Tardive Dystonia With Olanzapine

TO THE EDITOR: Tardive dystonia is usually considered a variant of tardive dyskinesia. However, the type of onset and the response to treatment clearly differentiate the two conditions with the notion that dystonias begin earlier and are more difficult to treat (1–3).

Mr. A was a 43-year-old man with a diagnosis of schizophrenia and polysubstance dependence who was in outpatient treatment. He spent 5 years in prison and was then in a state hospital for 1 year after an episode in which he stabbed his mother. He began taking neuroleptic medications at age 25, mainly chlorpromazine up to 1000 mg/day, for about 14 years. According to his records, Mr. A first noticed the presence of involuntary movements at age 35. These movements consisted of excessive blinking, which caused difficulty seeing, facial grimacing, jerky movements of the jaw resembling a yawn, and neck twisting accompanied by a gasping or barking sound that occasionally caused some respiratory distress.

Mr. A was evaluated by neurologists, who made a diagnosis of tardive dyskinesia and added that he might have late-onset Tourette's syndrome. Results of a magnetic resonance imaging of the brain were normal. Risperidone treatment was started, which he said seemed to help his movements; however, he remained markedly affected by his involuntary movements at the end of 2 years of risperidone therapy at 6 mg/day. When seen by one of us (M.E.J.), a diagnosis of tardive dystonia was made. His risperidone therapy was tapered, and he was started on olanzapine therapy, which was increased to 15 mg at bedtime. After being at this dose for 6 weeks, Mr. A experienced a marked decrease in his involuntary grunting, and his blepharospasms almost completely disappeared. After taking olanzapine for 7 months, his tardive dystonia improved further. He did not have any involuntary grunting or neck twisting, but he still had mild involuntary jaw movements.

While it is impossible to be definitive about the beneficial effects of olanzapine on this patient's movement disorder, the length of time it was present and the course of its improvement certainly suggest that olanzapine played a role in his improvement. Similar claims have been made for clozapine.

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Creutzfeldt-Jakob Disease Appearing as Paranoid Psychosis

TO THE EDITOR: Creutzfeldt-Jakob disease, also known as subacute spongiform encephalopathy, is a prion disease that is characterized by rapidly progressive dementia, often accompanied by myoclonus and other signs of central nervous system dysfunction. Psychiatric disturbances may precede neurologic deficits (1–3), which make the diagnosis of Creutzfeldt-Jakob disease elusive. We describe a patient with Creutzfeldt-Jakob disease who had three psychiatric evaluations before neurologic consultations.

Mr. A was a 49-year-old man with no past history of psychoactive drug use or psychiatric disturbances. He developed the symptoms of disorientation, psychomotor agitation, auditory hallucinations, and paranoid delusions over a month, which prompted his family to arrange for two successive psychiatric consultations. Short trials of haloperidol and risperidone did not relieve his psychiatric symptoms. When Mr. A developed ataxia, he was taken to an emergency room and admitted to the hospital for a examination of his "altered mental status." By this time, Mr. A was disoriented to time and place and inattentive; he had cogwheel rigidity and incoherent speech; and he appeared to respond to hallucinatory stimuli and voiced vague persecutory delusions. Antipsychotic drug therapy was discontinued, and a diagnosis of delirium was given. Once the psychiatric consultant noticed myoclonus, an EEG was recommended to rule out Creutzfeldt-Jakob disease. A neurologic consultation followed; a computerized tomographic (CT) scan showed diffuse cortical atrophy, and an EEG showed diffuse background slowing and periodic frontal sharp waves. An analysis of his CSF was positive for protein 14-3-3, which confirmed the diagnosis of Creutzfeldt-Jakob disease. Mr. A's neurologic condition worsened over the next 2 months; he developed incontinence and the inability to swallow. A feeding tube was

placed, and Mr. A was discharged to the custody of his family.

The early psychiatric symptoms of Creutzfeldt-Jakob disease previously described in the literature include depression, affective lability, sleep disturbance, personality change, and memory impairment (1–3). Psychosis, although infrequent, may be present; auditory hallucinations and delusional ideas coexist with fluctuations in the level of consciousness (2). The diagnosis of Creutzfeldt-Jakob disease is aided by an EEG. A characteristic pattern of repetitive sharp waves or slow spikes followed by synchronous triphasic sharp waves is seen in 70% of the patients (2). A CT scan and magnetic resonance imaging usually show cerebral atrophy (2), and a CSF analysis for detection of protein 14-3-3 can confirm the clinical and encephalographic diagnosis. There has been an increase in the prevalence of Creutzfeldt-Jakob disease in European countries in recent decades (1). Our case report highlights the importance of considering Creutzfeldt-Jakob disease in the differential diagnosis of delirium once subtle neurologic deficits are identified in conjunction with psychiatric disturbances.

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Treatment Augmentation With Opiates in Severe and Refractory Major Depression

TO THE EDITOR: Substantial evidence supports the antidepressant efficacy of opiates (1). This report summarizes our open-label experience using the μ-opiate agonists oxycodone or oxymorphone in patients with highly refractory and chronic major depression.

Mr. A was a 44-year-old man with severe and chronic depression. Numerous trials of antidepressants produced only limited benefit. Mr. A also had an extensive history of opiate abuse, and he noted that the only times he ever felt normal and not depressed was during opiate use. Because of the refractory nature of his depressive symptoms and his apparent self-medication with opiates, Mr. A was given a trial of oxycodone under strict supervision. After 18 months of oxycodone treatment (10 mg/day), Mr. A remained in his longest remission from depression without the emergence of opiate tolerance or abuse.

Ms. B was a 45-year-old woman with bipolar disorder and opiate abuse (in remission for 2 years). A trial with standard mood stabilizers had failed, and she had experienced mania with several standard antidepressant drugs. As with Mr. A, Ms. B reported feeling well only when taking opiates, particularly oxymorphone. Oxymorphone (8 mg/day) was thus cautiously added to ongoing lamotrigine therapy (as a mood stabilizer), and she remained well for a minimum of 20 months without drug tolerance or abuse.

Mr. C was a 43-year-old man with chronic major depression that was unresponsive to numerous antidepressants with and without augmentation. Detailed questioning revealed that he once experienced marked antidepressant effects from opiates that he received after a dental procedure. There was no history of opiate abuse, and a cautious trial of oxycodone was initiated. Mr. C experienced a dramatic and gratifying antidepressant response from oxycodone (10 mg t.i.d. for 9 months) without opiate tolerance or abuse.

This report describes three patients with chronic and refractory major depression who were treated with the μ-opiate agonists oxycodone or oxymorphone. All three patients experienced a sustained moderate to marked antidepressant effect from the opiates. The patients described a reduction in psychic pain and distress, much as they would describe the analgesic effects of opiates in treating nocioceptive pain.

Two of the three patients described in this report were previous abusers of opiates. Although the clinical use of opiates in patients with a history of opiate addiction is usually contraindicated, in these cases there was a strong indication that they were self-medicating their mood disorders (2) with illicit opiates. None of the patients abused the opiates, developed tolerance, or started using other illicit substances.

We used oxycodone in three additional patients without histories of opiate abuse. In two of these three patients, oxycodone produced a similar sustained antidepressant effect. Two of these patients experienced mild-to-moderate constipation, and one experienced daytime drowsiness from the opiates. Opiates should be considered a reasonable option in carefully selected patients who are desperately ill with major depression that is refractory to standard therapies.

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Bupropion-Induced Psychosis

TO THE EDITOR: Bupropion has characteristics, including excellent tolerability and few side effects or drug interactions, that suit it well for use in the elderly (1). However, bupropion has been associated with toxic effects, including seizures and psychosis, at rates higher than those found with other antidepressants (1). We present what is believed to be the first reported case of bupropion-induced psychosis in an elderly depressed individual with no known predisposition to psychosis who was neither delirious nor manic.

Mr. A, a 79-year-old, widowed, retired Hispanic man with no history of psychiatric or substance abuse came to

the emergency room after attempting suicide by slashing both of his wrists with a razor blade. On admission, his history and the results of a mental status examination were consistent with an initial episode of severe major depression. There was no evidence of delusions, hallucinations, or a thought, perceptual, or cognitive disturbance. Results of a physical examination, including an extensive hematological and metabolic screening, as well as an ECG and chest X-ray, revealed no significant abnormalities. His medical history was significant for the presence of osteoarthritis, gout, gastritis, and glaucoma, for which he took ibuprofen, sucralfate, and colchicine and used a betaxolol hydrochloride opthalmic solution. Bupropion treatment was started at a dose of 75 mg/day and titrated to a dose of 100 mg t.i.d. over the next 7 days. Despite a gradual improvement in mood, Mr. A began to exhibit some paranoid ideation on the fourth day of bupropion treatment. Mr. A's paranoia increased over the next 3 days, and he began experiencing auditory hallucinations. His dose of bupropion was decreased to 25 mg/day. Haloperidol treatment was initiated at a dose of 2 mg/day and subsequently titrated to 5 mg/day over the next 5 days. During the following week, Mr. A's psychotic symptoms decreased until they were entirely absent. Haloperidol treatment was discontinued, and his dose of bupropion was again titrated upward, this time to a final dose of 25 mg t.i.d. He did not experience a recurrence of either depressive or psychotic symptoms during the next 3 months of follow-up care.

Seven reports of emergent psychosis or delirium with psychotic features from bupropion treatment exist in the literature (2–8). After reviewing these case reports and a case series, one can conclude that bupropion-induced psychosis occurs primarily in patients with certain risk factors. Vulnerable patients include those with a history of psychosis or those who are taking other dopaminergic medications such as amantadine or levodopa. By blocking dopamine uptake, bupropion may cause dopaminergic overdrive (2) and thereby precipitate psychosis.

This case, coupled with the relative absence of reports of bupropion-induced psychosis in non-predisposed individuals, suggests that the elderly may be more vulnerable to bupropion-induced psychosis and other toxic effects than younger adults with depression. A report demonstrated that the half-life of bupropion is prolonged in the elderly and that the elderly accumulate bupropion metabolites (9). Potential toxic effects, including seizures and psychosis, may result from high bupropion plasma levels and the accumulation of bupropion metabolites in the elderly or in those with impaired liver function (10). Clinical reports in the elderly demonstrate that lower (75 to 225 mg/day) doses of bupropion are associated with fewer side effects and equal efficacy to those found with higher doses (11, 12).

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Geography of U.S. Psychiatric Disease by MEDLINE Publications, 1990–1997

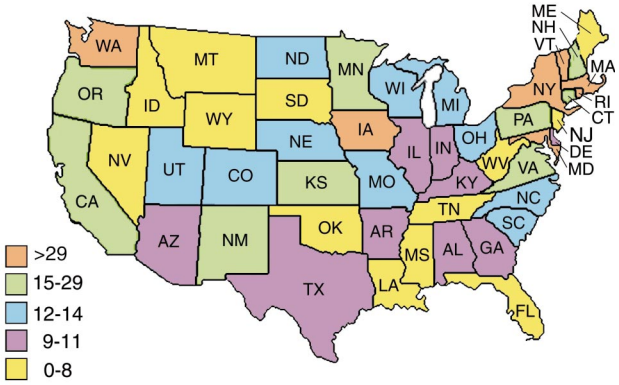
TO THE EDITOR: Thompson (1) recently evaluated the rates of MEDLINE publications from individual states in the United States. When they were normalized by resident populations, he found that several smaller states (Vermont, Washington, Maryland, Massachusetts, and Iowa) outperformed larger states in the number of MEDLINE publications per year per each 100,000 of the population. Benzer et al. (2) showed similar results on an international scale by using EMBASE publications. Curious as to how a subspecialty analysis might compare on a nationwide basis, we evaluated MEDLINE publications on psychiatric disease that were normalized by state populations.

The MEDLINE database was searched through the Internet provider PUBMED during the week of March 10–14, 1999. By means of the advanced search option, the "publication" field was searched for the dates 1990 to 1997. Next, the MSH field was searched for the term "mental disorders." This was limited to human studies only and combined with a search of the "author affiliation" field for each individual state. Population data were obtained from the Population Estimates Program's Bureau of the Census Web site.

The map [p. 2019] provides a color-coded breakdown of individual states by quintiles. States that appear in the orange group include Maryland, Massachusetts, Vermont, Rhode Island, New York, Washington, and Iowa. States that ranked high in publications dealing with psychiatric disorders that were not ranked high for total biomedical publications included Rhode Island and New York. New York, in particular, had a high number of total psychiatry publications (615 per year) and per population (34 publications per year per each 1 million of the population).

There are obvious limitations to this analysis. Simple publication numbers such as these are crude estimates of the research and scholarship among states. In addition, these data reflect neither the quality nor the usefulness of the published

articles. The data do highlight those states that are active in research and scholarship in psychiatric illness.



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Haloperidol and Alzheimer's Disease

TO THE EDITOR: D.P. Devanand, M.D., and colleagues (1) reported successful control with haloperidol of severe behavioral disturbances in outpatients with Alzheimer's disease. They rightly claimed that "the efficacy of nonpharmacologic interventions…remains to be established" (p. 1513). We wish to support the efficacy of nonpharmacologic interventions on behavioral disturbances with personal data taken from a controlled European study of demented individuals who were admitted to nursing homes.

Special care units for behaviorally disturbed patients with dementia are largely, although not exclusively, based on nonpharmacologic interventions such as appropriate staff attitudes and specific environmental features and have been proposed as an effective model of care. In 1995, the Regione Lombardia of northern Italy funded the establishment of a number of special care units in long-term care facilities. A pilot study show that care in special care units could effectively reduce behavioral disturbances with no increased resort to psychotropic drug load or physical restraints (2). A controlled study has recently been completed that confirms these preliminary results (3).

Patients who were capable of walking and had moderate to severe dementia (Mini-Mental State examination mean score=7, SD=5) and severe behavioral disturbances on the modified Neuropsychiatric Inventory (maximum score=108) were enrolled in 18 special care units (patients, N=39) and 25 traditional nursing homes (control subjects, N=41) (3). The patients were assessed at baseline (10 days after admission) and after 6 months. Although at baseline the patients had more severe behavioral disturbances (modified Neuropsychiatric Inventory mean score=37, SD=18, and mean score=28, SD=12, for patients and control subjects, respectively) (p=0.02), at the follow-up examination, these disturbances had significantly improved in both groups (decrease of 38% and 41%, respectively) (p<0.0001); there was no increase in the percentage of patients taking neuroleptic or other psychotropic drugs. Extrapyramidal signs were not assessed, but proxies of adverse effects of psychotropic medications (cognitive performance and falls) remained unchanged. It is noteworthy that in the patient group, the reduction of behavioral disturbances was achieved with a lower use of physical restraints: 10% of patients and 32% of control subjects (p=0.02) had to be restrained with a chest vest or a belt at follow-up.

Although implementing and testing the efficacy of environmental interventions in outpatients such as those in the study by Dr. Devanand and colleagues is doubtless more difficult than with institutionalized patients, we believe that environmental interventions should be the first-line option for inpatients, whereas they need further investigation in outpatients.

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Dr. Devanand Replies

TO THE EDITOR: Dr. Frisoni and colleagues report that in Alzheimer's patients with behavioral disturbances, a program of nonpharmacologic intervention in special care units was successful. Whereas this approach may indeed work in many patients with dementia, methodologic flaws in their study make it difficult to draw any firm conclusions. Patients were not randomly assigned to the special care units or to traditional nursing homes, and this probably contributed to the patients in the special care units having significantly more severe behavioral disturbances than the patients in traditional nursing homes. The well-known statistical phenomenon of regression to the mean, whereby outliers at one assessment time tend to drift closer to the mean at the next assessment, may partly explain the observed clinical improvement, especially because the group in the special care units started with more severe behavioral disturbances and, hence, was more likely to move down toward the mean. Also, placebo-controlled pharmacotherapy trials of behavioral disturbances in patients with dementia consistently report placebo response rates ranging from 20%–50%, and it is common for patients taking placebo to show considerable

improvements in behavioral symptoms (1–3). Therefore, in the absence of an adequate control group, the nearly identical decrease in symptoms in the special care unit and nursing home groups (38% and 41%, respectively) is difficult to interpret.

The group in the special care units had significantly less physical restraint than the group in traditional nursing homes, but apparently there was no difference in the use of psychotropic medications between the two groups. This suggests that physical restraints do not work well and may not be advisable but also that no conclusions can be drawn about the use of psychotropic medications. In essence, this de facto experimental intervention was to avoid physical restraint in the group in the special care units and to permit restraint in the group in traditional nursing homes. Therefore, the authors' claim that nonpharmacologic, environmental interventions should be the first-line option for Alzheimer's inpatients with behavioral disturbances is a fairly big leap beyond what their data show. To reach such a conclusion, a randomized, head-to-head, controlled comparison of pharmacologic and nonpharmacologic interventions needs to be conducted—something that has never been done.

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