Letters to the Editor

Gabapentin for the Treatment of Patients With Somatization Disorder

Sir: Somatization disorder is characterized by a pattern of multiple, clinically significant somatic complaints that cannot be fully explained by any known medical condition.[1] The pharmacologic treatment of somatization disorder has scarcely been investigated owing to methodological problems,[2] and no open or controlled trial has been conducted in patients with somatization disorder. Since pain is the most frequent symptom in somatization disorder, we selected gabapentin because it has demonstrated efficacy in patients with organic pain.[3]

We selected 29 patients (all of whom gave informed consent) from the Somatoform Disorders Unit at Hospital Universitario Miguel Servet (Zaragoza, Spain) who were diagnosed as having DSM-IV somatization disorder, with pain as the main symptom. Gabapentin was added to their previous treatment that consisted of neuroleptics, benzodiazepines, and serotonergic or tricyclic antidepressants. Gabapentin was titrated to a dosage of 1200 to 1600 mg/day, depending on the patient's symptoms and side effects. Patients accepted to maintain unchanged their previous treatment over the 3 months of the trial to evaluate the effect of gabapentin. They were assessed at baseline and at 3 months with the Pain Visual Analogue Scale,[4] the Clinical Global Impressions scale,[5] the McGill Pain Questionnaire,[6] the Global Assessment of Functioning,[7] and the Hospital Anxiety Depression Scale.[8]

Of the intent-to-treat subjects, 6 (20.6%) dropped out of the study owing to side effects or lack of efficacy. Analyses were completed for all subjects who took at least 1 dose of gabapentin (N = 29). Patients who dropped out of the study were included in the analysis with the last observation carried forward (LOCF) to replace their missing data. Mean LOCF scores were compared with baseline scores. The statistic used was the t test for related samples.

To our knowledge, this is the first open trial to assess the efficacy of any pharmacologic treatment in patients with somatization disorder. In this study, there was a statistically significant improvement ($p < .01$) in all measures but one, as seen in Table 1. Only the Hospital Anxiety Depression Scale showed no differences, indicating that improvement in these patients seems independent of depression and anxiety levels.

In conclusion, despite the limitations of open trials, gabapentin seems to be an effective treatment for patients with somatization disorder in whom pain is the predominant symptom.

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Table 1. Baseline and 3-Month (LOCF) Ratings for Patients With Somatoform Disorder (N = 29) Treated With Gabapentin[a]

	Baseline		LOCF		
Instrument	Mean	SD	Mean	SD	Significance
PVAS	69.0	9.1	48.8	14.9	$p < .01$
CGI	3.7	0.4	2.7	0.9	$p < .01$
MPQ	3.8	0.3	2.6	0.7	$p < .01$
GAF	51.1	2.3	63.8	6.1	$p < .01$
HADS	9.6	1.9	9.6	2.3	NS

[a]Abbreviations: CGI = Clinical Global Impressions scale, GAF = Global Assessment of Functioning, HADS = Hospital Anxiety Depression Scale, LOCF = last observation carried forward, MPQ = McGill Pain Questionnaire, NS = not significant, PVAS = Pain Visual Analogue Scale.

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Acronyms for Substance Use Disorders

Sir: One of the foundations of modern psychiatry is the consistent application of standardized diagnostic criteria, currently those of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[1] In our work with residents, we are frequently struck by the tendency to be much less rigorous in the diagnosis of substance use disorders than in the diagnosis of other Axis I conditions. Perhaps this is indicative of a residual bias within the profession against substance use disorders

Table 1. Acronyms for DSM-IV Criteria for Substance Dependence and Abuse

Substance Dependence: ADDICTD
Activities are given up or reduced (criterion 6)
Dependence, physical: tolerance (criterion 1)
Dependence, physical: withdrawal (criterion 2)
Intrapersonal (***I***nternal) consequences, physical or psychological (criterion 7)
Can't ***C***ut down or ***C***ontrol use (criterion 4)
Time-consuming (criterion 5)
Duration or amount of use is greater than intended (criterion 3)
Substance Abuse: WILD
Work, school, or home role obligation failures (criterion 1)
Interpersonal or social consequences (criterion 4)
Legal problems (criterion 3)
Dangerous use (criterion 2)

as legitimate psychiatric disorders. One is always expected to back up a diagnosis of, for example, major depression with specific signs and symptoms meeting diagnostic criteria. For substance use disorders, there is still a tendency for the diagnostic process to be much more impressionistic. It is not uncommon to see the diagnosis of alcohol dependence made on the basis of a single drunken presentation in an emergency setting, or a diagnosis of "polysubstance abuse" (not even a DSM-IV diagnosis!) made on the basis of the simple use of several classes of drugs.

Acronyms, frequently used as mnemonic devices in psychiatry, can help ensure that all diagnostic criteria are remembered and inquired about. Acronyms for a variety of psychiatric disorders have been published, including Berber's useful mnemonic for symptoms of generalized anxiety disorder, in the June 2000 issue of the *Journal*.[2] To improve diagnostic rigor of substance use disorders, we have created acronyms for the DSM-IV criteria for substance dependence and abuse: ADDICTD and WILD, respectively (Table 1).

We have found these acronyms helpful in our clinical teaching of residents and medical students, and we hope that others will find them useful as well.

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Topiramate Abuse in a Bipolar Patient With an Eating Disorder

Sir: Topiramate is a new anticonvulsant drug that has recently been introduced and marketed as a potentially useful mood stabilizer with a possible antimanic profile. Its mode of action is multifactorial and involves blockage of voltage-dependent sodium channels. Although the U.S. Food and Drug Administration has not approved its psychiatric use, several groups all over the world are assaying this promising drug with resistant bipolar patients, and some naturalistic evidence has been provided by open studies about its mild-to-moderate efficacy in the treatment of manic syndromes[1] or as a coadjunctive mood-stabilizing agent.[2,3]

Topiramate has the advantage of inducing weight loss, an issue of great interest when treating psychiatric patients because of the weight gain associated with some of the available psychiatric drugs and with some psychiatric syndromes. But this property might also present a serious problem due to the possibility of topiramate abuse in patients with serious weight concerns, as we present here.

Case report. Ms. A, a 30-year-old white woman, has suffered approximately 5 episodes of mania, from 8 to 10 depressive episodes with psychotic features, several mixed episodes, and a single psychiatric hospitalization due to a suicide attempt. In addition, she suffers from a serious unspecific eating disorder consisting of an intense fear of gaining weight and episodes of binge-eating and purging behavior (self-induced vomiting) occurring less than twice a week. She has regular menses and current weight within the normal range. Ms. A fulfills DSM-IV criteria for both bipolar I disorder and borderline personality disorder. After voluntarily withdrawing valproate and lithium carbonate due to her knowledge about their potential side effects on weight, and since she refused to take any drug with weight gain as a described side effect, she gave consent to start treatment with topiramate for a mixed episode, with an initial dose of 25 mg/day and a slow titration of 25 mg every 5 days until reaching a daily dose of 200 mg. Ms. A's weight at the visit during which topiramate was prescribed was 62 kg. At the following visit, a week later, she showed no side effects attributable to topiramate.

Fifteen days later, when she was supposed to have been taking 125 mg/day of topiramate, part of the mixed symptomatology had remitted, but Ms. A showed decreased cognition, dulled thinking, blunted mental reactions, blurred vision, paresthesias, moderate sleepiness, and gastrointestinal disturbances. After initial denial, she admitted that she had been taking substantially higher doses of topiramate during the last 2 weeks and that at that time she was taking 450 mg/day. When asked about the reasons for taking the higher doses, Ms. A argued impatience toward the weight loss, and she stated that she kept taking higher doses than prescribed to lose more weight even after noticing several side effects. Ms. A experienced a weight loss of 6 kg in a period of 15 days. After lowering the doses to 100 mg/day, all side effects rapidly disappeared.

This case addresses the problem of managing bipolar patients with serious weight concerns, concomitant personality and eating disorder, and, consequently, poor compliance.[4] As has been recently reported, topiramate may be efficacious in treating both binge-eating disorder[5] and bipolar disorder.[3] Weight loss, a possible advantage of topiramate over other antimanic agents, may result in its abuse by those subjects with body-image disorders. All the adverse symptoms Ms. A experienced have been described at high doses of topiramate—doses beyond 600 mg/day are often not well tolerated due to this cluster of symptoms[6]—but are very infrequent at low doses. Although the topiramate dose of 450 mg/day that Ms. A took remains within the therapeutic range, the voluntary rapid titration led to the described symptomatology, which might not have appeared if that dose had been reached correctly, with a slow titration. Clinicians should be aware of the potential risks of abuse of topiramate in patients with eating disorders.

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Seizure During Combination of Trimipramine and Bupropion

Sir: In recent years, published reports have suggested that the combination of bupropion with either selective serotonin reuptake inhibitors[1] or with tricyclic antidepressants (TCAs)[2] may be safe and effective options for patients with treatment-resistant depression. I report a patient who was successfully treated with the combination of bupropion and trimipramine, but experienced an unexpected and substantial increase in her plasma level of trimipramine associated with a witnessed generalized seizure.

Case report. Ms. A, a 62-year-old married woman, had a history of refractory DSM-IV major depressive disorder. She was otherwise medically healthy and had no history of seizures. Her depressive disorder consisted of symptoms of depressed mood (with diurnal variation), loss of interests and pleasure, fatigue, weight loss, initial insomnia, motor retardation, and anxiety. A medical workup, including brain computed tomography (CT) scan, revealed no abnormalities.

Serial trials of treatment with fluvoxamine, sertraline, moclobemide, venlafaxine, desipramine (adequate plasma level), and nortriptyline (adequate plasma level), plus augmentation with lithium, liothyronine, and lamotrigine, had produced no sustained benefit for her symptoms. She was referred for electroconvulsive therapy (ECT) and had a complete response to 8 right-unilateral treatments. Acute ECT was followed by continuation ECT at a frequency of 1 treatment per week. Each time an attempt was made to decrease the frequency of ECT treatments, significant depressive symptoms reemerged. Therefore, continuation ECT was combined with a different TCA, trimipramine. Plasma trimipramine levels were measured using high-pressure liquid chromatography.[3] The addition of trimipramine, 150 mg/day (resulting in a steady-state plasma level, drawn 10 hours postdose, of 305 ng/mL [trimipramine, 218 ng/mL; *N*-desmethyltrimipramine, 87 ng/mL]), and liothyronine, 25 μg/day, was insufficient to allow a reduction of the frequency of ECT treatments. Therefore, we elected to add bupropion to trimipramine and liothyronine. Trimipramine was decreased to 100 mg/day, and bupropion (sustained-release formulation) was initiated at 100 mg/day and titrated up to 150 mg b.i.d. Ms. A had a pronounced positive response. ECT treatments were tapered to every other week without reemergence of depressive symptoms, and she was scheduled to have her next ECT in 3 weeks.

Eleven days after her final ECT treatment, Ms. A was observed by her husband to have a generalized seizure (tonic and clonic motor manifestations and unresponsiveness). A second brain CT scan showed no abnormalities. Her plasma trimipramine level 15 hours after her last dose was in the "toxic" range (trimipramine, 351 ng/mL; *N*-desmethyltrimipramine, 214 ng/mL; total, 565 ng/mL). Ms. A's dose of trimipramine was reduced to 50 mg h.s., and her dose of bupropion was reduced to 150 mg/day. Twenty days later, her trimipramine level was 243 ng/mL (trimipramine, 162 ng/mL; *N*-desmethyltrimipramine, 81 ng/mL). No further ECT treatments were given. Ms. A has now been stable and euthymic on the combination of trimipramine, 50 mg h.s.; bupropion, 150 mg/day; and liothyronine, 25 μg/day, for 8 months. No further seizures have occurred.

The witnessed seizure in this patient occurred in the context of a toxic level of trimipramine and a bupropion dosage of 300 mg/day (the only other coadministered medication was liothyronine). Seizures have been associated with the use of both bupropion and TCAs, particularly with high doses of bupropion or excessive plasma levels of TCAs.[4,5] The excessive TCA level, bupropion alone, or the combination of bupropion and the TCA may have been related to the occurrence of a seizure in this case. The combination of trimipramine and bupropion was associated with a dramatic increase in the plasma level of trimipramine. Trimipramine, 150 mg (alone), yielded a plasma level of 305 ng/mL, whereas 100 mg of trimipramine in combination with bupropion yielded a plasma level of 565 ng/mL. These trimipramine plasma level findings are consistent with the known inhibitory effect of bupropion on cytochrome P450 2D6 isoenzyme (CYP2D6).[6] It is also conceivable that trimipramine caused an increase in the plasma level of bupropion or its metabolites. However, plasma levels of bupropion were not measured, so this cannot be confirmed or refuted. Nevertheless, this possibility warrants consideration, especially because the trimipramine level in the present case was at the lower end of the range of TCA levels observed in patients experiencing seizures while receiving TCAs.[7]

Bupropion appears to be predominantly metabolized by CYP2B6,[8] and in the past bupropion had not been thought to

inhibit P450 isoenzymes.[9] However, a possible interaction between bupropion and imipramine mediated by the 2D6 isoenzyme was reported in 1997,[10] and the package insert for bupropion now indicates that bupropion inhibits 2D6 to a substantial degree.[6] The metabolism of trimipramine is complex; it follows multiple metabolic pathways and involves 2D6 as well as other P450 isoenzymes.[11,12] Thus, a pharmacokinetic interaction involving the inhibition of 2D6 by bupropion explains the observed elevation of trimipramine plasma level in the present case.

Case reports,[1,2] including the present one, provide a preliminary indication that antidepressant combinations involving bupropion may be of value in treatment-resistant patients with major depressive disorder. However, clinicians should be aware that if a typical dose of bupropion is combined with a TCA, most patients who are extensive 2D6 metabolizers will experience significant inhibition of this enzyme and an elevated level of the TCA (and other 2D6 substrates). The use of TCA plasma level monitoring and a reduced dosage of the TCA are appropriate precautions.

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Clozapine in the Treatment of Hypomania With Neurosyphilis

Sir: Clozapine is effective for various psychiatric conditions, including psychosis in neurologic disorders.[1,2] Neurosyphilis is infrequent today with early treatment, but its psychiatric complications ranging from personality change to psychosis and dementia have been described.[3] I report a patient with hypomania and initially undetected neurosyphilis, who could not be stabilized with neuroleptics and finally responded to clozapine.

Case report. Mr. A, a 43-year-old man, first presented with an acute onset of disturbed behavior, insomnia, and talking nonsense. He had no family history of mental illness and no significant past medical history or substance abuse. A diagnosis of psychotic disorder not otherwise specified (DSM-IV) was made, and he was treated with haloperidol, 20 mg/day. Mr. A did not regularly keep follow-up appointments, was never symptom-free, and was unemployed. Records indicate that various medications had been tried, including risperidone, 2 mg/day, and sulpiride, 1200 mg/day. Side effects such as stiffness, tremors, and increased salivation were noted with those medications.

Three years later, Mr. A's family sought his admission to the hospital, since he had become increasingly disturbed and talkative. In addition, they noticed an abnormal gait. Mr. A appeared emaciated but was very loud, talkative, disinhibited, grandiose, and elated. He had a high-stepping gait, ankle areflexia, and Argyll Robertson pupils. He finally revealed a past history of visits to prostitutes. A VDRL test was reactive, and a *Treponema pallidum* hemagglutination assay was reactive. He was negative for human immunodeficiency virus, and cerebrospinal fluid (CSF) examination revealed that fluorescent treponemal antibody IgG was reactive (CSF was clear, white blood cell count = 1 cell/mm^3, glucose = 3, chloride = 119 U/L, total protein was within normal limits, globulin was negative). An electroencephalogram showed abnormalities, with excessive slow activity over both frontotemporal regions. A computed tomography scan showed cerebral atrophy and asymmetric dilation of the ventricles.

Ms. A's neurosyphilis was treated with injection procaine penicillin and oral probenecid. He was given sodium valproate, 1600 mg/day, and lithium carbonate, 1 g/day, but he continued to be disturbed, interfering with and provoking other patients in the ward. Neuroleptics such as thioridazine, risperidone, and even depot flupenthixol decanoate were added with little effect. Mr. A frequently needed restraint and seclusion in the ward. He also experienced recurrent urinary tract infections from a neurogenic bladder. There were no clear exacerbations of his mood state during the urinary tract infections. His score on the Mania Rating Scale (MRS) from the Schedule for Affective Disorders and Schizophrenia-Change Version[4] was 44. Mr. A was started on clozapine treatment a year later. The dose was gradually titrated up and the mood stabilizers were tapered off. He was eventually stabilized on clozapine, 450 mg/day. His score on the MRS fell to 27. Although the grandiose ideas remain, he is no longer elated, talkative, or quarrelsome, and he is able to return home on weekend leave. On clinical assessment, there were cognitive deficits such as memory impairment and disturbed executive functioning, suggestive that a dementing process had occurred.

This case serves as a reminder that although neurosyphilis and its psychiatric and neurologic sequelae are rarely encountered today, they can present with symptoms characteristic of a psychiatric disorder. Parenchymatous changes in the central nervous system can lead to tabes dorsalis, meningovascular syphilis, and general paresis in which a "grandiose and expansive form" is often the most frequent.[3] With the initial acute-onset illness and "absence" of any significant history, a wider investigative net should have been cast for this patient.

In addition, to the best of my knowledge, there have been no published reports on the use of clozapine in treating patients

with psychiatric complications of neurosyphilis. Clozapine effectively led to behavior and symptom control and reduced the need for combination treatment.

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Internet-Observed Suicide Attempts

Sir: The Internet has a powerful impact on society and psychiatry.[1,2] It offers suicide prevention services and has even become a source of information about how to commit suicide.[3] We report 2 separate cases in which threats of suicide were made somewhat indirectly and discovered over the Internet.

Case 1. Ms. A is a 38-year-old, married white woman with a history of major depression. She was brought to the emergency room involuntarily by police after making a suicide threat in an Internet chat room while using America Online (AOL). Suicidal ideation by Ms. A was noticed by another AOL subscriber and reported to customer service. The AOL representative notified the police. Ms. A revealed being a regular Internet user and acknowledged planning to take a medication overdose. The episode was related to the anniversary of the birthday of her child who had died 3 years before. She was hospitalized and treated for depression.

Case 2. Mr. B is a 42-year-old, married white man with no previous psychiatric history. He was in the process of divorce. One evening, Mr. B was in a chat room used by his friends and, using a camera, was broadcasting a video of himself on the Internet. One friend saw that while on video, Mr. B loaded a pistol and pointed it at his head in an overt suicide threat saying that he would shoot himself. The friend notified police who then brought Mr. B to the emergency room. A therapeutic intervention was implemented.

These cases are not exclusive. In a more dramatic example, a man from the United States rescued the life of a woman in Britain after she posted a suicide threat on the Internet.[4] She then attempted suicide by ingesting a cocktail of pills and alcohol but was found by the police in time to be saved.

As seen in the first clinical vignette, the Internet user made a suicidal threat in the impersonal isolation or anonymity of the Internet. Perhaps the perceived anonymity of this means of communication allows some individuals with suicidal thoughts to feel comfortable enough to announce their private intent. The other case represents Internet interaction with friends in which suicidal ideation is expressed through means of electronic communication rather than in person. Apparently, however, the Internet is not consistently an anonymous medium since Internet users notice the commentary and behavior of other Internet users. Customer service at AOL indicates that the use of official Internet observers is for monitoring children's Web sites as well as chat rooms.

The Samaritans, an organization that offers suicide prevention services, hosts an Internet crises intervention Web site. It is available at http://www.samaritans.org.uk/ and functions as a nonprofit, charity help line that is accessible 24 hours a day. It received 25,000 confidential e-mail contacts in 1999, with over half of them from individuals expressing suicidal concerns.[5] The Samaritans Web site is a form of social networking that provides crises help which people can access from their own computer when they are feeling suicidal.

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Changing Paradigms: Depressed Patients as Treatment Partners

Sir: Not long ago, I was diagnosed with invasive breast cancer. I had none of the risk factors, yet, there I was, 46 years old, wife and mother of 3 children, learning that my life was about to change. Decisions, treatment, recovery, and the concern about metastasis or recurrence were issues that had to be addressed, some of them very quickly. Within about a week of my diagnosis and visits to the surgeon, internist, radiation oncologist, and medical oncologist, I had more information about my cancer and its potential treatment than I could absorb. An expandable 4-inch folder was filled with handouts, brochures, booklets, and reference lists. In addition, I had been shown 2 videotapes and completed 1 CD-ROM interactive learning session. I had been invited to participate in 3 research studies and had agreed to 2 of them. My physicians spent ample time with me, answering questions, drawing pictures, and seeking my input about treatment options. They welcomed my husband and friends who accompanied me. Ultimately, I knew that we all would make these big decisions together. And I felt prepared and involved.

In the midst of this flurry of activity, I began to reflect on my diagnosis of cancer versus the diagnosis of depression. Not only had I experienced depression in my life, but as a mental health provider, I work with people experiencing depression. Isn't this curious, I thought, that patients with depressive disorders come for an evaluation, get a diagnosis, and usually walk away with

an SSRI prescription, perhaps a handout, and only a rudimentary understanding, if any, about their diagnosis. There is no 4-inch folder of materials when you get a diagnosis of depression. In fact, the differences between getting a diagnosis of breast cancer and a diagnosis of depression are profound. From what I have seen over the years, not just in our clinic, but throughout the mental health system, most patients are advised of a recommended treatment. If they agree, they leave with a prescription or follow-up appointment for therapy. If they don't agree, they are labeled "difficult," "character disordered," or "not motivated." My guess is that within 1 week of a diagnosis of depression, most patients couldn't tell you much about their illness, medication, therapy, or their expected clinical course and outcome. I can't imagine that most patients feel as though they are a valued partner in the treatment of their depression. And I suspect that most families are reeling from the difficult dynamics of a loved one's depression and continue to be painfully unaware of depression as a complex biological disorder.

Whereas my husband and friends were openly welcomed by my health care providers during my breast cancer treatment, in the mental health arena, family members and significant others are usually left out, feeling frustrated, and wondering what is happening to their loved one, often under the guise of "confidentiality." A friend of mine has an 18-year-old daughter who was recently diagnosed with bipolar disorder. When I spoke to her, she was crying, describing her telephone conversation with her daughter's psychiatrist, who told her that he was "refusing to talk to her" due to confidentiality. And, true to his word, he did not respond to her calls, notes, or faxes. My friend did not want specific details about her daughter; she wanted to know what she could do to help, provide him with information about her daughter's behavior at home, ask how she could get some information about the illness of bipolar disorder, and find out what support mechanisms were available to her and her husband. A similar scenario had happened last year to a friend of mine whose brother was admitted to the hospital for severe depression. She didn't know his whereabouts for days and was hysterical that he had committed suicide somewhere or had been the victim of foul play. Her brother's psychiatrist who had admitted him to the hospital refused to even let her know that her brother was safe. Interestingly, my friend is a physician herself who happened to be paying her brother's medical expenses.

So I say to my fellow mental health practitioners—*what are we doing?* Why do we continue to operate from an old paradigm in which the provider knows best, patients with psychiatric problems are not capable of being involved in their care and treatment decision making, families can't have information, and patients don't really need to know that much about their treatment? Have we really sat down and examined the perspective from which we provide treatment to persons with depression or any type of mental illness? Do we try to involve patients in their healing, or do we unwittingly, or knowingly, try to maintain our position of authority? Information is powerful and we do not do a good job of educating depressed patients. What do we tell them and what do we provide? How good are the materials we have and how often do we use them? How often do we create innovative educational materials that aid patients in making informed choices about their treatment for depression? Why have we, for the most part, not embraced patients and their families as joint decision makers about the treatment options? Why don't our patients have knowledge about depression, including its biology, its symptoms, its clinical course, its potential for recurrence? Why don't they have coaching about symptom management, and what they can do to monitor for prodromal symptoms, and improve exercise, nutrition, and stress reduction for the long haul? Why aren't significant others given materials about their loved one's depression and at least listened to and offered supportive services?

Depression is a deadly disorder. It kills. It causes personal pain and anguish. It destroys families and damages careers. It is associated with illness and death from other disorders such as cardiovascular disease. We cannot continue in our current modes of practice when it comes to depression. In spite of our good intentions and best scientific knowledge, public reactions and attitudes about depression will not change until we do some truthful self-examination. Until we begin working with patients as involved partners in the treatment of their devastating illness, we cannot expect to change old paradigms. Our jobs shouldn't be just to treat symptoms, but to educate and advocate for patients and their loved ones and to facilitate *their* role, not just ours, in managing their illness. It's time to stop preaching that attitudes toward depression and mental illness need to change and do something about it. We have come a long way with breast cancer: we can make a difference. It's time to do the same with depression. What are we waiting for?

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Clozapine in the Treatment of Aggression in an Adolescent With Autistic Disorder

Sir: The pharmacotherapy of autism and pervasive developmental disorders primarily targets central serotonin or dopamine pathways. The use of haloperidol in treating autism in children was well studied in several double-blind, placebo-controlled studies by Campbell and associates.[1–3] In addition, a double-blind, placebo-controlled study by McDougle et al.[4] showed that the selective serotonin reuptake inhibitor (SSRI) fluvoxamine reduced repetitive thoughts and behavior, maladaptive behavior, and aggression in adults with autistic disorder.

However, the literature describing the treatment of autism with atypical neuroleptics is relatively new. Two case reports and 1 prospective, open-label study have described positive clinical responses to the atypical agent olanzapine.[5–7] In a double-blind, placebo-controlled study, McDougle et al.[8] demonstrated the reduction of repetitive behaviors, aggression, and anxiety by a 12-week trial of risperidone in adult patients with autism or pervasive developmental disorder. Zuddas et al.[9] demonstrated the efficacy and long-term safety of risperidone administration in children and adolescents with autism or pervasive developmental disorder for up to 12 months. However, data are limited on the use of clozapine in autistic disorder. There has been 1 case report describing the successful reduction by clozapine of hyperactivity and aggression in 3 autistic children.[10] We report here the successful short-term use of clozapine in the treatment of aggression in an adolescent male with autistic disorder.

Case report. Mr. A, a 17-year-old Hispanic male with autism, severe mental retardation, and episodic aggression, was admitted to our inpatient adult psychiatric unit after being transferred from his residential home after several weeks of increasing aggression toward the staff and other patients. Mr. A's behavioral patterns had been poorly controlled in the past with typical neuroleptics, mood stabilizers, SSRIs, and β-blockers at

various doses and in multiple combinations. He had been previously treated with quetiapine, olanzapine, and risperidone without clinical improvement. On the basis of previously published literature demonstrating the potentially favorable effects of clozapine in autistic children, we initiated a 15-day trial of clozapine.

A 21-question, modified version of the Children's Psychiatric Rating Scale (CPRS)[11] was used to evaluate the efficacy of clozapine. Prior to the institution of the clozapine treatment, Mr. A's score was 85 out of a possible 126 points on the modified CPRS, which evaluated items such as speech, hyperactivity, withdrawal, affect, and rhythmic motions. He exhibited episodes of clinging behavior, signs of overt tension, hyperactivity with repetitive motions, and underproductive speech. During his hospital stay prior to beginning clozapine treatment, Mr. A was maintained in 4-point restraints within institutional guidelines to protect him and the staff. His restraints were occasionally reduced to 3-point and rarely to 2-point, but he was always returned to 4-point restraints within a period of 24 hours. Clozapine was started at 12.5 mg/day and advanced to a dose of 275 mg/day over the course of 10 days.

The dose of 275 mg/day was maintained for the duration of the observation period. Over the course of the 15-day observation period, the frequency of undesirable behaviors diminished significantly. Mr. A's CPRS score improved to 45 on day 15 of the observation period. He exhibited fewer undesirable behaviors and was completely removed from restraints on day 10 for a period of 3 days. He became more compliant with the staff and performed some routine functions of daily living independently, including eating, bathing, and using a urinal. There were no adverse reactions to clozapine during the trial period except for mild constipation and sialorrhea.

Studies of clozapine in autistic disorder are uncommon; however, the study by Zuddas et al.[10] of 3 children aged 8, 8, and 12 years treated with doses up to 450 mg/day demonstrated an improvement in autistic behavior in 2 of the 3 children over 3 months. In this trial, we found that clozapine in a 17-year-old autistic male improved overall behavior both objectively and subjectively and was well tolerated at the doses used.

It should be emphasized that this study had a short period of observation, and it is uncertain whether this initial response would continue over time. Considering that 33% of autistic patients have a comorbid seizure disorder[12] and that clozapine can alter seizure threshold,[13] clozapine administration could have serious neurologic complications. Also, sequelae associated with agranulocytosis such as infection may be difficult to initially diagnose because of the communication difficulties of autistic patients.

In light of these serious potential complications, clozapine should be administered judiciously; however, this report suggests that clozapine may be a pharmacologic alternative to antidepressants and other neuroleptics in treating severe, refractory behavioral disturbances in patients with autistic disorder.

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Correction

In the article "Medication Supervision and Adherence of Persons With Psychotic Disorders in Residential Treatment Settings: A Pilot Study" (May 2001 issue, pp. 394–399) by Michael F. Grunebaum, M.D., et al., the Global Assessment of Functioning score for the higher functioning group should be GAF > 40 (page 395, right column, line 27).

The staff regrets the error.