Severe Atypical Symptoms Without Depression in SAD: Effects of Bright Light Therapy

Sir: Seasonal affective disorder (SAD) is characterized by the recurrence of depressive episodes during specific seasons. In most cases, the episodes begin in fall or winter and remit in the following spring or summer.[1] SAD patients typically fulfill the diagnostic criteria for recurrent major depressive disorder or type II bipolar affective disorder, according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV).[2] Furthermore, the patients mostly suffer from atypical symptoms such as hypersomnia, hyperphagia, and carbohydrate craving along with consequent weight gain and fatigue. Bright light therapy is a popular treatment strategy for SAD, winter type.[3] The presence of carbohydrate craving and hyperphagia has been shown to be a predictor of a patient's positive response to bright light therapy.[4] We present a patient with SAD who did not exhibit depressed mood or lack of drive but presented with only the atypical symptomatology.

Case report. Ms. A, a jovial, heavy-set 46-year-old professional, had been suffering from fatigue, an increase in duration of sleep of more than 4 hours per day, carbohydrate craving, and weight gain of 4 to 7 kg in fall and winter for 20 years. Because of her serious concern about an overwhelming desire to fall asleep on any occasion, such as at work or while driving, which impaired her daily functioning, Ms. A was referred to our SAD outpatient clinic for treatment with bright light therapy after pickwickian syndrome was excluded and because the symptoms presented only in winter. Ms. A described herself as and appeared to be a joyful and optimistic person and never considered herself to suffer from depression. During the interview, Ms. A. denied any depressive symptomatology. Her Hamilton Rating Scale for Depression (HAM-D, 21-item version) score[5] was 5 and her 7-item HAM-D-Supplement for atypical symptoms score[6] was 17. Ms. A began standardized bright light therapy with 30 minutes each morning and afternoon (10,000 lux measured at eye level). After 2 weeks of treatment, the patient reported that her complaints had disappeared, and she was very grateful for being relieved of them. At that time, her HAM-D score remained at 5, and her HAM-D-Supplement score dropped to 1.

Our case report gives preliminary evidence that even in the absence of depressive symptomatology, patients can present with distinct atypical symptoms. Such symptoms, although a placebo response to bright light cannot be ruled out, can respond remarkably well to bright light therapy. Interestingly, the so-called seasonal energy syndrome (SES) described by Mueller et al.[7] sounds very similar to the symptom-picture reported here. Because of the potential benefit and the apparent lack of adverse effects of bright light therapy, it seems worthwhile to further study patients with atypical symptoms of SAD even if they do not present with depressive symptomatology.

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Is Divalproex a Cost-Effective Alternative in the Acute and Prophylactic Treatment of Bipolar I Disorder?

Sir: A recent pharmacoeconomic study[1] concluded that divalproex is a less costly treatment than lithium in the acute and prophylactic treatment of patients with bipolar I disorder.

Such a decision-analytic study must rest on hard data, and hard data supporting the prophylactic properties of divalproex are unavailable. The authors did mention that no controlled study assessed the prophylactic efficacy of divalproex, and, to our knowledge, no such study has been published since then. In the absence of data, this part of the proposed model is speculative: we still do not know whether divalproex prevents both manic and depressive episodes.

As concerns the acute phase of the treatment, the authors did not choose the most conservative approach for crucial variables, namely the response rate to initial therapy and the mean length-of-stay during hospitalization. The 10% difference in response rate in favor of the divalproex results from a mean of heterogeneous sources, and its statistical significance is unknown. The mean response rates computed from controlled studies comparing divalproex and lithium[2,3] would give a rate of 61% for lithium against 51% for divalproex, just the opposite figure (respective response rates in these studies were 92% [N = 13] and 49% [N = 36] for lithium, and 64% [N = 14] and 48% [N = 69] for divalproex). In the absence of a meta-analysis combining the results of the controlled studies, equality of response rates would have been more conservative.

The estimates of length-of-stay for the initial hospitalization are "parameters with high uncertainty," which the authors underline, but are derived from a single local source with specific characteristics, preventing their generalization. These data clearly favored divalproex with a shorter length-of-stay (14.3 days) compared with lithium (18.4 days). The sensitivity analysis of the authors reveals that "the total costs of treatment with the drugs would be equal given…a 30% increase in the length-of-stay for divalproex," i.e., a length-of-stay of 18.6

days. It means that under the most conservative hypothesis (i.e., equal length-of-stay for both drugs), costs of treatments are the same.

Economic evaluation of interventions relies on the assessment of their clinical effectiveness. Such data are still lacking for divalproex in the prophylaxis of bipolar disorder. Furthermore, a fair comparison has to take the most conservative approach, which means the null hypothesis of equality, when crucial variables are not ascertained. The authors' conclusions should read: If prophylactic efficacy of divalproex is demonstrated and if length-of-stay for divalproex is demonstrated to be generally and significantly shorter than lithium's length-of-stay, then divalproex is a less costly treatment than lithium in the acute and prophylactic treatment of patients with bipolar I disorder. In the absence of such data, one cannot say that "savings of this magnitude are too large to be ignored by those making the medical care decisions about treatment of bipolar illness."

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Dr. Keck and Colleagues Reply

Sir: We thank Drs. Dardennes and Even for their interest in our article and for their comments. Our conclusions from the decision-analytic model proposed in our article were that, based on the available evidence, divalproex appeared to be less costly overall in the treatment of patients with bipolar disorder, but that cost differences were also dependent on the type of manic syndrome. For patients with classic mania, lithium appeared to be less costly, whereas for mixed mania or rapid cycling, divalproex appeared to have a cost advantage. We agree that a decision-analytic study should rest on hard data. Where such data were available, they were fully utilized. However, as Drs. Dardennes and Even point out, and as we specified in our paper, such data are not yet available for divalproex. We agree that this component of the model rests on more speculative inferences. The model will allow for recalculation of costs when such data are available.

Regarding the calculation of initial response rates, we again gathered the best available data from studies that provided information on response to divalproex versus lithium among patients with classic mania, mixed mania, and rapid cycling. These data, in fact, suggest that there is not equality of response between lithium and divalproex among these patient groups. The parameters regarding length-of-stay are, in fact, derived from a single source and do limit generalizability. However, they are supported by the only other study that we are aware of that examined hospital length-of-stay according to treatment by mood stabilizer.[1] If other data from other sources become available, these data can be entered into the model to determine their effects on cost.

On the basis of the available data, we stand by the conclusions reached in our article. In our paper, we clearly specified the limitations of the available data and their corresponding effect in producing the limitations of the model. When data become available from other centers regarding hospital length-of-stay of patients treated with lithium and divalproex and regarding comparisons of lithium and divalproex in the maintenance treatment of patients with bipolar disorder, they can be incorporated into the model.

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Resolution of Fluoxetine-Induced Sexual Dysfunction With the 5-HT_3 Antagonist Granisetron

Sir: Sexual dysfunction is a common and troubling side effect of serotonin reuptake inhibitors (SRIs).[1] The incidence of sexual dysfunction associated with SRIs has been estimated to be as high as 34%.[2] The mechanism underlying sexual dysfunction associated with SRIs has not been fully characterized, but is thought to be partly mediated by direct serotonergic effects.[3] The specific serotonin receptor(s) involved has not been identified. However, nefazodone, which blocks the 5-HT_2 receptor, and mirtazapine, a new antidepressant agent, which blocks the 5-HT_2 and 5-HT_3 serotonin receptor subtypes, have been reported to have low incidences of sexual side effects.[4,5] These results suggest that increasing serotonergic activity at these receptors may be involved in producing sexual dysfunction. Pharmacologic agents that block the 5-HT_3 receptor have been found to enhance sexual behavior in female rats, suggesting a role for this subtype in the modulation of sexual functioning.[6] The possibility that medications known to block this receptor may counteract the enhancement of serotonergic neurotransmission caused by antidepressants, and thus reduce sexual side effects, prompted us to initiate a trial of the 5-HT_3 antagonist granisetron in a patient with SRI-induced sexual dysfunction. We report here the case of a woman who experienced a complete resolution of fluoxetine-induced sexual side effects after treatment with granisetron.

Case report. Ms. A, a 46-year-old woman, presented for treatment of premenstrual dysphoric disorder (PMDD). Although the PMDD symptoms abated almost entirely with the initiation of fluoxetine treatment at a dose of 40 mg, she also experienced a near complete loss of sexual interest at this dose. In addition, she noticed a substantial delay in reaching orgasm. She had not been troubled by either of these symptoms prior to taking fluoxetine. Moreover, Ms. A was physically healthy and was taking no other medication. She had not received treatment for drug-induced sexual dysfunction in the past, but consented to a trial of granisetron. She was informed that granisetron is a drug approved for the treatment of nausea associated with chemotherapy. She was instructed to take 1 mg of granisetron approximately one hour prior to engaging in sexual activity. On three out of three trials, Ms. A noticed a complete recovery of sexual interest and ability to achieve orgasm after administration of granisetron.

Other treatments reported to decrease sexual dysfunction caused by SRIs include the α_2 antagonist yohimbine,[2] amantadine,[7] the 5-HT_2 antagonists cyproheptadine[8] and nefazodone,[9] bupropion,[10] buspirone,[11] *d*-amphetamine,[12] and pemoline.[12] Although this case represents only a single patient, it suggests a possible role for the 5-HT_3 receptor in producing sexual side effects. Further trials of granisetron in patients with SRI-induced sexual dysfunction appear warranted to test this hypothesis.

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Olfactory Reference Syndrome Responds to Clomipramine But Not Fluoxetine: A Case Report

Sir: Some psychiatric conditions have features that are comparable to the intrusive thoughts and repetitive behaviors that characterize obsessive-compulsive disorder (OCD). These are recognized as obsessive-compulsive spectrum disorders.[1] Beyond a similar symptom profile and associated features, it has also been postulated that these disorders resemble OCD in their neurobiology and etiology.[2] Another important similarity between OCD and its spectrum disorders may be their overlapping pharmacologic response. The following case report describes a patient with olfactory reference syndrome who selectively responded to a serotonin uptake blocker.

Case report. Mr. A, a 40-year-old single black man of Caribbean descent, had believed for the past 3 years that his perspiration and body odor were offensive to others. He reported excessive showering and bathing. His delusion had led to serious social and vocational problems. He had ended a relationship, believed that his coworkers ostracized him, and avoided being close to persons in public. He had consulted with several physicians, most recently dermatologists, who had prescribed antibiotics, powders, and antiseptic lotions without success. He had never consulted with a mental health professional nor been prescribed psychotropics.

Mr. A's diagnosis was that of a delusional disorder, somatic type (DSM-IV 297.1), specifically olfactory reference syndrome.[3] Mr. A also had a 7-month history of secondary depressive symptoms, reflected by a score of 46 (severe intensity) on the Beck Depression Inventory. In addition, he scored high on the anxiety, paranoid ideation, interpersonal sensitivity, depression, and psychoticism factors of the 90-item Symptom Checklist. His Global Assessment of Functioning score was 45.

Brief focused therapy was initiated twice a week. Cognitively, the patient was steadily challenged as to his false beliefs and their implausible consequences. Fluoxetine, prescribed at 20 mg/day, was increased to 40 mg/day after 4 weeks, and to 60 mg/day after 8 weeks. The focused therapy was stopped after 12 weeks. He was unchanged. Mr. A continued on pharmacotherapy and supportive therapy. After 15 weeks of treatment, with adequate serum levels (fluoxetine 521 ng/mL, norfluoxetine not reported), fluoxetine was discontinued and clomipramine started.

After 4 weeks on clomipramine 150 mg/day, he began to report minimal improvement. The dosage was increased to 225 mg/day. After 12 weeks, he reported that clomipramine was helpful in "blocking these thoughts." He became less preoccupied about his body odor, and, with time, his insight improved. Although he remained suspicious of some of his coworkers for other reasons, his social life also improved. Mr. A started a new relationship, felt comfortable in social settings, and was attending night school. His excessive showering and bathing had stopped. In addition, his secondary depressive symptoms faded. His improvement has endured for more than 1 year with clomipramine therapy.

Our literature review reveals no case reports of pharmacologic treatment of olfactory reference syndrome with serotonin uptake blockers in the United States. A similar case was recently reported in the Japanese literature,[4] although it is unclear if this patient's symptoms were of delusional magnitude. The temporal relationship between the prescription of clomipramine and Mr. A's gradual improvement suggests that clomipramine was helpful in treating his symptoms. Another possibility is that his increasing depression perpetuated his delusional symptoms, which were initially unresponsive to brief cognitive therapy and fluoxetine, but later responded to clomipramine.

Efforts have been made to characterize and conduct controlled treatment studies of some of the OCD spectrum disorders,[2,5,6] but there are no systematic studies of the treatment of olfactory reference syndrome. Neuroleptics, as well as other psychotropics, have also been recommended for its treatment.[7–9] Symptomatically, olfactory reference syndrome seems more closely related to body dysmorphic disorder (BDD) than are other OCD spectrum disorders.[3] Some serotonin uptake blockers are reported to be helpful in the treatment of delusional and nondelusional BDD.[6,10,11] These disorders exist within a spectrum that comprises delusional and nondelusional variants, and even the delusional subtype may be responsive to serotonin uptake blockers.[12] However, as with OCD, for a particular patient a preferential response to one serotonin uptake blocker over another is possible.[13]

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Affective Illness and Epilepsy

Sir: We read with interest the paper by Dr. Blumer[1] because affective illness in patients with epilepsy is an important problem, but we do not believe the data he presents adequately support his hypothesis. The concept of "subictal affective illness" was popular some years ago. Some patients with temporal lobe seizures experience affective symptoms acutely as an ictal phenomenon, but cases in which chronic affective symptoms are due to epileptic discharges have not been documented. The concept of "forced normalization" (the emergence of affective symptoms when seizures are controlled) is controversial. Although there are certainly patients whose affective symptoms worsen when seizures are controlled, clinicians would be biased to report significant depression rather than improvement in, or lack of, affective illness. Systematic study might demonstrate that equal numbers of patients have improvement in affective symptoms.

Blumer's concept that "inhibitory and excitatory" neural mechanisms (with unclear anatomical or neurotransmitter basis) associated with epilepsy are responsible for affective illness is overly simplistic. The antiepileptic medications currently available are believed to work by one of three mechanisms: (1) stabilizing of voltage-activated sodium channels, (2) increasing inhibitory activity via GABA-A receptors, and (3) decreasing excitation via excitatory amino acid transmitters. Phenobarbital increases inhibition via GABA transmission and also increases the risk of depression. Carbamazepine works via sodium channels and has some antidepressant properties. Yet phenobarbital and carbamazepine are equally effective in controlling seizures. Thus, the prodepressant or antidepressant properties of antiepileptic drugs are independent of their efficacy in controlling seizures. Blumer refers to the antidepressants as having "proconvulsant" properties that counteract the effects of anticonvulsant drugs. Clearly, the situation is much more complicated.

Patients with epilepsy who achieve good seizure control, whether by means of medication or epilepsy surgery, may be at risk of affective illness. This may be related to epilepsy as in the forced normalization hypothesis, but may also be a separate and unrelated condition. In each case report, adequate antidepressant treatment led to relief of depression, just as depressed patients without epilepsy benefit from adequate treatment. We agree that epileptic patients should be prescribed adequate antidepressant medication when they become depressed. We hope to address the issue of forced normalization and the relationship between epilepsy and affective illness by prospectively following epileptic patients administered a standardized psychiatric interview, neuropsychological testing, and serial depression inventories before and after seizure control is achieved, whether with medication or surgery.

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Dr. Blumer Replies

Sir: The remarkable effectiveness of antidepressant and double antidepressant treatment for the intermittent and pleomorphic affective-somatoform disorder of epilepsy (termed the *interictal dysphoric disorder*) has led to the hypothesis that the proconvulsant antidepressants may be helpfully antagonistic to inhibitory, seizure-suppressing mechanisms. The latter have been assumed to be responsible for the psychiatric changes of epilepsy. Seizure-suppressing mechanisms undoubtedly develop in the course of chronic epilepsy and assert themselves whenever a seizure occurs to bring it to termination, but their nature is little known, and our hypothesis admittedly remains based chiefly on indirect clinical evidence.

Carbamazepine is an antiepileptic drug with antimanic properties and without antidepressant effect in monotherapy. Like the more sedative and psychotoxic phenobarbital—or like any other antiepileptic drug—it may at times provoke a marked dysphoric disorder upon suppression of seizures (as illustrated by Case 1 in my article[1]). However, one has to agree that the concept of "forced normalization" is unsatisfactory. It has to be emphasized that not only suppression of seizures but also recurrence of seizures may precipitate a dysphoric disorder, presumably by nocuous stable inhibition in the first, and by enhanced inhibitory mechanisms in the second instance. The dysphoric disorder will respond to antidepressant medication in both instances.

Excellent psychiatric outcome after temporal lobectomy for epilepsy is ultimately related to freedom from seizures, presumably as the inhibitory mechanisms fade over a period of months, after an operation has achieved virtually total elimination of the epileptogenic zone (Blumer D, Wakhlu S, Davies K, et al. Manuscript submitted). If, on the other hand, a dysphoric disorder remains after surgery in spite of freedom from seizures, one

may assume that subictal activity has remained. Again, this is difficult to prove. Nevertheless, such patients are then successfully treated with the combination of antidepressant and antiepileptic drug. The earlier concept of an atypical, labile-pleomorphic psychiatric disorder termed *temporal lobe syndrome* (requiring combined treatment with antidepressant and antiepileptic medication)[2] needs to be replaced by the more specific concept of the interictal or subictal dysphoric disorder.

It was not the purpose of my article to prove a pathophysiologic hypothesis for the psychiatric morbidity of epilepsy. While the pathogenetic mechanisms proposed for the interictal dysphoric disorder and its treatment remain hypothetical, we are presently satisfied that an effective treatment for the large number of patients with psychiatric disorder related to epilepsy is available. Finally, it has to be emphasized once more that the antidepressants, in combination with an antiepileptic drug, tend to be effective for the entire range of symptoms of the interictal (or subictal) dysphoric disorder, of which depressive symptoms are only one component. The action of antidepressants prescribed for the dysphoric disorder is clearly different from their traditional mechanism, as is particularly demonstrated by their almost immediate effectiveness at a relatively small dose.

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Blood Clozapine Levels Elevated by Fluvoxamine: Potential for Side Effects and Lower Clozapine Dosage

Sir: We report a case in which very high blood clozapine levels occurred during concomitant use of fluvoxamine. Previous reports have indicated that close monitoring should be done when these two medications are coprescribed because of fluvoxamine's ability to inhibit hepatic microsomal enzymes that metabolize clozapine.[1,2] However, on the basis of this case and the microsomal enzyme profiles of these two medications, we believe that extreme caution is warranted. Additionally, we believe there is a potential cost savings if the two medications are used together with caution.

Case report. Ms. A, a 35-year-old single white woman, had numerous previous psychiatric hospitalizations. Originally, her diagnoses were major depression and/or bipolar disorder. Numerous treatments (including ECT) had been tried, with partial, but not lasting, benefits. Fluvoxamine was started and titrated up to 300 mg/day with questionable clinical benefits. Over time, psychotic symptoms began to predominate. Trials of haloperidol and risperidone were unsuccessful in helping the psychotic symptoms. She was hospitalized and agreed to try clozapine. Therapy was started using a standard titration at our facility so that at 3 weeks Ms. A would be on 300 mg/day of clozapine. Besides fluvoxamine, other concurrent medications included zolpidem 10 mg p.o. q.h.s. and levothyroxine 0.075 mg/day.

When the patient was taking 200 mg/day of clozapine, a routine blood level of clozapine was drawn because of the aforementioned concerns of the combination of clozapine and fluvoxamine. Ms. A had also begun to complain of dizziness and had mild hypotension. A blood clozapine level of 1950 ng/mL was obtained (with a second confirmatory level of 2040 ng/mL). Because the patient had some relief of psychotic symptoms and the efficacy of fluvoxamine had been in doubt, Ms. A and the treatment team opted to discontinue fluvoxamine therapy and continue close clinical monitoring with blood clozapine levels. Three days after the discontinuation of fluvoxamine, the clozapine level had dropped to 693 ng/mL, and, on the fifth day after fluvoxamine discontinuation, the clozapine level was 175 ng/mL. The side effects noted above disappeared.

Clozapine is metabolized by cytochrome P450 3A3/4 and 1A2, as well as to a minor extent by 2D6 and 2C19.[3] Fluvoxamine inhibits both 3A3/4 and 1A2 (Solvay Pharmaceutical's package insert for fluvoxamine, October 1996). Based on such information, it should come as no surprise that clozapine levels would substantially rise in the presence of fluvoxamine. Fluvoxamine's package insert does state that caution is in order when the two medications are used together. However, our experience and that of others[1,2] seem to indicate that simple caution is not enough. In four cases reported,[1,2] stable serum clozapine levels rose 3–10 times from additions of fluvoxamine; in one instance, an addition of 25 mg of fluvoxamine increased clozapine levels nearly fivefold. Ms. A's case differs from the other cases in that fluvoxamine was the established medication, and clozapine was then added as the second medication.

The profile of microsomal isoenzyme inhibition by fluvoxamine seems to match that of clozapine's isoenzymes needed for metabolism. Given these metabolic profiles and the high risk for seizure at high blood levels of clozapine, the data suggest that these two drugs should not be used concomitantly or that very low doses of clozapine (e.g., 50 mg/day or less) should be used with fluvoxamine until blood levels can confirm that the clozapine level is safe.

Finally, in those patients who require high doses of clozapine for therapeutic efficacy, we wonder if clozapine doses could be substantially reduced with the addition of low doses of fluvoxamine. A similar strategy was used to show an overall cost reduction of 80% in 43 cardiac transplant patients who were being treated with cyclosporine, an expensive immunosuppressive agent,[4] which is metabolized by 3A3/4. Keogh et al.[4] added ketoconazole, a known inhibitor of 3A3/4, to patients taking cyclosporine and demonstrated substantial cost savings. Provided that blood clozapine levels are used early to establish the degree of enzymatic inhibition by fluvoxamine, this method could theoretically be safe and efficacious and achieve the potential of substantial cost reduction. Controlled trials would be indicated to demonstrate this potential.

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