

Comment on “Lithium and Clozapine Rechallenge: A Retrospective Case Analysis”

Sir: We refer to the interesting article from Drs. Kanaan and Kerwin¹ concerning the adjunctive use of lithium to treat clozapine-induced neutropenia.

Immediate discontinuation of clozapine treatment has always been the first therapeutic step in cases of severe to moderate neutropenia and impending agranulocytosis. However, some physicians are reluctant to terminate or even to interrupt clozapine treatment in patients with neutropenia, as the drug is often a last resort for those with complex symptomatology.

The retrospective study by Drs. Kanaan and Kerwin suggests that lithium coadministration is an effective and safe strategy that may allow continuation of clozapine treatment despite the occurrence of neutropenia. This result is of considerable clinical relevance because it potentially provides an alternative to the interruption of clozapine treatment in severe cases in which other antipsychotic drugs are ineffective.

However, some clozapine-associated neutropenia may be transient and harmless, and therefore may not require discontinuation of the drug treatment nor lithium adjunction. Transient neutropenia (defined as a return of the neutrophil count to normal values without changing the clozapine dosage) has been shown to occur in 22% of 68 patients treated with clozapine for the first time.² Neutropenia of short duration (2–5 days) and weekly benign variations of the neutrophil count have been reported. Marked circadian variations in the number of circulating neutrophils, i.e., morning pseudoneutropenia, have also been described in several clozapine-treated patients.^{3,4}

It seems therefore essential, before interrupting clozapine treatment, to determine whether drug-induced neutropenia is transient or malignant. Laboratory screening tests, including the use of a hydrocortisone test, are being devised to make such a distinction.⁵ Until these tests become available for routine use, it is necessary to increase the frequency with which neutrophil counts are determined. As first suggested by Ahokas and Elonen,³ when the absolute neutrophil count is below the normal range in the morning, the test should be repeated the same day in the afternoon before a decision to stop clozapine treatment or to consider lithium coadministration is made.

Dr. Esposito reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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Dr. Kanaan Replies

Sir: We are grateful to Dr. Esposito for his comments on distinguishing benign from malignant neutropenia. We agree that tests to distinguish the two may be of considerable benefit to clinical decision making where continuing with clozapine is a possibility. However, as our article¹ describes, the rules in the United Kingdom are quite strict about clozapine prescription, so that persevering with clozapine despite the occurrence of a neutropenia is not normally possible. It is perhaps worth reiterating that our article dealt with clozapine rechallenge—where clozapine had already been discontinued once due to a blood dyscrasia, whether neutropenia or agranulocytosis. In the rechallenge situation, the likelihood of a second dyscrasia is very high indeed, and its avoidance difficult to predict, even in a group selected as low risk.²

Novartis provided hematologic data, the national rechallenge rates, and information on the procedures of the Clozaril Patient Monitoring Service for the study referenced in this letter; Novartis provided no direct support for the study and had no authorial or editorial role in the writing of the article derived from the study.

Dr. Kanaan reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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Vagus Nerve Stimulation Improves Restless Legs Syndrome Associated With Major Depression: A Case Report

Sir: Vagus nerve stimulation (VNS) has shown effects in treatment-resistant epilepsy¹ and major depressive episode.² Epidemiologic studies have described restless legs syndrome (RLS) to exist in varying degrees of severity in 2.5% to 10% of the population.³ Treatment of first choice is dopamine agonists, but agents that enhance inhibitory mechanisms in the way that anticonvulsive drugs do are effective, too.

Case report. We report on the case of Ms. A, a 69-year-old woman with RLS and major depressive episode (DSM-IV criteria) whose restless legs resolved after VNS. After approval by a local ethics committee and receipt of written consent, VNS treatment was given for 10 weeks from August to November 2005. VNS was applied with an intensity of 1.0 mA, a pulse width of 250 μ s, a frequency of 20 Hz, and device-on-time of 30 seconds (off-time: 5 minutes). Continuous treatment with duloxetine (60 mg/day) was administered 4 weeks prior to and throughout the stimulation. We conducted 2 consecutive polysomnographic evaluations. Clinical efficacy was assessed using the Hamilton Rating Scale for Depression (HAM-D-21),⁴

the Inventory of Depressive Symptomatology (IDS),⁵ the Montgomery-Asberg Depression Rating Scale (MADRS),⁶ and the International Restless Legs Syndrome scale (IRLS).⁷

RLS severity improved from 19 points to 8 points on the IRLS after VNS, which corresponds to the effectiveness of other treatment strategies.^{8,9} Comparison of the polysomnographies showed a reduction in the amount of myoclonus with arousal (from 124 to 109) and periodic leg movements per time (from 19.7/h to 16.9/h). Total sleep time was almost identical (378 minutes vs. 385 minutes), and sleep efficiency was unaltered (78.7% vs. 79.0%). In line with recent reports,² scores in HAM-D-21 (29 points), IDS (56 points), and MADRS (26 points) stayed unchanged after 10 weeks of treatment.

This is the first report to describe a beneficial effect of VNS in RLS. A VNS-induced increase in nucleus tractus solitarius concentration of γ -aminobutyric acid (GABA) and a decrease in nucleus tractus solitarius glutamate level could theoretically explain the antiseizure activity of VNS.¹⁰ VNS is supposed to modulate the cortical excitability of brain areas, and GABA receptors probably contribute to this effect. The pathophysiology of RLS is referred to as a defect of A11 dopaminergic neurons (A11 is an area in the diencephalon of mammals with a high density of dopaminergic neurons) and descending spinal pathways,³ and dopaminergic agonists are effective for relieving symptoms. New anticonvulsive drugs working via potentiation of GABA transmission have shown promising results in the treatment of RLS.³ Thus, the beneficial effects of VNS in RLS might be due to its anticonvulsive properties mechanism of action, which had already been described in VNS-treated depressive patients.¹¹ In line with findings in previous research in epilepsy¹² and depression patients,¹³ additional modulation of dopaminergic pathways may have contributed to the observed effects. Maintaining stable doses of the psychotropic medication for at least 4 weeks before baseline assessment and throughout the subsequent VNS trial should have minimized medication effects on change measures; however, we cannot rule out the possibility that the reduction in IRLS after the VNS trial is attributable to the combination of VNS plus pharmacotherapy, rather than to VNS alone. Another possibility is that the observed effect might be due to spontaneous remission.

The authors report no financial affiliations or other relationships relevant to the subject of this letter.

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Remarkable Antidepressant Augmentation Effect of Raloxifene, a Selective Estrogen Receptor Modulator, in a Partial Responder to Fluvoxamine: A Case Report

Sir: Although selective serotonin reuptake inhibitors (SSRIs) have a relatively low occurrence of adverse events, some patients cannot tolerate certain adverse reactions to SSRIs, such as nausea and dizziness. In these situations, patients often undergo a protracted course of depression because an effective dose cannot be administered. We report a recent case of major depressive disorder in which the administration of raloxifene, a selective estrogen receptor modulator (SERM), in addition to a prior small dose of fluvoxamine, resulted in a remarkable improvement leading to a complete remission of depressive symptoms.

Case report. Ms. A was a 75-year-old woman who presented to our hospital in October 2005 with chief complaints of severe insomnia, loss of appetite, headache, and autonomic symptoms such as frequent elevations of blood pressure, tachycardia, and nocturnal sweating. Two of her 5 siblings had experienced depression and committed suicide. She had completely lost interest in flower arrangement, a hobby that she had previously enjoyed, and said her entire body felt lethargic. She was diagnosed with DSM-IV major depressive disorder (Hamilton Rating Scale for Depression [HAM-D],¹ 21 Item score: 36/64), and was treated with paroxetine at a dose of 10 mg/day. A week after the first examination, she complained about the adverse effects of paroxetine, such as nausea and severe dizziness. We proposed changing from paroxetine to fluvoxamine. At first she objected, but finally reluctantly consented to the administration of a 25-mg/day prescription. In November 2005, 2 weeks after the second examination, we explained that since there had been partial improvements in her insomnia and appetite loss following fluvoxamine treatment, we proposed increasing its dose to 50 mg/day. Again, the patient resisted but cautiously agreed to the increase. In February 2006, after 3 months of 50-mg/day

fluvoxamine treatment, her insomnia and loss of appetite had almost resolved. She was able to do minimal household chores and shopping. We proposed increasing the dose of fluvoxamine, but she refused (HAM-D score: 13/64; insomnia score (3 items): 0/6 from 6/6; somatic symptoms score (3 items): 3/8 from 8/8).

In May 2006, 6 months into the treatment with 50-mg/day fluvoxamine, an obvious improvement was noticed in the patient's facial expressions and her manner of speech. She regained interest in flower arrangement and described that she had come to enjoy her life. Her husband had been hospitalized at the time, but she was able to stay calm and collected. Wondering what had caused such improvement, we asked her if there had been any change in her life. We found out that she had been diagnosed with osteoporosis at the orthopedic surgery department 2 weeks prior (April 2006) and that she had started taking 60-mg/day raloxifene. No symptoms of depression were present for the next 3 months, which means that complete remission was achieved, suggesting the potential augmentation effect of raloxifene during fluvoxamine treatment.

To the best of our knowledge, this case report may be the first that suggests a potential raloxifene augmentation of fluvoxamine. It has been predicted that SERM acts as an agonist in the bone, the cardiovascular system, and the central nervous system and acts as an antagonist in the uterus, ovary, and mammary gland.² Although there have been a few studies showing that estrogen may augment antidepressant response of SSRI in depressed postmenopausal women,³ there have also been studies that failed to show such an effect.⁴ Given that raloxifene has an augmentation effect in elderly postmenopausal, not perimenopausal, women, we propose the following hypotheses: (1) raloxifene acts on the estrogen receptor in serotonergic neurons in a novel and uniquely different manner from estrogen, or (2) there is an as-yet-unrecognized effect of raloxifene in the brain.

In many countries, raloxifene is approved only for the treatment of osteoporosis in postmenopausal women. At present, the use of raloxifene for the purpose of augmentation therapy is much less common in the psychiatric field. Despite this limited usage, there is some evidence that raloxifene treatment may have an impact on mood. Jarkova et al.⁵ reported a mood effect of raloxifene. Although their subjects were nondepressed healthy postmenopausal women, the decrease in HAM-D depression index was significantly greater in the raloxifene-treated group. Grigoriadis et al.⁶ have reported a small pilot study concerning the raloxifene augmentation response to SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs) (fluvoxamine was not included). Although the doses of SSRIs or SNRIs in their trial were sufficient (e.g., paroxetine dose was 40 mg/day), the effect of raloxifene needed a very long duration (at least 2 or 3 months) of combination treatment, and few patients achieved complete remission. However, mean HAM-D score of the patients taking SSRIs or SNRIs in combination with raloxifene was significantly reduced after 4 weeks. Combined with safety assurances that raloxifene does not increase the risk of gynecological tumors or coronary heart disease,⁷ these previous preliminary trials and our case report provide a certain degree of rationale for recommending raloxifene usage with SSRIs in depressed postmenopausal women. We believe that antidepressant augmentation with raloxifene may become a novel therapeutic option, particularly for postmenopausal women who experience adverse effects with maintenance doses of SSRIs. We hope this case report provides a platform for warranting larger scale, placebo-controlled double-blind trials.

The authors report no financial affiliations or other relationships relevant to the subject of this letter.

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Lamotrigine-Associated Stevens-Johnson Syndrome After Discontinuation of Interferon, Ribavirin, and Filgrastim: A Case Report

Sir: The 2002 National Institutes of Health Consensus Development Conference recommended that treatments for hepatitis C virus (HCV) be extended to groups previously thought to be high-risk candidates for receiving interferon treatment. These high-risk groups include those with severe and persistent mental illnesses such as bipolar disorder.¹ Interferon is known for inducing or causing relapse to depression. We report a case of interferon-induced bipolar depression treated with lamotrigine in which the patient developed Stevens-Johnson syndrome after discontinuation of interferon, ribavirin, and filgrastim.

Case report. Mr. A, a 41-year-old man, was seen in our mental health clinic approximately 21 weeks into a 48-week treatment with interferon and ribavirin for HCV. His care was transferred to the Veterans Administration because he had lost his outside health care coverage. His HCV was genotype 1, with bridging fibrosis, and it is unknown how he obtained HCV. He had a history of alcohol dependence, but no intravenous drug use or other risk factors for HCV. Immediately prior to his diagnosis with HCV, the patient developed an irritable hypomania and began having problems with his coworkers. He sought mental health treatment at that time and was diagnosed with bipolar II disorder and, soon after, HCV. He had a sibling who was suspected of having bipolar disorder.

After starting interferon therapy, Mr. A noted increased irritability, fatigue, and poor sleep. He also developed additional symptoms of depression including low mood, poor appetite, anhedonia, and passive suicidal ideation. The patient became neutropenic with a white blood count of 2.5 K/cmm (normal

level, 4.4–10.8 K/cmm) and anemic with a hemoglobin level of 11.5 g/dL (normal level, 13–18 g/dL) and was started on the colony stimulating-factor filgrastim 300 µg/day twice per week, on week 24 of treatment.

Interferon and ribavirin can cause hematologic abnormalities including leukopenia. Dose reductions of these medications can decrease the likelihood of response to treatment; filgrastim support is given to patients to prevent the need for antiviral dose reductions. Maintaining adequate doses of interferon and ribavirin is particularly important with HCV genotype 1, this patient's genotype, which is less responsive to antiviral therapy. In addition to the anemia and the side effects of the interferon, Mr. A noted social stressors related to HCV treatment, particularly loss of employment as he was too ill to work.

Mr. A presented to our specialty mental health clinic, which follows high risk patients being treated with interferon. At the time of our initial evaluation, his psychotropic medications included venlafaxine XR 225 mg/day and gabapentin 600 mg q. a.m. and 300 mg q. h.s. He thought venlafaxine had been effective, but its efficacy was reduced after interferon treatment was started, and he did not feel that the gabapentin was helping him. He had previously had a 6-month trial of paroxetine that was ineffective and a 1-week trial of valproic acid that he discontinued due to feeling dizzy and weak, but the agent did not cause a rash. Mr. A had been previously offered, but declined, lithium.

Several medication changes were made. Initially at week 21, venlafaxine therapy was stopped because of concern that it would induce rapid cycling and potentially was the cause of Mr. A's poor sleep. Gabapentin treatment was also stopped because it was felt to be ineffective for either the patient's irritability or mood. Quetiapine treatment was started at 25–50 mg q. h.s. for sleep, but its dose was limited because Mr. A thought it caused leg cramps. On week 31 of interferon treatment, olanzapine therapy was started and increased to a total dose of 20 mg/day, which significantly improved his sleep and decreased his irritability. Concurrently, lamotrigine therapy was started and gradually increased to a dose of 50 mg q. a.m. and 100 mg q. h.s. by week 35. Mr. A remained on this dose of lamotrigine through week 48 of antiviral therapy.

Mr. A felt that lamotrigine improved his mood, and he remained on the medication until the end of his treatment for HCV. On week 47, interferon was stopped; on week 48, ribavirin was stopped; and on week 49 (3 days after discontinuation of ribavirin), he received his last injection of filgrastim. On approximately week 50, Mr. A developed dusky red macules over 90% of his body (with no blister formation or skin necrosis), consistent with Stevens-Johnson syndrome.² The patient discontinued all of his psychotropic medications at that time, the rash resolved, and he suffered no sequelae from the episode.

At the time of the rash formation, in addition to lamotrigine, interferon, ribavirin, and filgrastim, the patient was taking the following medications: albuterol, codeine, hydrocodone/acetaminophen, mirtazapine, and rabeprazole. He was not taking any medications generally associated with the development of Stevens-Johnson syndrome. These include sulfonamide antibiotics, aminopenicillins, quinolones, cephalosporins, carbamazepine, phenobarbital, phenytoin, valproic acid, oxicam and other nonsteroidal anti-inflammatory drugs (NSAIDs), allopurinol, and corticosteroids.³ Other factors associated with increased risk of lamotrigine-associated rash have included having had a rash while taking another antiepileptic drug and age less than 13 years.^{4,5}

Despite a difficult course of treatment for his HCV that resulted in loss of his job, several months of irritable hypomania that made his daily life almost intolerable, and Stevens-Johnson

syndrome, Mr. A successfully cleared the HCV virus. His viral load was undetectable at the end of treatment and 6 months following treatment.

Lamotrigine is a mood stabilizer that has been found to be effective in the treatment of bipolar depression without inducing mania.⁶ It is particularly effective in preventing relapse to bipolar depression. One of the major serious adverse events associated with lamotrigine is Stevens-Johnson syndrome. The mechanism for the development of Stevens-Johnson syndrome is still unclear, but it is thought to involve T-cell-dependent reactions causing cell-mediated cytotoxicity. Research has shown that Stevens-Johnson syndrome is most likely to develop when lamotrigine is first introduced and doses are being increased, usually within the first 8 weeks.^{7,8} The case above suggests that another period of high risk may be when there are changes in doses or discontinuation of concurrently used drugs that act on the immune system.

There are case reports of the development of Stevens-Johnson syndrome with the concurrent use of valproic acid and lamotrigine,^{9,10} but no reports that we are aware of describing possible drug interactions with medications used to treat HCV.^{11,12} In this case, 3 drugs were stopped consecutively: interferon, ribavirin, and filgrastim. Interferon replicates the innate indirect antiviral immune response by a mechanism involving inducing interferon-stimulated genes that establish a non-virus-specific antiviral state within the cell. Ribavirin is thought to act as a viral mutagen by misincorporation into ribonucleic acid (RNA) by HCV-RNA polymerases, thus causing early chain termination.¹³ Filgrastim acts as a granulocyte colony-stimulating factor, a cytokine that is naturally produced by monocytes, activated T-cells, fibroblasts, and endothelial cells to induce cell proliferation.¹⁴

Because all of these medications were stopped at the same time, it is unclear which of them may have triggered the Stevens-Johnson syndrome. Our suspicion is that both interferon and ribavirin were providing immunosuppression, while filgrastim was enhancing the immune response. Discontinuation of the immunosuppressive medications in the context of continued use of filgrastim promoted lamotrigine's effects on T-cells and may have triggered the Stevens-Johnson syndrome.

Stevens-Johnson syndrome usually has a prodrome of fever and influenza-like symptoms 1 to 3 days before the development of the rash lesions.² These symptoms were very likely masked in this patient because he was already quite ill with flu-like symptoms from interferon. As has been described extensively elsewhere, interferon is known to cause both a flu-like illness and changes in mood including depression and, more rarely, mania or psychosis.^{15,16}

Considering the proposed risk of an enhanced T-cell response when discontinuing treatment for HCV, we make the following recommendations for the use of lamotrigine in those treated with interferon, ribavirin, and filgrastim. Both mental health and medical providers should be aware that patients taking lamotrigine who are treated for HCV may be at increased risk of Stevens-Johnson syndrome when their antiviral treatment is changed or discontinued. We recommend that these patients be monitored closely when there is any dose change in their antiviral regimen and be warned of the possible increased risk of Stevens-Johnson syndrome, even if they have been on a stable dose of lamotrigine. In patients receiving filgrastim support, we would recommend discontinuing lamotrigine at least 1 week prior to discontinuing any component of their antiviral regimen. The 1 week recommendation is based on the fact that lamotrigine has a half-life of 25 to 33 hours and should be cleared in 5 half-lives (approximately 7 days). White counts

usually return to the normal range in 4 to 7 days after the discontinuation of filgrastim, and we would recommend that patients wait at least 1 week before restarting lamotrigine after discontinuation of filgrastim. Lamotrigine would then have to be titrated, as if started new, up to the previous therapeutic dose.

This patient did successfully clear the HCV virus despite having both a difficult-to-treat genotype of HCV virus and a difficult-to-treat mood disorder, made worse by interferon. As more of these challenging patients are treated for HCV, it is likely that further complex drug interactions similar to the one described above will be discovered.

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Antidrenergic Treatment of Antidepressant-Induced Excessive Sweating in 3 Patients

Sir: Excessive sweating is a common adverse effect of many antidepressant medications. Its prevalence with selective serotonin reuptake inhibitors (SSRIs) is between 7% and 19% depending on the drug.¹ In a meta-analysis² of clinical trials pooled across SSRIs, the rate of sweating as an adverse effect was 10%. In a prospective study of a variety of medications using a structured instrument to elicit adverse effects,³ sweating was reported as an adverse effect in 8.3% (moclobemide) to 40% (bupropion) of the patients. Excessive sweating can be quite distressing and can cause considerable impairment in social and occupational functioning. Tolerance often does not develop, even after 6 or more months of treatment,⁴ and, in clinical practice, we see patients who have had substantial suffering from this adverse effect for many years. Unfortunately, in our practice, we often see patients for whom excessive sweating has gone unidentified as an adverse effect by the patient and the physician.

The potential use of antidrenergic drugs for antidepressant-induced excessive sweating is suggested by both theoretical considerations and some empirical evidence. Sweat glands are innervated by the sympathetic nervous system even though, uniquely, acetylcholine is the neurotransmitter at the peripheral nerve ending. Sweat glands are stimulated primarily by centers in the hypothalamus. Yohimbine, an α_2 -antagonist that increases adrenergic transmission, has been shown to cause excessive sweating.⁵

Potential strategies for treatment of excessive sweating may include reduction in dose of the antidepressant or switching to another antidepressant.⁶ Clonidine, a centrally acting antiadrenergic drug (α_2 -agonist), has long been used to reduce excessive sweating associated with menopause.⁷ Excessive sweating due to an antidepressant showed “dramatic” reduction with low-dose clonidine in 1 patient,⁸ although clonidine worsened sweating due to imipramine in another case report.⁹ Terazosin, an α_1 blocker, was found to be highly effective for autonomic dysreflexia, including excessive sweating.¹⁰ It was also found to be effective (in a 2-mg dose) for 1 case of imipramine-induced sweating.⁹ In addition, case reports of the use of anticholinergics,¹¹ cyproheptadine,¹ and mirtazapine¹² to treat antidepressant-induced excessive sweating have been published. We report here 3 cases of antidepressant-induced excessive sweating that showed an excellent response to treatment with antidrenergic medication.

Case 1. Ms. A, a 57-year-old woman, had depressive disorder not otherwise specified since her early teens and a long history of limited benefit from several antidepressants. She finally showed considerable improvement with venlafaxine 150 mg/day but had distressing and persistent excessive sweating within a month of starting it. Bupropion 300 mg/day was added, but an attempt to taper off venlafaxine resulted in a relapse. Terazosin 1 mg/day was added and increased after a week to 2 mg at bedtime. Within a few days, the sweating was, in the patient’s words, “99.99% less than before.” No adverse effects were noted, and Ms. A’s blood pressure remained stable. Ms. A was tapered off bupropion due to lack of benefit, and later tapered off terazosin as a trial at her request. The excessive sweating did not immediately return, but gradually it started and progressed so that in about 4 months it was as severe as before. Restarting terazosin resulted once again in complete resolution of the excessive sweating. Nearly 2 years after she first took terazosin, Ms. A again stopped taking terazosin on her own. Within 2 weeks, marked sweating returned.

Case 2. Mr. B, a 67-year-old treatment-naive patient with major depressive disorder, had an excellent response to sertraline 75 mg/day but reported episodes of severe sweating that were noticeable to others and led to embarrassment. For example, while he was eating at a restaurant, beads of sweat were dropping onto the table, and when he wiped himself with a napkin, it was completely soaked. Terazosin was started at 1 mg/day and, after 2 weeks, was increased to 2 mg at bedtime. The episodes of excessive sweating decreased by 75% within 4 weeks, without any adverse effects or hypotension. Eight weeks after starting terazosin, he reported almost complete resolution of the excessive sweating. During 6 months of follow-up, Mr. B had a brief period of return of excessive sweating during the summer, but it again resolved completely without any change in treatment.

Case 3. Mr. C, a 36 year-old man with a history of disabling, chronic major depressive disorder, had failed multiple medication trials. Mr. C's depression responded well to a combination of nortriptyline 150 mg/day and paroxetine 40 mg/day, which he took for several months. However, at the point when paroxetine was titrated to 40 mg/day, the patient began to have marked excessive sweating. For example, after just a brief walk, he would be drenched in sweat, which was not usual for him. The results of medical evaluation, including thyroid function tests, were negative, and there was a direct temporal relationship between titrating up the paroxetine and onset of the excessive sweating. Treatment of the excessive sweating with cyproheptadine 4 mg/day for several weeks and then 8 mg/day for several weeks had only minimal benefit. He was then started on treatment with clonidine 0.1 mg twice daily, and, after about 3 weeks of treatment, he reported with excitement that the sweating was "60% to 70%" resolved. Because Mr. C was not experiencing any of the potential common adverse effects at this dosage, he was reluctant to increase the amount for fear of "rocking the boat." He has continued on this regimen for more than 2 years with continued benefit for the excessive sweating.

We were unable to find any published clinical trials for the treatment of antidepressant-induced excessive sweating. Although antidepressant-induced excessive sweating is not rare and is clinically significant, there is considerable lack of awareness among clinicians about its occurrence and treatment.

Our case reports suggest that antiadrenergic agents may emerge as a highly effective and well-tolerated treatment option for antidepressant-induced excessive sweating. As discussed above, a number of other treatments can be tried as well. However, all of these may have certain limitations. Dose reduction or addition of cyproheptadine may lead to worsening of depression in many patients, especially treatment-resistant patients like 2 of the 3 cases described here. Switching to another antidepressant may not be feasible or effective in some patients.

Dizziness or hypotension may occur with terazosin or clonidine, and, therefore, care must be taken, particularly in elderly patients, those patients taking other antihypertensive medications or psychotropic medication with potential hypotensive effects, and patients with preexisting cardiovascular disease. Clonidine may potentiate the effects of central nervous system depressant medications.¹³ No other significant drug interactions are likely between psychotropic medications and terazosin or clonidine.¹³

The mechanism of action of antiadrenergic medications in reducing antidepressant-induced excessive sweating is not precisely known, but presumably is related to reduction in central sympathetic outflow since sweating is mediated by the sympathetic nervous system but the peripheral synapses are cholinergic.⁶ Possibly, the balance of α and β receptor stimulation may

be involved.^{9,14} We are currently conducting a clinical trial (ClinicalTrials.gov identifier NCT00237510) to more systematically evaluate the usefulness of terazosin for the treatment of antidepressant-induced excessive sweating.

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Aripiprazole-Induced Hyponatremia: A Case Report

Sir: Up to 70% of institutionalized psychotic patients consume greater than average amounts of water and 7% develop hyponatremia.¹ Also, psychotropics are known to induce hyponatremia.² We report a case of a patient with bipolar affective disorder developing hyponatremia, possibly due to aripiprazole.

Case report. Mr. A is a 69-year-old man, with a known case of bipolar affective disorder (DSM-IV) with 2 previous manic episodes in 2001 and 2003. He was on a regular mood stabilizer, sodium valproate 1000 mg/day, and was known to have a

history of diabetes, for which he was taking metformin (1000 mg/day) and glibenclamide (5 mg/day). He was also on thyroxine supplements, 100 µg/day for hypothyroidism. He presented in August 2005 with relapse of manic symptoms for 1 week. Aripiprazole 10 mg/day was added; 2 days later, he developed persistent hiccoughs. A comprehensive clinical examination revealed no neurologic deficits. Blood investigations showed glucose levels of 97 mg/dL, serum sodium levels of 122 mEq/L, and serum potassium levels of 4.5 mEq/L. Thyroid and renal function tests and lipid profiles were normal. Urine specific gravity was 1.010 (no ketonuria). It was found that he had been drinking 3 to 4 L of water per day over the prior 3 weeks. Immediate water restriction to 1.5 L/day was initiated. Because of its temporal association with hiccoughs, aripiprazole was withheld. Sodium levels stabilized to 133 mEq/L (all sampling done at 6:00 a.m.). Aripiprazole 10 mg/day was restarted 2 days later. On the next day, sodium levels dropped again to 120 mEq/L. Aripiprazole was stopped. Quetiapine was started and increased to 400 mg/day over 2 weeks. Subsequently, sodium levels gradually increased and reached normal levels of 135 mEq/L (1 week later). The hiccoughs spontaneously subsided with correction of sodium levels. Fluid restriction was stopped at this time. The patient maintained euthymia with normal sodium levels over the next 8 months of follow-up.

Aripiprazole premarketing studies reported hyponatremia as an infrequent occurrence.³ Recently, aripiprazole-induced hyponatremia in schizophrenia was reported.⁴ To our knowledge, this is the only other report of hyponatremia possibly due to aripiprazole. The temporal correlation between aripiprazole and reduction in sodium levels in both occasions points toward hyponatremia induced by drug. Hiccough is a frequent manifestation of hyponatremia, and a decrease in sodium levels of 10 mEq/L can increase incidence of hiccough 17 times.⁵ The risk of hyponatremia with psychotropics is maximum during the first 2 weeks of treatment and is unrelated to drug dose.⁶ Withdrawing aripiprazole led to stabilization of sodium levels within 1 week, which corresponds to aripiprazole's washout period. The decrease in the patient's sodium levels on admission could be related to increased water consumption; however, this possibility is unlikely due to the following reasons: (1) for water intake by itself to be the sole basis for hyponatremia, one has to drink greater than 10 L/day,⁷ (2) the fall in sodium levels persisted despite fluid restriction, and (3) the patient did not develop hyponatremia in the prior episodes despite increased fluid intake

of similar quantity. The normal thyroid serology ruled out hyponatremia secondary to hypothyroidism. Hence, it is possible that aripiprazole might have caused the syndrome of inappropriate antidiuretic hormone secretion resulting in hyponatremia.³ An earlier case of adjunctive treatment with quetiapine in polydipsia, intermittent hyponatremia, and psychosis syndrome has been reported.⁸ It is possible that quetiapine might have helped in correcting hyponatremia. Given the clinical significance of hyponatremia, one has to be cautious when initiating aripiprazole, especially in elderly individuals.

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