

Bupropion for SSRI-Induced Fatigue

Sir: While depression, dysthymia, and panic disorder can often be effectively treated with the selective serotonin reuptake inhibitors (SSRIs), patients are sometimes left with treatment-emergent sedation or fatigue that can itself be quite disabling.^{1,2} Although Keck and McElroy³ postulated that, for fluoxetine, this may be related to an elevated norfluoxetine/fluoxetine ratio, personal experience has shown this fatigue to be present in some cases where the tested ratio was less than one.

Bupropion is an activating antidepressant⁴ whose clinical efficacy is thought to be mediated through the dopamine system and which has been used to treat fluoxetine-resistant chronic fatigue syndrome,⁵ fatigue due to multiple sclerosis,⁶ and apathy due to organic brain syndromes.⁷ Three cases where the addition of bupropion was associated with relief from SSRI-induced fatigue are presented.

Case 1. Ms. A, a 50-year-old bank worker, was referred 6 years ago with a 5-year history of low energy, partial anhedonia, increased social isolation, moodiness, irritability, nervousness, feeling keyed up, poor sleep, poor concentration, trouble coping with stress, and excessive worrying. She responded favorably to fluoxetine 20 mg/day, but within 2 months had started feeling more tired during the day. Attempts to decrease the dose to 20 mg every other day resulted in partial relapse. She opted to continue with 20 mg q.d. because of the efficacy. Her 5-year bout with this fatigue ended within a week of adding bupropion 75 mg q.a.m. to her fluoxetine, and there were no adverse effects. She now feels continued relief from her dysthymia with no daytime fatigue.

Case 2. Mr. B, a 46-year-old teacher, was referred 2 years ago because of a lifelong history of angry outbursts, irritability, being "too intense," occasional restless sleep, carbohydrate cravings, and obsessive-compulsive personality traits. He responded well to sequential trials of fluoxetine, sertraline, and nefazodone, but had side effects to all, including decreased sexual functioning, sweating, gassy abdominal bloating, fatigue, overeating, and weight gain. He did best on paroxetine 20 mg/day, complaining only of continued fatigue and trouble taking off extra weight. The fatigue had started to creep back the second month after starting paroxetine, and by Month 3, he felt like a "couch potato," lacking energy and motivation in addition to "sleepiness." During his previous fluoxetine trial, his target symptoms had returned when dosage reduction from 20 to 10 mg/day was attempted. Therefore, instead of reducing the paroxetine dose, bupropion was added. He noted no improvement after 1 week at 75 mg q.a.m., but when the dose was increased to 150 mg q.a.m., his daytime fatigue disappeared within a week. He continues to maintain the efficacy from the paroxetine, and there have been no new side effects attributable to the bupropion.

Case 3. Ms. C, a 47-year-old teacher, was originally seen 3 years ago owing to worsening symptoms for several years, including depressed and anxious mood, anhedonia, crying spells, decreased energy, feeling overwhelmed, weight loss, social uneasiness, and hypervigilance. She could not tolerate sertraline owing to extreme dizziness. Fluoxetine 10 mg/day resulted in partial improvement, but within 3 weeks, she noted she was more fatigued even though she was sleeping 8 to 10 hours per night. When the dose was increased to 20 mg/day, she began to feel restless, with decreased appetite, sleep, and libido. With a dose reduction to 20 mg q.o.d. alternating with 10 mg q.o.d., she

had no depression but continued to have some anxiety, worrying, shakiness in social situations, fatigue, and poor sleep quality. These latter symptoms, with the exception of the fatigue, responded well to clonazepam 0.25 mg q.h.s. Bupropion 75 mg q.a.m. was begun, and her fatigue disappeared within 2 weeks. Again, there have been no problems associated with the addition of this stimulating antidepressant.

When significant fatigue complicates otherwise effective SSRI treatment, management options might include (1) titrating downward to lowest efficacious SSRI dose, (2) making certain any insomnia is alleviated, (3) changing to a different antidepressant, and (4) adding a chemical stimulant such as caffeine, T₃ or T₄, or bupropion.

Although bupropion was useful in the above cases, combining bupropion with other antidepressants should be undertaken with caution because potential problems might include lowering the seizure threshold, confusion, delirium, marked anxiety or panic, agitation, psychosis, or the precipitation of mania.

REFERENCES

1. Hellerstein DJ, Yanowitch P, Rosenthal J, et al. A randomized double-blind study of fluoxetine versus placebo in the treatment of dysthymia. *Am J Psychiatry* 1993;150:1169-1175
2. Beasley CM Jr, Potvin JH. Fluoxetine: activating and sedating effects. *Int Clin Psychopharmacol* 1993;8:271-275
3. Keck PE Jr, McElroy SL. Ratio of plasma fluoxetine to norfluoxetine concentrations and associated sedation. *J Clin Psychiatry* 1992;53:127-129
4. Lineberry CG, Johnston JA, Raymond RN, et al. A fixed-dose (300 mg) efficacy study of bupropion and placebo in depressed outpatients. *J Clin Psychiatry* 1990;51:194-199
5. Goodnick PJ, Sandoval R, Brickman A, et al. Bupropion treatment of fluoxetine-resistant chronic fatigue syndrome. *Biol Psychiatry* 1992;32:834-838
6. Duffy JD, Campbell J. Bupropion for the treatment of fatigue associated with multiple sclerosis [letter]. *Psychosomatics* 1994;35:170-171
7. Marin RS, Fogel BS, Hawkins J, et al. Apathy: a treatable syndrome. *J Neuropsychiatry Clin Neurosci* 1995;7:23-30

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Novel Use of Tramadol Hydrochloride in the Treatment of Tourette's Syndrome

Sir: Studies have demonstrated that symptoms of Tourette's syndrome can be attenuated by modulation of the opioid system.¹⁻⁴ However, the response to opioid agonists or antagonists is often limited by side effects and the development of tolerance. Additionally, these compounds have significant abuse potential. The opioid tramadol hydrochloride (Ultram) has low abuse potential, low physical dependency, and mild tolerance.⁵ It binds to opioid receptors and also inhibits the reuptake of norepinephrine and serotonin.⁵ We report the successful use of tramadol in the treatment of a patient with severe Tourette's syndrome.

Case report. Ms. A, a 23-year-old woman with both Tourette's and obsessive-compulsive disorder (OCD) since the age of 5 years, had been inadequately responsive to treatment with pimozide, haloperidol, risperidone, diazepam, clonidine, clonazepam, lorazepam, and propranolol. Initially, her tics de-

creased during trials of codeine (up to 120 mg/day) and naltrexone 100 mg/day. However, she became tolerant to these medications and experienced a significant loss in efficacy. Her OCD had been inadequately responsive to treatment with fluoxetine and fluvoxamine. Additionally, fluvoxamine precipitated a mixed manic state, which persisted at her hospital admission despite fluvoxamine discontinuation 2 weeks earlier.

Tramadol 50 mg every 6 hours was initiated, and the patient kept a daily diary to document the onset and duration of therapeutic effect. An immediate (within 15–30 minutes) and dramatic decrease in tics lasting 3.5 to 4 hours was observed by the patient, treating physicians, and nursing staff. Tramadol 100 mg produced approximately 5 hours of marked reduction in tics, but the patient's rebound in tics appeared more robust. At Ms. A's request, tramadol was rescheduled at 50 mg every 4 hours, which produced 3.5 to 4 hours of decreased symptoms and reduced interdose breakthrough symptoms. She reported that her tics usually awakened her during the night, and with tramadol 50 mg every 4 hours, she reported significantly fewer awakenings.

In contrast to previous trials with codeine and naltrexone, the decrease in tics with tramadol was also associated with a significant decrease in OCD symptoms. Although the patient's obsessions continued in an attenuated form, her need to complete her rituals was nearly extinguished. Because of her persistent racing thoughts, divalproex (1500 mg at bedtime) was subsequently initiated with good response. The patient was discharged with a substantially improved condition after a week-long hospitalization. A physician-rated Yale Tourette's Syndrome Symptom List (Revised)⁶ showed a score of 32 at baseline and 7 at discharge (where the lower score represents fewer symptoms). Furthermore, 6 months after discharge, Ms. A continues to report good results from tramadol.

Neuroanatomical and neurochemical interactions between basal ganglia dopamine and opioid neurotransmitter systems have recently been described.⁷ The striatonigral GABAergic projection neurons express dynorphin, and the prodynorphin gene is positively regulated by D₁-like dopamine receptors. In contrast, the striatopallidal GABAergic neurons express enkephalin, and the preproenkephalin gene is under the tonic inhibitory influence of D₂-like dopamine receptors.⁸ It is possible that perturbations of dopaminergic neurotransmission, which may occur spontaneously or which may have been caused by use of dopamine antagonists, such as haloperidol and pimozide, may elicit alterations in the activity of these two distinct opioid peptide systems, which normally are in relative equilibrium. The use of an opioid agonist or antagonist may therefore restore the functional equilibrium within the basal ganglia opioid/dopaminergic systems.

Tramadol may be a safe and effective alternative to current Tourette's syndrome treatments. It is also possible that the reduction this patient experienced in OCD symptoms is related to the simultaneous opioid, noradrenergic, and serotonergic activity of tramadol. Long-term follow-up of this patient and double-blind controlled trials are necessary to assess the effectiveness of tramadol in the treatment of Tourette's syndrome as well as OCD.

REFERENCES

1. Sandyk R, Iacono RP, Crinnian C, et al. Effects of naltrexone in Tourette's syndrome [abstract]. *Ann Neurol* 1986;20:437
2. Kurlan R, Majumdar L, Deeley C, et al. A controlled trial of propoxyphene and naltrexone in patients with Tourette's syndrome. *Ann Neurol* 1991;30:19–23

3. Meuldijk R, Colon EJ. Methadone treatment of Tourette's disorder [letter]. *Am J Psychiatry* 1992;149:139–140
4. McConville BJ, Norman AB, Fogelson MH, et al. Sequential use of opioid antagonists and agonists in Tourette's syndrome [letter]. *Lancet* 1994;343:601
5. Lee CR, McTavish D, Sorkin EM. Tramadol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs* 1993;46:313–340
6. Cohen DJ, Leckman JF, Shaywitz BA. The Tourette syndrome and other tics. In: Shaffer D, Ehrhardt AA, Greenhill LL, eds. *The Clinical Guide to Child Psychiatry*. New York, NY: The Free Press; 1985:3–28
7. Gerfen CR, Engber TM, Mahan LC, et al. D₁ and D₂ dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* 1990;250:1429–1432
8. Gerfen CR. The neostriatal mosaic: multiple levels of compartmental organization. *Trends Neurosci* 1992;15:133–139

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Safety of Amobarbital

Sir: I agree with Dr. Marcum's conclusion that sedative interviews are of questionable value in recovering repressed affects and memories.¹ In fact, prior placebo-controlled studies have shown that intravenous sedatives have minimal value in the anamnesis of the neurotic patient.² By comparison, the superiority of a sedative versus placebo in a medication-facilitated interview has been demonstrated in catatonia.³ Dr. Marcum suggests that midazolam-facilitated interviews should be safer than the less expensive amobarbital since midazolam has a short half-life and its effects could be reversed with flumazenil if necessary. The argument in favor of the greater safety of midazolam would be stronger if there were reports in the *modern* literature of medical complications arising from intravenous amobarbital. I know of none.

REFERENCES

1. Marcum JM. The use of midazolam with pulse oximetry in the drug-assisted interview. *J Clin Psychiatry* 1996;57:111–113
2. Hain JD, Smith BM, Stevenson I. Effectiveness and process of interviewing with drugs. *J Psychiatr Res* 1966;4:95–106
3. McCall WV, Shelp FE, McDonald WM. Controlled investigation of the amobarbital interview for catatonic mutism. *Am J Psychiatry* 1992;149:202–206

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Transient, Paroxysmal, Shock-Like Paresthesias Associated With Paroxetine Initiation

Sir: We report three cases of transient, paroxysmal, shock-like paresthesias associated with the initiation of paroxetine treatment.

Case 1. Ms. A, a 25-year-old Hispanic woman diagnosed by DSM-IV criteria with a major depressive episode and associated anxiety, was placed on paroxetine 20 mg/day. For the first 3 days, shortly after taking her morning 20-mg dose, she experi-

enced facial paresthesias of a mild, electric-shock-like nature that were also associated with the subjective sense of facial twitching. Each episode lasted approximately 5 minutes. No involuntary facial movements were ever verified by direct observation in a mirror or by observations of others. She noticed a heightened intensity of the paresthesias in the circumoral area if she smoked a cigarette after taking her medication. She could recall no associated hyperventilation, shortness of breath, coughing spells, or preceding heightened anxiety. After the third day, these symptoms never recurred despite continuation of the medication.

Case 2. Ms. B, a 29-year-old Eurasian woman diagnosed by DSM-IV criteria with dysthymia and borderline personality traits, was placed on paroxetine 20 mg/day. On the second day of treatment, shortly after taking this medication, she experienced several paroxysms of electric-shock-like paresthesias isolated to the left side of her face and head. These came on repeatedly over a 3-minute period, with each "burst" lasting 5–10 seconds. Because these symptoms were so bothersome to the patient, she discontinued the medication permanently. No muscular symptoms, exacerbating or relieving factors, precipitating movements or actions, or other associated features were recalled. However, the singularity and brevity of these adverse effects may have limited such identification. The patient was subsequently placed on sertraline treatment without incident.

Case 3. Ms. C, a 22-year-old Native American woman diagnosed with major depression, was placed on paroxetine 20 mg/day 2 weeks after failing a trial of sertraline 50 mg/day secondary to gastrointestinal complaints. Within minutes of taking the medication, she experienced a paroxysm of electric-shock-like paresthesias isolated to her head. They seemed unrelated to any other activity and lasted for approximately 15 seconds, remitting without residua. These symptoms recurred daily after each morning dose for the first 5 days of pharmacotherapy. Ms. C, however, was able to continue on paroxetine treatment and suffered no adverse effects thereafter.

Paroxetine has been noted to have several adverse effects related to the nervous system including somnolence, dizziness, insomnia, tremor, nervousness, anxiety, paresthesias, agitation, myoclonus, and confusion.¹ Previously, Frost and Lal² described three patients who experienced electric-shock-like sensations upon discontinuation of paroxetine (in two) or sertraline (in one). This was the first time paroxysmal paresthesias of an electrical character had been described associated with paroxetine. In each case, they lasted "a few seconds" or less and "traveled" or radiated from one region to another, often to the limbs. Interestingly, this description is very similar to Lhermitte's sign, "sudden 'electrical' pains occurring with neck flexion down the spine and into the upper extremities."³ Of note, one of their patients could avoid these sensations by "keeping his head motionless." Although commonly associated with multiple sclerosis, Lhermitte's sign has been associated with over a dozen spinal cord disorders, but never with transient drug effects.⁴

By contrast, our patients represent the first cases described of paroxysmal, shock-like paresthesias associated with the initiation of paroxetine. Although each of the paroxysms of paresthesias was short-lived as in the previous cases, lasting 5 seconds to 5 minutes, all were isolated to the head or face and did not radiate or travel. All of Frost and Lal's patients had involvement of the trunk, two also had involvement of the extremities, but only one had involvement of the face or head. All of our patients were female, while all of their patients were male, but they were of very similar age ranges and averages (25.3 years and 27.3 years, respectively). All of our cases and two of the previous three cases had prominent anxiety features, and all

patients in both groups described their paresthesias as electrical in character.

Each of our three patients reported their symptoms independently of each other over a 1.5-month period, and none knew one another. Our patients were taking no concurrent medications, their medications came from separate pharmaceutical batches, and they had no underlying medical or neurologic disorders that might have contributed to their presenting complaint. Two of the three patients had not previously received psychotropic medications. The third patient had been off sertraline therapy for 2 weeks and did not appear to be experiencing withdrawal symptoms. Although all three were nicotine dependent, only one patient reported more intensified and focused symptoms while smoking. Additionally, she was the only patient who also sensed subjective facial twitching, which may have represented fasciculations, although no objective observation occurred to confirm this.

In each of our patients, the reported paroxysmal, shock-like paresthesias had a clear proximal link to the ingestion of paroxetine, during the period of medication initiation. These cases are reported in order to alert physicians who prescribe paroxetine to the possibility of this adverse effect upon its initiation.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, Department of Defense, or the U.S. Government.

REFERENCES

1. Paroxetine hydrochloride. Physicians' Desk Reference. Montvale, NJ: Medical Economics; 1997:2681–2686
2. Frost L, Lal S. Shock-like sensations after discontinuation of selective serotonin reuptake inhibitors [letter]. *Am J Psychiatry* 1995;152:810
3. Gordon TR, Goldstein JM, Waxman SG. Sensory abnormalities of the limbs and trunk. In: Bradley WG, Daroff RB, Fenichel GM, et al, eds. *Neurology in Clinical Practice: Principles of Diagnosis and Management*. 2nd ed. Boston, Mass: Butterworth-Heinemann; 1996:401
4. Vollner TL, Brass LM, Waxman SG. Lhermitte's sign in a patient with herpes zoster. *J Neurol Sci* 1991;106:153–158

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Benzotropine in the Treatment of Venlafaxine-Induced Sweating

Sir: Sweating is a relatively common side effect seen with serotonin selective reuptake inhibitors (SSRIs) and has been reported in 7% to 11% of patients treated with SSRIs and 12% of patients treated with venlafaxine, an antidepressant with the ability to inhibit the reuptake of serotonin and norepinephrine.¹ The following case indicates that this side effect can cause severe social disruption and limit effective treatment of depression. A possible management strategy is also suggested.

Case report. Ms. A, a 48-year-old school teacher with a 4-year history of depression, was diagnosed as having major depressive episode and dysthymia, but was refractory to trials of fluoxetine, sertraline, and psychotherapy. A trial of venlafaxine was then initiated with dosage titrated up to 75 mg b.i.d. The patient noted partial improvement in her depression, but experienced "hot flashes" occurring several times a day and lasting 5

to 10 minutes. Symptoms included a feeling of heat all over her body and perspiration on the back of her neck. Follicle-stimulating hormone and lutein-stimulating hormone levels were consistent with premenopause. The increase of venlafaxine to 75 mg t.i.d. was accompanied by complete remission of depression, but such severe and socially embarrassing sweating that the patient felt compelled to discontinue the drug. Ms. A was encouraged to restart venlafaxine at 75 mg b.i.d. with benztropine added at 0.5 mg b.i.d. The "hot flashes" did not recur, and venlafaxine was then increased to 75 mg t.i.d. with subsequent remission of depression and no side effects.

The eccrine sweat glands are stimulated by the sympathetic nervous system; however, the postganglionic fibers that reach the muscarinic receptors on the end organ are cholinergic. The preoptic and anterior hypothalamic nuclei are the areas of the hypothalamus that contain heat sensitive and cold sensitive neurons and are mainly responsible for the stimulation of these sweat glands.²

The exact mechanism of antidepressant-induced sweating is unknown. It has been reported that the use of clonidine is successful in the treatment of tricyclic-induced sweating³ and that propranolol increases sweating.⁴ These findings suggest a role for norepinephrine in the mechanism of antidepressant-induced sweating. Presumably SSRIs enhance sweating either indirectly by affecting the sympathetic system or directly by acting on the hypothalamus.

The use of the anticholinergic benztropine was effective in preventing the excess sweating in our patient and allowed her to continue treatment with venlafaxine. Benztropine most likely blocked the acetylcholine receptors on the eccrine sweat glands and thereby caused a reduction in sweating. Anticholinergic agents deserve further research as possible adjuncts to the management of excess sweating induced by SSRIs.

REFERENCES

1. Feighner JP. The role of venlafaxine in rational antidepressant therapy. *J Clin Psychiatry* 1994;55(9, suppl A):62-68
2. Guyton AC. Textbook of Medical Physiology. 8th ed. Philadelphia, Pa: WB Saunders Company; 1991
3. Feder R. Clonidine treatment of excessive sweating [letter]. *J Clin Psychiatry* 1995;56:35
4. Butt MM. Managing antidepressant-induced sweating [letter]. *J Clin Psychiatry* 1989;50:146-147

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Stereotypic Movement Disorder

Sir: Castellanos et al.¹ (March 1996 issue) recently reported that DSM-IV stereotypic movement disorder can be diagnosed in intellectually normal adult patients. This paper is another in a series of fascinating studies conducted by Rapoport and colleagues on the differential response of unwanted repetitive behaviors such as hair pulling² and nail biting³ to clomipramine and desipramine. The idea that such behaviors fall on an obsessive-compulsive disorder (OCD) spectrum of conditions may provide a valuable heuristic in both clinical and research settings.⁴

In their paper, Castellanos et al.¹ reported the response of three patients to both clomipramine and desipramine, two of whom used limited doses. In two of the three subjects, there

seemed to be a better response to clomipramine than desipramine. In only one of the three patients, however, was there a marked response of the stereotypic behavior to clomipramine.

In agreement with these findings, we have found that intellectually normal patients with stereotypic behaviors occasionally do present to our OCD Clinic. Previously, we have described the use of fluoxetine in patients with skin picking.⁵ In addition, we have recently used serotonin specific reuptake inhibitors for other patients who would meet DSM-IV criteria for stereotypic movement disorder.

Case 1. A 34-year-old man presented with repetitive rocking behaviors and repetitive face picking. The patient exhibited schizotypal and borderline personality disorder traits. He stated that the repetitive behaviors had been present since adolescence. On fluoxetine 20 mg/day, the patient experienced a decrease in anxiety, which he stated allowed him to have better control over his repetitive behaviors. These exhibited a mild to moderate improvement within a few weeks. The patient elected to continue medication for over a year.

Case 2. A 48-year-old woman presented with lifelong repetitive lip biting. She met DSM-IV criteria for major depression. Previous episodes of depression had responded to fluoxetine 20 mg/day, and this regimen was again initiated. There was a marked improvement in mood within a few weeks, but only a minimal improvement in lip biting. Increasing the dose to 40 mg daily had no additional effects on this behavior. The patient continued taking fluoxetine for over a year.

Case 3. A 22-year-old woman presented with repetitive head banging prior to falling asleep. This behavior consumed more than an hour of time each night and had persisted since childhood. Paroxetine 20 mg/day was initiated. The patient had no improvement in his behavior on this regimen and elected to discontinue the medication after 4 weeks.

Case 4. A 53-year-old woman presented with repetitive checking behaviors that met criteria for OCD. In addition, she complained of repetitive rubbing of her nose. She stated that this was simply a habit, rather than a compulsion that she did to get rid of intrusive thoughts. Both OCD and nose rubbing had been present since childhood. The patient was treated with citalopram at doses of up to 60 mg/day. There was minimal improvement in OCD symptoms over 3 months and no change in nose rubbing.

Case 5. A 32-year-old woman presented with symptoms of hair pulling since age 10. She met DSM-IV criteria for trichotillomania. The patient noted that when she was unable to pull hair, for example, in public situations, she would then rock back and forth repetitively. The patient was treated with citalopram up to 40 mg/day. Within a few weeks of medication, there was improvement in both hair pulling and rocking, but over time both symptoms returned.

Case 6. A 30-year-old man presented with complaints of excessive nose picking of about 6 years in duration. The patient was ashamed of this behavior, which he felt unable to control. Citalopram 20 mg/day was initiated. After 4 weeks of treatment, the patient reported minimal improvement in his behavior. However, in view of difficulty with ejaculation on the medication, he elected to discontinue treatment.

Case 7. A 28-year-old man presented with contamination fears and excessive hand washing that met DSM-IV criteria for OCD. The patient also gave a history of rhythmic shaking of the right foot, which he described as leading to a reduction of tension. There was no response of symptoms to dothiepin 150 mg/day for 6 weeks or to clomipramine 150 mg/day for 8 weeks. However, on fluoxetine 60 mg/day, there was marked improvement in both OCD and foot shaking over the course of 16 weeks.

Case 8. A 49-year-old woman presented with intrusive sexual thoughts and with excessive washing, cleaning, and checking that met DSM-IV criteria for OCD. In addition, she gave a history of excessive nose picking that frequently resulted in bleeding and of stereotypic pelvic-thrusting movements. The patient showed no response of symptoms to clomipramine 200 mg/day. However, on citalopram 60 mg/day, there was marked improvement in OCD symptoms, and mild to moderate improvement in nose picking and pelvic thrusting, over the course of 12 weeks.

Our clinical experience, although also scant, does suggest some differences between stereotypic behaviors and classical OCD compulsions. First, stereotypic behaviors are regarded by patients as unwanted habits that can serve to release tension, rather than as neutralizing responses to obsessions. Second, compared with the response of compulsions, the response of stereotypic behaviors to SSRIs is not as robust, although it may on occasion be seen rapidly after low doses of such medication.

There is preclinical evidence that dopamine agonists lead to stereotypic behaviors,⁶ suggesting that the dopamine neurotransmitter system may also play a role in humans with stereotypic movement disorder. Also of interest is the finding that socially isolated primates develop striatal cellular disorganization and stereotypic behaviors,⁷ suggesting at least some overlap with the neuroanatomy of OCD. Future research will hopefully shed more light on the neurobiological underpinnings and environmental antecedents of stereotypic movement disorder in humans.

REFERENCES

1. Castellanos FX, Ritchie GF, Marsh WL, et al. DSM-IV stereotypic movement disorder: persistence of stereotypies of infancy in intellectually normal adolescents and adults. *J Clin Psychiatry* 1996;57:116-122
2. Swedo SE, Leonard HL, Rapoport JL, et al. A double-blind comparison of clomipramine and desipramine in the treatment of trichotillomania (hair pulling). *N Engl J Med* 1989;321:497-501
3. Leonard HL, Lenane MC, Swedo SE, et al. A double-blind comparison of clomipramine and desipramine treatment of severe onychophagia (nail biting). *Arch Gen Psychiatry* 1991;48:821-827
4. Stein DJ, Hollander E. Obsessive-compulsive spectrum disorders [letter]. *J Clin Psychiatry* 1995;56:265-266
5. Stein DJ, Hutt C, Spitz J, et al. Compulsive picking and obsessive-compulsive disorder. *Psychosomatics* 1993;34:177-181
6. Goodman WK, McDougle CJ, Price LH, et al. Beyond the serotonin hypothesis: a role for dopamine in some forms of obsessive compulsive disorder? *J Clin Psychiatry* 1990;51(8, suppl):36-43
7. Martin LJ, Spicer DM, Lewis MH, et al. Social deprivation of infant monkeys alters the chemoarchitecture of the brain, I: subcortical regions. *J Neurosci* 1991;11:3344-3358

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Drs. Castellanos and Rapoport Reply

Sir: We welcome the observations of Stein et al. regarding patients who meet criteria for DSM-IV stereotypic movement disorder and who are intellectually normal, and we wonder whether systematic investigation would demonstrate a positive family history for similar behaviors. Also of interest is whether patients who were partially or totally refractory to serotonin selective reuptake inhibitors would respond to the cautious addi-

tion of a neuroleptic as suggested by McDougle et al. for obsessive-compulsive spectrum disorders.¹

REFERENCE

1. McDougle CJ, Goodman WK, Price LH. Dopamine antagonists in tic-related and psychotic spectrum obsessive compulsive disorder. *J Clin Psychiatry* 1994;55(3, suppl):24-31

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Pharmacologic Properties of Venlafaxine

Sir: Findling et al.¹ (May 1996 issue) report on their study of venlafaxine in adult ADHD. Their rationale for the research was simply that venlafaxine is an antidepressant; the fact that the medication and its metabolite, O-desmethylvenlafaxine (ODV), are weak inhibitors of dopamine reuptake is not mentioned. Even in the brief paragraph on the pharmacology of venlafaxine, its dopaminergic property is not alluded to, although there is a general statement that, like tricyclic antidepressants, venlafaxine inhibits synaptic monoamine reuptake.

The dopaminergic property of venlafaxine and ODV would have been, for me, the primary reason for its trial in ADHD. This action of venlafaxine admittedly was brought home to me in the following case: A patient, whose drug-induced auditory hallucinosis was well controlled by a small dose of risperidone, experienced breakthrough hallucinosis shortly after venlafaxine was started.

REFERENCE

1. Findling RL, Schwartz MA, Flannery DJ, et al. Venlafaxine in adults with attention-deficit/hyperactivity disorder: an open clinical trial. *J Clin Psychiatry* 1996;57:184-189

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Dr. Findling and Colleagues Reply

Sir: We appreciate the interest Dr. Smith has taken in our work which examined venlafaxine in adults with attention-deficit/hyperactivity disorder (ADHD).¹ However, our rationale for initiating a clinical trial with venlafaxine in adults with this syndrome was not simply due to the fact that venlafaxine is an antidepressant. The reason we initiated a trial with venlafaxine was that the effect of venlafaxine on both serotonergic and noradrenergic neural transmission is a pharmacologic profile shared with the tricyclic antidepressants.^{2,3} Tricyclic antidepressants have been described as being effective in the treatment of ADHD in adults.⁴

Dr. Smith is correct in asserting that venlafaxine does affect dopaminergic neural transmission. However, the effects of venlafaxine on both serotonergic and noradrenergic reuptake are of a much greater magnitude than its effects on dopaminergic reuptake.^{2,3} Although the dopaminergic properties of venlafaxine may have contributed to the salutary effects of this medicine, we would hypothesize that these effects were primarily mediated by the serotonergic and noradrenergic properties of venlafaxine.

In regard to the case Dr. Smith described, we also agree that the dopaminergic effects of venlafaxine may have led to the hallucinosis in her patient. However, due to the relatively weak effect venlafaxine has on dopaminergic neural transmission, another form of drug-drug interaction may have led to the recurrence of psychosis in her patient.

REFERENCES

1. Findling RL, Schwartz MA, Flannery DJ, et al. Venlafaxine in adults with attention-deficit/hyperactivity disorder: an open clinical trial. *J Clin Psychiatry* 1996;57:184-189
2. Muth E, Haskins JT, Moyer JA, et al. Antidepressant biochemical profile of the novel bicyclic compound Wy-45,030, an ethyl cyclohexanol derivative. *Biochem Pharmacol* 1986;35:4493-4497
3. Bolden-Watson C, Richelson E. Blockade of newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. *Life Sci* 1993;52:1023-1029
4. Mann HB, Greenspan SI. The identification and treatment of adult brain dysfunction. *Am J Psychiatry* 1976;133:1013-1017

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Impact of a Smoking Ban on a Locked Psychiatric Unit

Sir: Drs. Haller, McNeil, and Binder argue that the implementation of a smoking ban on a locked psychiatric unit does not promote aggressive behavior.¹ My experience has been otherwise. Paranoid and psychotic patients addicted to nicotine who refuse nicotine patches are prone to aggressive acting out behavior. Nicotine, by its agonist action on nicotine receptors in the central nervous system, is known to reduce aggression.² In addition, nicotine facilitates memory. I have observed elderly psychotic patients on a locked unit, deprived of nicotine after having been chain smokers for many years and refusing nicotine patches, become acutely hypotensive and develop marked sinus bradycardia because of the abrupt loss of catecholamine agonist activity, which occurs when nicotine is withdrawn. Contrary to the reassurances provided by the authors, depriving heavy cigarette smokers of smoking privileges may be associated with the risk of escalating aggressiveness and decompensating cardiovascular function.

REFERENCES

1. Haller E, McNeil DE, Binder RL. Impact of a smoking ban on a locked psychiatric unit. *J Clin Psychiatry* 1996;57:329-332
2. Goodman LS, Gilman A. *The Pharmacological Basis of Therapeutics*. 8th ed. New York, NY: Pergamon Press; 1990:546

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Dr. Haller and Colleagues Reply

Sir: Dr. Pearlman states that "paranoid and psychotic patients addicted to nicotine who refuse nicotine patches are prone to aggressive acting out behavior," yet he does not provide data to support this statement. We do not doubt that some patients who refuse nicotine gum or patches may become agitated as part of the nicotine withdrawal syndrome. In the DSM-IV, the diagnosis of nicotine withdrawal requires at least four of the following signs: "dysphoric or depressed mood; insomnia; irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness or impatience; decreased heart rate; and increased appetite or weight gain."¹ Our study² prospectively measured for an increase in violence, in the use of seclusion and restraints, and in p.r.n. medication use after the implementation of a complete smoking ban and found no significant difference. Although escalating aggressiveness related to nicotine withdrawal is a risk and should be carefully assessed when hospitals consider implementing smoking bans, such escalation was not demonstrated by our prospective study.

Anecdotally, our previous experience with altering smoking policies over the years suggests that a total smoking ban may be less disruptive to the milieu of a locked unit than are graduated restrictions in smoking, such as asking staff to take patients off the ward to smoke. Graduated restrictions can have the unintended effect of focusing many patient-staff interactions on negotiating smoking privileges, thereby leading to increased conflict. In any event, our study found that, while many staff voiced concerns such as Dr. Pearlman's before implementation of the total smoking ban, these attitudes became much more favorable after the ban was in effect and the feared ward disruption did not materialize.

In addition, Dr. Pearlman cautions that the elderly, in particular, risk developing altered cardiovascular function when withdrawn from nicotine due to the abrupt discontinuation of chronic catecholamine stimulation. Our study did not formally collate and evaluate data on cardiovascular function; however, all patients on the unit have their vital signs checked regularly, and no patients developed acute hypotension or sinus bradycardia directly related to nicotine withdrawal. Nonetheless, we share Dr. Pearlman's concern about the possibility of precipitating these symptoms in elderly patients and caution physicians to follow patients closely if they refuse nicotine replacement.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association; 1994:244
2. Haller E, McNeil DE, Binder RL. Impact of a smoking ban and locked psychiatric unit. *J Clin Psychiatry* 1996;57:329-332

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