Letters to the Editor

Venlafaxine-Induced Increase in Urinary Frequency in 3 Women

Sir: Urinary incontinence and increased frequency are listed as uncommon side effects of antidepressant treatment. Only 2 reports exist in the literature on the association between venlafaxine and incontinence, comprising 2 male patients and 1 female patient. These patients were receiving a combination of venlafaxine and lithium.[1,2] The present letter reports on 3 women, all in their 30s, who experienced de novo increased urinary urge, frequency, and incontinence after commencing treatment with the antidepressant venlafaxine. None of these women had a previous history of urologic or gynecologic problems. Only 1 of these patients was receiving concomitant treatment at the time (olanzapine). They were all treated for depression as outpatients by the local psychiatric team after having been referred by their general practitioners.

Case 1. Ms. A, a 38-year-old white woman, was initially started on treatment with venlafaxine 37.5 mg b.i.d. in April 2003 after a DSM-IV diagnosis of major depressive episode, moderate degree, had been established. Her symptoms had previously been treated with sertraline, without effect, by her general practitioner. Almost immediately after commencing venlafaxine treatment, she experienced an increase in urinary frequency and urge. She experienced no pain or discomfort during micturition. She did, however, consult her general practitioner in the belief that she was suffering from cystitis, which was disconfirmed. Ms. A received no other medication during this period and had no urogynecologic history of note and no deliveries. She started to experience nocturia 3 times a night, which worried her immensely and further deteriorated her already poor sleeping pattern. She decided to stop taking venlafaxine after 2 weeks of treatment, 3 weeks before her follow-up appointment. The patient's nocturia ceased 48 hours after discontinuation of venlafaxine, but she was assessed at her appointment to be severely depressed after 3 weeks without treatment. She later improved rapidly on treatment with mirtazapine 30 mg/day.

Case 2. Ms. B, another 38-year-old white woman, had her venlafaxine dose increased in April 2003 from 75 mg/day to 150 mg/day due to residual symptoms of depression (DSM-IV criteria). She had been taking the lower dose for 2 months. During her initial contact, the patient revealed that as a child she had suffered from nocturnal enuresis until 13 years of age. There was a strong history of bed-wetting in her family. She received no other medication during this period and had no other urogynecologic history of note, with no deliveries.

During the following appointment, she tearfully announced that after 25 years of continence she had begun experiencing renewed bed-wetting 4 to 5 nights a week. Despite the incontinence, Ms. B did feel mentally better. She only reluctantly agreed to change to a selective serotonin reuptake inhibitor (SSRI) antidepressant, with which she remains well and continent. The incontinence disappeared approximately 2 weeks after the start of the tapering process, around the time the venlafaxine dose was reduced to 37.5 mg/day.

Case 3. Ms. C, a 31-year-old white woman with DSM-IV personality disorder and comorbid depression, had her medication dosages increased in January 2002 from venlafaxine 150 mg/day and olanzapine 10 mg/day to venlafaxine 225 mg/day and olanzapine 15 mg/day. The medication had stabilized her illness to a degree that her 4 children could return home to her care from their foster parents. Ms. C was, however, arrested by the police because she had urinated publicly the week after the increase in the venlafaxine and olanzapine dosages. She explained that she had been unable to wait and that she would have had an accident if she had not relieved herself in the street. Ms. C had no history of urologic problems or incontinence. She described a considerable increase in both urge and frequency following the change in medication. She is currently awaiting trial. Because of the obvious benefits of the medication on her overall functioning, she remains on treatment with the same doses.

Sexual side effects of antidepressants are known to be reported less often than other antidepressant side effects.[3] It is reasonable to assume that the same is the case with urogenital problems. There may be various reasons for this underreporting: embarrassment, lack of association due to lack of knowledge of the underlying mechanism, and, finally, masking by polypharmacy.

In cases 1 and 2, venlafaxine was the only drug prescribed. To our knowledge, no other case of increased urinary frequency and incontinence with venlafaxine as monotherapy has been described in the literature. It is, however, acknowledged on the venlafaxine package insert[4] that 3% of patients treated with venlafaxine will experience increased urgency compared with 2% receiving placebo. The patient in case 3 was prescribed olanzapine in addition to venlafaxine. Olanzapine has anticholinergic properties and is therefore more likely to offset an increase in urinary frequency. Stress incontinence is common in women postpartum, but only the woman in case 3 had given birth, and in that case the problems were temporally unrelated to childbirth (her youngest child was 5 years old).

It seems much more likely that the increased frequency, urgency, and incontinence, all hallmarks of an overactive bladder or detrusor instability, were caused by the introduction or dose increase of venlafaxine in all 3 cases. Venlafaxine is a bicyclic antidepressant with a dual mechanism of action. It is a potent inhibitor of both serotonin and norepinephrine reuptake. At higher doses, venlafaxine also has a weak dopaminergic action. The mechanism causing urinary incontinence and increased frequency, though, is largely unknown. Case reports describing incontinence associated with SSRIs (paroxetine, sertraline) have been published.[2,5] Animal studies have suggested 5-HT_4 receptor involvement. Other 5-HT_4 agonists, e.g., cisapride, have increased micturition in patients treated for gastrointestinal disturbances.[6] The contribution of the noradrenergic action is

possibly synergistic through changes in the contractility in the urethra caused by α_1 receptor blockade. One case report describes incontinence in a male patient receiving another dual-action antidepressant, mirtazapine, a potent adrenergic and serotonergic antagonist.[7]

There is little doubt that nocturia, increased urinary urge/frequency, and incontinence can pose serious added problems for the already vulnerable group of patients with depression. For the clinician, it seems important to take a urologic history and directly inquire into changes during the treatment period. It is possible that certain groups of patients are more at risk than others for developing these side effects, for example, women and patients with a history of enuresis or urogenital surgery. Only independent randomized controlled trials investigating urologic changes during antidepressant treatment would be able to answer these questions.

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

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Transient Hyperproinsulinemia During Treatment With Clozapine and Amisulpride

Sir: Impaired glucose metabolism may occur during treatment with second-generation antipsychotics, predominantly clozapine, olanzapine, and quetiapine.[1,2] The mechanisms involved in this metabolic side effect of antipsychotic therapy seem to be complex and are a point of ongoing discussion, especially as they relate to the use of antipsychotic combination therapy in treatment-resistant patients.[3]

Besides causing weight gain and subsequent insulin resistance, antipsychotics could modulate pancreatic insulin secretion as a consequence of β-cell toxicity and derangement of the processing of proinsulin into biologically active insulin. Furthermore, an increase in proinsulin levels has been shown to be an independent risk factor for cardiovascular diseases.[4,5]

Case report. Mr. A, a 24-year-old male patient, was first admitted to the psychiatry department in 1998. At that time, he was diagnosed with paranoid schizophrenia (ICD-10). Neither the patient nor members of his family had diabetes mellitus. At the time of admission, Mr. A had a normal body mass index (BMI) of 21. He was originally treated with risperidone in a double-blind clinical trial (risperidone vs. haloperidol). During that treatment, the patient showed improvement of psychotic symptoms but gained 10 kg (22 lb) over 14 months. In January 2000, the patient was discontinued from the study because he withdrew consent, and his medication was switched to olanzapine, 10 mg/day.

In September 2001, Mr. A was readmitted to the hospital because of a severe exacerbation of psychotic symptoms (acoustic hallucinations, delusions, and suicidality) despite continuous treatment with olanzapine. At that time, the patient had gained another 15 kg (33 lb) and reached a BMI of 25, but his fasting glucose level was within normal limits. Therapy with quetiapine, up to 800 mg/day, was started. Gemfibrozil, 450 mg/day, was administered concomitantly to treat the patient's hyperlipidemia (triglycerides = 410 mg/dL, high-density lipoprotein [HDL] cholesterol = 25 mg/dL).

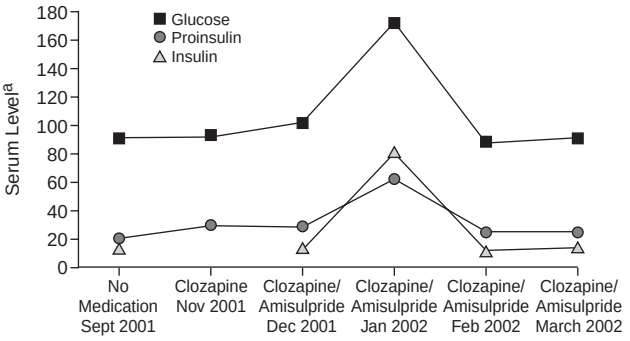
Because Mr. A's psychotic symptoms persisted, we switched his medication to clozapine, 400 mg/day. Sialorrhea was treated with pirenzepine, 50 mg/day, and treatment with gemfibrozil was continued. As the patient's psychiatric symptoms did not improve over the course of the next 5 weeks and an increase of dosage was not possible due to sedation, we decided to add amisulpride at a dose of 400 mg/day. Amisulpride is a specific D_2/D_3 antagonist that is not associated with disturbances of lipid or glucose metabolism.

Within 3 weeks after starting amisulpride therapy, the patient developed severe hyperproinsulinemia paralleled by an increase in plasma glucose as well as insulin levels (Figure 1). The patient had no concomitant somatic disease, especially symptoms of pancreatitis, that would have explained these laboratory findings. Mr. A did not receive antidiabetic treatment, but he received low-cholesterol nutrition.

With respect to his psychiatric disorder, the patient responded favorably to this combination therapy, and therefore we decided to continue the treatment with strict monitoring of laboratory values. All pathologic parameters normalized within 4 weeks (Figure 1), and Mr. A was discharged in March 2002. Since then, he has been psychopathologically stable, laboratory parameters relating to glucose and lipid metabolism have remained within normal range, and his weight has stabilized.

Our observation of transient hyperproinsulinemia and an increase in plasma glucose and insulin levels seems to support the

Figure 1. Glucose, Insulin, and Proinsulin Levels in a Patient Treated With Clozapine and Amisulpride



[a]Units of measure are as follows: glucose, mg/dL; insulin, μU/mL; proinsulin, pmol/L.

hypothesis of a possible modulation of pancreatic insulin secretion by some antipsychotics.[6] Serotonergic mechanisms have also been hypothesized to be related to impaired glucose metabolism, but data remain controversial.[7] Antipsychotic drug–induced weight gain and lower levels of physical activity are associated with a decrease in insulin sensitivity.[2,7] Another factor possibly involved in alterations of glucose metabolism during antipsychotic treatment is hyperprolactinemia induced by antidopaminergic medication,[2,7–9] which could lead to insulin resistance as well.[10] Unfortunately, no prolactin levels are available for the patient from the time period under study. As amisulpride is known to increase prolactin, a contribution of this hormone cannot be ruled out in our patient. A derangement in the processing of proinsulin into biologically active insulin could occur as a consequence of a potential β-cell defect caused by antipsychotics. Defects in proinsulin processing precede the onset of overt hyperglycemia.[11] Therefore, hyperproinsulinemia could be an indicator for early detection of the possible development of diabetes mellitus in patients treated with second-generation antipsychotics.

As there are differences in the half-lives of insulin and proinsulin,[12] circulating concentrations during the fasting state do not reflect what is actually released from the β-cell granules. To get a better estimate of the granule content of insulin and proinsulin, one would have to measure directly after acute stimulation of insulin secretion.[13]

Our data indicate that alterations of metabolic parameters can be transient, thus offering the opportunity for patients to continue previous medication with regular monitoring of the relevant laboratory parameters.

In this patient, the diabetogenic effect of clozapine may have been triggered by the addition of amisulpride, potentially via an increase of prolactin. Alternatively, the effect may just have represented a delayed onset of a clozapine-induced disturbance of glucose metabolism, and the connection to the addition of amisulpride may have been purely coincidental. Besides the possible effect of antipsychotics on β-cell function, insulin resistance may also have occurred as a consequence of impaired glucose uptake into muscle tissue.

Several lessons can be learned from this case. Overweight is possible with normal levels of lipids and glucose, and glucose metabolism pathology may develop later or may be potentially triggered by comedication. Another important finding was that such disturbances can be transient.

This case report also lends support to the recommendation of regular monitoring of glucose and lipid levels in patients receiving antipsychotic treatment.

Dr. Hummer has been a consultant for Bristol-Myers Squibb, has received grant/research support from Eli Lilly, and has received honoraria from Bristol-Myers Squibb and Pfizer. Dr. Fleischhacker has been a consultant for Johnson & Johnson; has received grant/research support from Eli Lilly and Sanofi Synthelabo; has received honoraria from Pfizer, Johnson & Johnson, Bristol-Myers Squibb, AstraZeneca, and Eli Lilly; and has served on speakers/advisory boards of Otsuka, Fujisawa, Bristol-Myers Squibb, Johnson & Johnson, AstraZeneca, Sanofi Synthelabo, and Pfizer. Drs. Rettenbacher and Lechleitner report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Comments on Cost Analysis of Risperidone Versus Olanzapine

Sir: Taylor et al.[1] report a naturalistic nonrandomized retrospective study comparing inpatient costs for risperidone with olanzapine. The disadvantages inherent to a nonrandomized study (with no blinding) are not the only shortcomings of the study, and therefore, its results should be interpreted with caution.

First, the study reflects a viewpoint from a hospital's perspective as opposed to a societal perspective. A consequence of this narrow viewpoint of studying only inpatients is that it is not known whether patients discharged early differ from those discharged late in their utilization of outpatient resources and subsequent course of illness. For example, frequency of visits to psychiatrist/therapist, number of emergency room visits and home visits, subsequent relapse and rehospitalization, and implications of long-term adverse effects could significantly affect the cost estimates. Thus the finding that risperidone is associated with shorter hospitalization in patients with schizophrenia/schizoaffective disorder may not translate into lower costs in treating the illness per se.

Second, although the authors mention the primary outcome measure as the "mean daily cost of inpatient drug use," other costs of inpatient services besides the cost of acquisition of drugs are not discussed. It is not clear whether this cost is similar at baseline across the 11 study centers. Cost analysis is not broken down into utilization of resources and unit price.

Third, because this study was conducted in the United Kingdom, the practice pattern and prices may not apply to those in the United States. Although drug prices may vary among countries, the relative prices of these drugs may also show some variation. For example, a 1-month supply of 6 mg of risperidone and 15 mg of olanzapine in the United States (closer to mean doses in this study), costs approximately $361 and $402, respectively.[2] The ratio of cost of risperidone to olanzapine is 0.89, which is slightly different from that used by the authors to estimate sample size (112 Luxembourg francs [LUF] for risperidone and 150 LUF for olanzapine, ratio 0.76). As the price difference between risperidone and olanzapine is less in the United States compared with the standard used in the study, the effect size is smaller, which translates into the need for a bigger sample to reach the same results. This price difference may assume a greater significance when hospitals negotiate contracts with drug companies to purchase a particular drug in bulk at lower prices, which is a common practice in this country.

Fourth, the authors do not state any exclusion criteria, other than age and diagnosis, for the subjects in the study, making it difficult for the average clinician to apply the results to clinical practice.

Finally, the study undertakes no sensitivity analysis using variable drug doses, and it allows for use of more than one antipsychotic at a time. Thus, a subgroup analysis of patients with and without concomitant antipsychotics may have been more meaningful.

The authors report no financial or other relationship relevant to this topic.

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Dr. Taylor Replies

Sir: Duggal and Gandotra make some important observations on our cost analysis of risperidone and olanzapine. Our study was designed to evaluate drug treatment costs in a UK hospital setting. Costs incurred after discharge were not recorded, and it is possible that differences in postdischarge outcome and resource utilization could have led to rather different conclusions. However, we are not aware of any clinical trial data that suggest different long-term outcome for risperidone and olanzapine.

We examined only inpatient drug treatment costs because we assumed that other costs such as those associated with accommodation and subsistence would be the same for patients taking each drug, at least in the same study center. Differences in these costs between centers would not have an important effect because similar numbers of subjects received risperidone or olanzapine in each center.

Your correspondents rightly point out that the purchase price differential will have a direct effect on savings provided by the use of risperidone compared with olanzapine. However, we are not aware of any country in which the purchase price of risperidone is greater than that for olanzapine. This consistency of pricing suggests that, whatever the context, the use of risperidone will always prove to be less expensive than the use of olanzapine, except where locally negotiated contracts reverse the advertised purchase price differential. The change in effect size would not have affected the validity of our overall sample size because we calculated sample size for each center, as reported, not all centers combined.

Exclusion criteria were implicit from inclusion criteria outlined: patients aged under 65 years with a diagnosis of schizophrenia or schizoaffective disorder and either discharged within 120 days or with 120 days of follow-up were included; those not meeting these criteria were excluded.

We did not perform a subanalysis of those without concomitant antipsychotics for 2 reasons. First, a large majority of subjects received concomitant antipsychotics at some point, but few received them throughout the study period, which would have made subgroup analysis complicated and perhaps unhelpful. Second, the use of concomitant antipsychotics is common practice in the United Kingdom,[1] and our aim was to evaluate naturalistic practice.

We thank Duggal and Gandotra for their observations but do not agree that their comments should lead to any change in our overall conclusion or in interpretation of our results.

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Venlafaxine XR and Chronic Pelvic Pain Syndrome

Sir: Venlafaxine, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), has been shown to have analgesic effects in neuropathic[1–3] and postsurgical pain[4] and in pain and uncomfortable physical symptoms associated with premenstrual dysphoric disorder.[5] This agent has also been reported to both prevent and resolve hyperalgesia in rats with experimentally produced painful neuropathic lesions.[6] To my knowledge, there are no reports of the use of venlafaxine in the treatment of chronic pelvic pain syndrome associated with chronic nonbacterial prostatitis. This disorder is a common problem encountered by urologists. Prostatitis represents 8% of urology office visits and is the most common urologic diagnosis in men younger than 50 years.[7] The following report describes the case of a 32-year-old male graduate student whose symptoms of urinary frequency and low back pain resolved after treatment with venlafaxine extended release (XR).

Case report. Mr. A presented to a urologist in May 2002 with 1 week of urinary frequency often so pronounced that he had to urinate every 10 minutes. Urination was frequently associated with low back pain, and he experienced nocturia 3 to 4 times per night. He had experienced about 2 days of burning during urination, but there had been no discharge from his penis or erythema at the penile meatus. Urinalysis results were significant for 3+ blood; gross hematuria was absent. Urine microscopy revealed 11 red blood cells and no white blood cells, and the culture was

negative for bacteria. His urine was never purulent or malodorous and was always clear or straw-colored.

At physical examination, his prostate was mildly tender on palpation but was not noted to be enlarged, nodular, or boggy. Results of an abdominal examination were notable for suprapubic fullness on palpation. All vital signs and results of all routine blood tests including complete blood count and Sequential Multiple Analyzer (SMA) 20 were within normal limits. A computed tomographic urogram ruled out any calculi or gross anatomical abnormality. This was followed by a renal ultrasound, which also was negative for pathology. An intravenous pyelogram was not performed.

Mr. A was treated with a 14-day course of ciprofloxacin for a presumed case of subacute prostatitis. During the course of this treatment, his symptoms were reduced but did not completely ameliorate. The patient also noticed that if he was experiencing stress or happened to be focusing on his urinary frequency, the problem was exacerbated. After the course of antibiotics was completed, he again saw his urologist, still complaining of residual symptoms. A urinary sonogram at this time revealed no post-void residual urine. Follow-up urinalysis and microscopy were negative for hematuria or infection.

The patient did not seek treatment for the next 4 months, although his symptoms waxed and waned. He still had episodes of urinary frequency associated with mild low back pain, but the problem was not present if he was distracted by his work or athletics, and for up to 14 consecutive days he could be symptom free. Mr. A still at times experienced suprapubic fullness, a sensation that he was not completely emptying his bladder, and low back pain and continued to experience anxiety that there was significant pathology affecting his urinary tract. He again saw the urologist to discuss this problem.

At this meeting, the urologist described to the patient that he was most likely suffering from chronic pelvic pain syndrome and pseudo-dyssynergia,[8] a functional disturbance of urine storage and bladder emptying, which could be treated with psychoeducation and biofeedback. However, since there had been red cells present in the urinalysis, a cystoscopy was again recommended (initially deferred by the patient) to rule out any lesions, the result of which was negative. After Mr. A was reassured that his symptoms resulted from a benign process and most likely were stress-related, biofeedback was recommended for pelvic floor muscle retraining. However, because of his busy schedule, the patient did not feel that this was an option. Because of mild symptoms of depression in addition to the pelvic symptoms, a trial of venlafaxine XR was undertaken with the supervision of a psychiatrist and was titrated to a dose of 75 mg p.o. taken in the morning. Over the course of the following 2 weeks, the patient noted near-complete resolution of his symptoms. At 6-month follow-up, his symptoms have remained in remission. His mild depression also resolved.

Although anecdotal and uncontrolled, this report may suggest that venlafaxine XR, an SNRI, has properties that are useful in the treatment of young men who have chronic pelvic pain syndromes with comorbid symptoms of mild depression. Possible mechanisms may be a direct analgesic effect on the patient's low back pain; a modulation of detrusor smooth muscle behavior, perhaps via a parasympathetic effect; or a nonspecific reduction in symptoms secondary to an amelioration of the patient's anxiety and dysphoria about, and vigilance toward, the unpleasant bodily sensations. Future work is needed to determine if medications in this class will be useful for treating this common disorder.

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Dr. Karp has been a member of the speakers/advisory board for Pfizer and AstraZeneca.

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Bupropion and Breastfeeding: A Case of a Possible Infant Seizure

Sir: Little is known about the use of bupropion during breastfeeding. Published data are restricted to 3 case reports of 1 toddler[1] and 2 infants[2] exposed to bupropion through breast milk. No adverse effects were reported, with the exception that Briggs and colleagues[1] reported a high milk-to–maternal plasma ratio. Neither bupropion nor its metabolites were quantifiable in the infants' or the toddler's plasma.[1,2] We describe the first case, to our knowledge, of a possible adverse reaction to sustained release bupropion (bupropion SR) in a breastfeeding infant.

Case report. Ms. A, a 31-year-old pediatrician, had a history of recurrent major depressive disorder (DSM-IV criteria) previously successfully treated with bupropion SR 150 mg q.d. Ms. A discontinued bupropion SR before becoming pregnant. She did well during the first and second trimesters but noted depressive symptoms during the third trimester. She continued her pregnancy without medication and delivered a full-term healthy girl. The infant was exclusively breastfed until 6 months of age, when she began to receive solid foods.

At 6 months postpartum, Ms. A requested medications for treatment of increasing depressive symptoms including depressed mood, loss of appetite, weight loss, crying, decreased concentration, and decreased motivation. A risk-benefit analysis was conducted. Ms. A had a history of positive response to bupropion SR and a history of poor response to and side effects with 3 selective serotonin reuptake inhibitors. Therefore, treatment with bupropion SR 150 mg was initiated.

Ms. A took 2 doses of bupropion SR 150 mg approximately 36 hours apart. She ingested the first dose on Thursday evening and then breast-fed the infant. On Friday, Ms. A expressed milk

twice and saved the milk for later use. The infant nursed on Friday night without problems. Ms. A took her second dose of medication on Saturday morning and nursed the infant throughout the day and night. On Sunday, Ms. A's husband fed the infant the expressed breast milk. Exact feeding times and amounts were not reported. On Sunday evening at approximately 9 p.m., Ms. A observed the infant arching her back, rolling her eyes, and smacking her lips for approximately 10 to 15 seconds. Ms. A believed the infant was having a seizure. She also described a 5- to 10-minute postictal state that included staring and nonresponsiveness. The infant returned to her normal activity but was extremely restless throughout the night.

The infant was 6 months old, had no history of seizures, and was developing normally. The infant had a mild upper respiratory infection but was not febrile. There was no family history of seizure disorders. Following the incident, the infant was evaluated by a specialty pediatric seizure clinic. The evaluating clinician confirmed that the symptoms reported were consistent with a seizure presentation in a 6-month-old infant. Results of a physical examination, laboratory tests, and an electroencephalogram were unremarkable. Neither infant nor maternal levels of bupropion were obtained. Ms. A immediately discontinued bupropion SR and began sertraline treatment. She discontinued sertraline treatment after 5 days due to side effects. Six weeks later, the infant had displayed no further seizure activity and was continuing to nurse. The mother did not resume antidepressant treatment.

To our knowledge, this is the first report of possible seizure activity related to bupropion SR exposure through breast milk. Because milk and plasma medication levels were not obtained at the time of the seizure, a causal effect cannot be proved. Because bupropion has been linked to an increased incidence of seizures in the general adult population, a possible link in this case must be considered. Studies indicate that there is a 0.1% incidence of seizures with bupropion SR doses up to 300 mg and a 0.4% incidence with doses greater than 400 mg.[3] Studies of bupropion conducted in children are virtually nonexistent, and therefore the incidence of seizures in children and infants with bupropion exposure is unknown. One open-label study in adolescents with attention-deficit/hyperactivity disorder and depression failed to detect seizures over a 10-week period.[4]

A wide range of factors influence infant plasma medication concentrations. Transmission of medication in breast milk is affected by molecule size, lipid solubility, pH, and diffusion rate. Drug absorption, half-life, dissociation constant, and volume of distribution may alter levels of exposure in nursing infants.[5] Bupropion is known to reach peak plasma levels in 2 to 3 hours, with a mean elimination half-life of up to 21 hours and a half-life of up to 40 hours for its major metabolite, hydroxybupropion.[3] The sustained release formulation, used in this case, has a 50% lower peak plasma concentration but is comparable with regard to time to peak plasma level and half-life.[3,6] The relationship of the timing of nursing to the peak maternal plasma medication levels and, in turn, peak milk medication levels may affect infant exposure. Because the exact timing of the nursing and medication ingestion was not available, we do not know the relationship of the timing and the peak concentration after ingestion in this case.

Infants' metabolic abilities also influence plasma levels of medications. By the gestational age of 42 weeks, infants' livers are able to metabolize most drugs, though long-acting agents may prove more difficult to completely clear from plasma. Bupropion undergoes extensive hepatic metabolism with elimination primarily (90%) via the kidneys.[6] There is no indication that this infant's renal or hepatic function was impaired.

Without further data, we can only speculate about how bupropion may have contributed to a seizure in this infant. Because of the clinical situation and timing of the neurologic assessment, no tests confirm that the infant did have a seizure. However, the patient is an experienced pediatrician who has witnessed infant seizures, and the description is consistent with seizures in a 6-month-old infant. Therefore, despite a lack of objective laboratory confirmation, we presume that the event witnessed was a seizure. In determining causation of the seizure, several clinical elements must be considered. The infant had a respiratory illness. Although the infant was not objectively febrile, a febrile seizure cannot be ruled out. An underlying predisposition, while not discovered, cannot be excluded completely. Bupropion may have contributed to a multifactorial seizure etiology or may have had an independent effect; however, without knowing milk and infant plasma medication levels at the time of the event, we cannot confirm a causal effect. It is plausible that active metabolite was present in the stored breast milk and may have contributed to a greater-than-expected infant plasma concentration. To our knowledge, there are no data regarding how expressed milk storage may alter potential exposure to, metabolism of, and excretion of medication.

This report raises further questions for study. Does storage of breast milk and freezing and thawing of milk alter available drug levels? How do changes in frequency of feeding and increased breast milk volumes as infants grow alter steady-state levels? Finally, more data are needed to determine accurate levels of transmission of bupropion to infants via breast milk and to better understand clinical ramifications of exposure. The use of all psychotropic medications during lactation requires a thorough risk-benefit analysis and discussion with the patient. This case reminds us to use caution and to inform our patients of the known and unknown risks and benefits to them as well as to their infants. We must also inform them of the small number of reported cases and the limitations of the cases upon which we make our recommendations.

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