Letters to the Editor

Venlafaxine and Vivid Dreaming

Sir: Dreams and nightmares most often occur during rapid eye movement (REM) sleep. Venlafaxine is a serotonin-norepinephrine reuptake inhibitor whose serotonergic activity produces a dose-related suppression of REM sleep[1] and would therefore be expected to reduce or suppress dream activity. In contrast to this expectation, we report the appearance of especially vivid nightmares after introduction of venlafaxine.

Case report. Ms. A, a 35-year-old woman with a known dysmorphophobia (ICD-10 code F45.2), was referred to our outpatient department with depressive symptoms. She had suffered pavor nocturnus and somnambulism during childhood, without having any sleep alterations as an adult so far. Five years ago, she began complaining about a discrete alopecia, which was treated with cyproterone. She subsequently developed a very disabling dysmorphophobia related to her hair, washing and styling it compulsively for up to 5 hours per day. Ms. A had been treated in the past with lithium and citalopram without any modification of dream activity. When she was referred, her treatment consisted of citalopram, 20 mg/day, and cyproterone, 50 mg/day, each for 10 days per month; and clorazepate, 40 mg/day, all of which had been administered for several months.

Citalopram was discontinued, and venlafaxine (immediate-release formulation, b.i.d.) was titrated to 225 mg/day over 21 days, reaching a plasma level of 99 ng/mL. No other modifications of the treatment were done. One week after reaching the dose of 225 mg/day of venlafaxine, Ms. A began experiencing particularly vivid dreams every night, which she described as more memorable and intense, with frequently unpleasant content and from which she would often awake sweating and trembling. She tried to treat them by herself with lormetazepam, up to 4 mg/day, without relief. Four days after venlafaxine discontinuation, the nightmares ceased, and her dreams became less vivid and less memorable.

Vivid dreaming is a well-known side effect of dopaminergic drugs such as L-dopa[2] and bupropion.[3] Venlafaxine is a serotonin-norepinephrine reuptake inhibitor without significant direct dopaminergic activity. Serotonergic drugs have only occasionally been associated with changes of dream activity.[4] Two explanations are conceivable, one related directly to REM sleep alterations and a second involving stimulation of serotonin-2 (5-HT_2) receptors. First, although venlafaxine has a dose-related suppression effect on REM sleep, a tolerance to this effect could be developed after some time, which may induce vivid dreaming. In addition, the stimulation of 5-HT_2 receptors may in some cases be associated with alterations of dreaming activity, such as nightmares. This is supported by the efficacy of 5-HT_2 receptor antagonists such as cyproheptadine, mirtazapine, and nefazodone in the treatment of nightmares, especially in posttraumatic stress disorder (PTSD). A serotonergic mechanism could therefore be involved in dreaming processes in at least some patients. Finally, the involvement of the noradrenergic system should not be excluded, since the α_2 agonists clonidine and guanfacine have some efficacy in the treatment of nightmares associated with PTSD.[5,6]

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Risperidone Metabolism and the Impact of Being a Cytochrome P450 2D6 Ultrarapid Metabolizer

Sir: We read with great interest the recent article by Bork et al.[1] concerning the impact of hepatic enzyme cytochrome P450 (CYP) 2D6 activity on risperidone metabolism. The authors discuss the possibility that ultrarapid metabolizers, who have multiple copies of an active CYP2D6 gene[2] and who represent 1% to 7% of the white population,[2,3] could have subtherapeutic concentrations of the CYP2D6 substrate risperidone. However, no such subjects were identified in their study.[1] In previous studies, CYP2D6 ultrarapid metabolizers have been shown to have very low concentrations and to be unresponsive to average doses of other CYP2D6 substrates, such as tricyclic antidepressants.[4,5] In this report, we present 2 patients with low risperidone concentrations who subsequently were found to be CYP2D6 ultrarapid metabolizers.

For several years, determination of serum concentrations of risperidone and its active metabolite 9-hydroxyrisperidone has been a routine part of our therapeutic drug monitoring service. The samples were previously analyzed by high-performance liquid chromatography and are now analyzed by liquid chromatography and mass spectrometry with methods developed in our laboratory. The limits of quantification were 2 ng/mL for both

substances with the old method and 0.4 ng/mL with the new method. In patients with very low or very high concentrations of the active moiety in relation to the prescribed dose, or with extreme risperidone/9-hydroxyrisperidone ratios, we regularly suggest genotyping to elucidate whether the results could be explained by the CYP2D6 genotype.

CYP2D6 genotyping and the identification of ultrarapid metabolizers are performed by methods described earlier.[6,7] In brief, genomic DNA was isolated from peripheral leukocytes and the inactivating alleles were determined by allele-specific polymerase chain reaction (PCR) analysis and restriction fragment length polymorphism (RFLP). The subjects were tested for the inactivating mutations *3, *4, *5, *6, and *7. In white individuals, this procedure will predict the poor metabolizer phenotype with at least 93% certainty.[8] Alleles in which none of these mutations were found were classified as *1 (wild-type) alleles. The samples were also tested by long-PCR analysis for the duplicated/multiduplicated gene (the *2Xn mutation). The exact number of copies of this allele could, however, not be identified. Of the approximately 200 subjects from whom at least 1 therapeutic drug monitoring sample was analyzed for risperidone, genotyping has been carried out in 16 subjects. Among these, 2 ultrarapid metabolizers (and 3 poor metabolizers) were identified. The 2 ultrarapid metabolizers are described below.

Case 1. Mr. A, a 15-year-old male, was treated with risperidone, 4 mg/day, in monotherapy. Owing to lack of therapeutic response, his serum concentrations of risperidone and 9-hydroxyrisperidone were measured and were found to be < 2 ng/mL and 22 ng/mL, respectively. For comparison, the mean total concentration with this dose based on samples analyzed in our laboratory is 32 ng/mL, and the risperidone/9-hydroxyrisperidone ratio usually ranges from 0.1 to 0.3. These results are in accordance with the findings in other studies.[9,10] CYP2D6 genotyping revealed Mr. A to be an ultrarapid metabolizer (CYP2D6*2Xn and homozygous for the CYP2D6*1 [wild-type] allele).

Case 2. Mr. B, a 44-year old man, was also treated with risperidone, 4 mg/day, in monotherapy. Owing to lack of therapeutic response, his serum concentrations of risperidone and 9-hydroxyrisperidone were measured and were found to be < 0.4 ng/mL and 9.6 ng/mL, respectively. CYP2D6 genotyping revealed that he was an ultrarapid metabolizer with the same genotype as Mr. A (described above).

These 2 patients illustrate that in CYP2D6 ultrarapid metabolizers, the concentration of risperidone seems to be very low, whereas the concentration of 9-hydroxyrisperidone seems to be as expected or somewhat lower than expected. Consequently, the concentration of the active moiety most probably would be slightly lower, but not necessarily considerably lower, than in extensive metabolizers. Unfortunately, we were not able to identify the exact number of copies of the active allele. Because we were not testing for all known inactivating mutations, we cannot completely exclude that one or both subjects might have in addition one of these inactivating mutations. On the basis of the differences in the concentrations between the subjects, one could at least not exclude this possibility in the patient with the higher total concentration.

The 2 cases presented suggest that defining a subject as an ultrarapid metabolizer by genotyping might be of value to predict nonresponse with conventional risperidone doses. Thus, this report adds some knowledge to the recently published article by Bork et al.,[1] indicating that genotyping might be a suitable tool for individualizing dosage regimens during treatment with risperidone. Knowledge of an ultrarapid CYP2D6 genotype will also be helpful if it would be necessary to commence treatment with other psychotropic drugs, since most are CYP2D6 substrates.[11]

In addition, CYP2D6 genotyping might be helpful in the management of patients with a low concentration in relation to the prescribed dose because it makes it possible to distinguish between ultrarapid metabolism and noncompliance more precisely than employing the parent substance/metabolite ratio. This is an important issue, since unjustified accusations of noncompliance might adversely affect the therapeutic alliance between the patient and the doctor and could thus have a negative impact on outcome.

This study was supported in part by a grant from Janssen-Cilag.

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Olanzapine-Induced Urinary Incontinence: Treatment With Ephedrine

Sir: We previously reported using ephedrine to successfully treat clozapine-induced urinary incontinence in a population of patients with treatment-refractory schizophrenia and schizoaffective disorder (DSM-IV).[1] It was postulated that the anti–α-adrenergic effects of clozapine were involved and that an α-adrenergic agonist (ephedrine) would reduce urinary inconti-

nence. A transient, dose-related urinary incontinence has also been noted to occur in schizophrenic patients beginning treatment with risperidone.[2] Atypical antipsychotics are used to treat a wide range of populations. In addition to treating schizophrenia and schizoaffective disorder, they are increasingly being used in conjunction with mood stabilizers to control psychotic inpatients with bipolar disorder. The following case report describes a patient with bipolar disorder who was treated with olanzapine and then developed urinary incontinence, which was successfully treated with ephedrine.

Case report. Mr. A, a 61-year-old white male veteran with a history of bipolar I disorder and alcohol abuse, was admitted to our hospital for acute mania, psychosis, agitation, and verbalization of homicidal thoughts. Previous treatment with thioridazine and lithium as well as a double-blind, experimental drug (either risperidone or haloperidol taken with lithium) had been unsuccessful owing to noncompliance and severe extrapyramidal symptoms, respectively. Therefore, on admission, Mr. A was started on treatment with olanzapine in addition to lithium, which he was already taking. Four days later, he complained of urinary incontinence. Urinalysis, culture, and sensitivity results and physical findings were within normal limits. Urodynamic testing was not conducted. On day 6, Mr. A was started on ephedrine, 25 mg daily, and his urinary incontinence resolved within 24 hours. Eight days after admission, he was discharged on treatment with olanzapine, lithium, ephedrine, and a multivitamin.

This case suggests that ephedrine may be useful to treat olanzapine-induced urinary incontinence in patients with bipolar disorder. Similar to clozapine and risperidone, olanzapine possesses significant α_1-antagonist effects.[3] This may account for the occurrence of urinary incontinence with olanzapine as well as ephedrine's efficacy in resolving this disorder. The use of ephedrine may be a viable clinical intervention to counteract urinary incontinence induced by atypical antipsychotic medication when treating the spectrum of psychosis.

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Possible Connection Between Panic Disorder and Epilepsy

Sir: Roy-Byrne and colleagues[1] found that epilepsy appeared concurrently with panic disorder at a statistically significant rate in their patient sample. They make, however, only brief note of and do not discuss this finding.

There are other reports that epilepsy appears with a higher incidence in panic patients than in the general population. Some authors suggest the existence of a connection between panic attacks and seizures, and perhaps between panic disorder and epilepsy.[2,3] It may therefore be of interest if the authors could describe how many of their patients with panic and epilepsy had generalized seizures versus partial seizures. How many patients were given anticonvulsants? (Anticonvulsants are not included in their list of medications.) Of these, in what proportion of cases was the anticonvulsant the antipanic medication? And what, if any, was the cost of diagnosis, treatment, and disability specifically related to epilepsy in the panic patients?

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Dr. Roy-Byrne Replies

Sir: Data on medical illness in our study[1] were derived from prescribed medications reportedly used by patients. Hence, we know nothing about the kinds of seizures patients may have had. Of the 4 patients (4.9%) in this category, 3 were taking phenytoin and 1, valproate. It is unlikely that these patients were taking these medications, prescribed by primary care physicians, for panic. The cost of diagnosis, treatment, and disability related to epilepsy cannot be estimated from this small number of patients.

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A Possible Case of Quetiapine Withdrawal Syndrome

Sir: We present a possible case of a previously unreported discontinuation syndrome from quetiapine. The syndrome consisted of diaphoresis, elevated blood pressure, emesis, lightheadedness, nausea, nervousness, orthostatic hypotension, and tachycardia.

Case report. Ms. A, a 21-year-old woman, had symptoms of schizophrenia, undifferentiated type, for 7 years. She had tolerated prior treatment with haloperidol, lorazepam, paroxetine, quetiapine, risperidone, and venlafaxine, but without satisfac-

tory improvement. This lack of improvement led to her frustration with treatment and suicidal ideation for which she was hospitalized. Her daily medications were benztropine, 1 mg; haloperidol, 6 mg; and quetiapine, 300 mg. On admission, we stopped those medications and started fluoxetine, 10 mg/day, and risperidone, 2 mg/day.

Ms. A became diaphoretic 20 hours after her outpatient regimen was stopped. About 36 hours after her last quetiapine dose, she complained of light-headedness, nausea, nervousness, and vomiting. Her orthostatic pulse and blood pressure were 120 b.p.m. and 130/80 mm Hg supine and 140 b.p.m. and 118/75 mm Hg standing. Her baseline supine pulse and blood pressure were 80 b.p.m. and 110/60 mm Hg, respectively.

We speculated that Ms. A was withdrawing from quetiapine and gave her quetiapine, 100 mg, and promethazine, 25 mg. Her symptoms resolved in 1 hour, and her vital signs returned to baseline levels. Ms. A then received 300 mg of quetiapine in addition to fluoxetine, 10 mg/day, and risperidone, 2 mg/day, without similar incident. There was also no similar incident as quetiapine was slowly cross-tapered with risperidone during a month of outpatient treatment. Haloperidol and benztropine were not restarted.

Ms. A reported 3 similar episodes upon stopping quetiapine on her own in the 4 months she had been taking benztropine, haloperidol, and quetiapine. Her symptoms resolved each time within an hour of resuming the medication. She stated that she stopped quetiapine because it sometimes made her feel "drugged up." Each time, Ms. A denied missing her other medications because the regimen generally helped make her thinking more "clear."

Possible explanations exist for the withdrawal syndrome. One is the "adrenergic overdrive theory."[1] Quetiapine is an α-adrenergic and serotonin-2 (5-HT_2) antagonist.[2] Both actions can result in adrenergic receptor up-regulation. Therefore, discontinuing the drug can result in adrenergic rebound, which could explain the patient's tachycardia and increased blood pressure from baseline. A possible problem with this explanation is that quetiapine has been shown to decrease striatal 5-HT_2 receptor density.[2] However, its effect on 5-HT_2 receptor density in other parts of the brain has not yet been clearly established in published studies.

The second potential mechanism is supersensitivity to dopamine. Quetiapine's antidopaminergic activity[2] is antiemetic and can cause up-regulation of dopamine receptors in specific parts of the brain. Supersensitivity to dopamine on withdrawal could lead to nausea and vomiting.[3] These symptoms may explain the patient's dehydration and orthostasis. A possible limitation with this explanation is that chronic administration of quetiapine has not been shown to increase the density of striatal dopamine D_2 receptors in rats.[2] However, quetiapine is known to act preferentially on mesolimbic dopaminergic neurons.[4] Its effect on dopaminergic receptor density in other parts of the brain is not yet established in published studies.

The third potential mechanism is supersensitivity to acetylcholine. Dopamine antagonists can inhibit acetylcholine release, causing an up-regulation of cholinergic receptors and supersensitivity to acetylcholine.[3] Upon withdrawal of quetiapine, the supersensitivity may explain the patient's symptoms of diaphoresis, emesis, nausea, nervousness, and tachycardia, all consistent with possible cholinergic rebound. Dopamine antagonism's effect on postsynaptic acetylcholine may explain the resolution of cholinergic rebound on restarting quetiapine.

Quetiapine is also a histamine H_1 antagonist and has affinity for the sigma receptor.[5] However, it is unclear how these actions affected our patient because there are no clearly published studies on discontinuation syndromes from pure antihistaminergic or sigma agents.

Finally, withdrawing benztropine and haloperidol may explain the patient's symptoms. However, the rapid response to quetiapine reintroduction and the patient's history of similar symptoms on withdrawal of quetiapine alone make quetiapine withdrawal a more likely explanation. Further investigation is needed, but this experience suggests that tapering quetiapine is better tolerated and likely to improve patient treatment adherence.

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