Psychiatric Genetics

Sir: The recent survey by Dr. Finn and colleagues[1] (July 2005) provided useful insight into a psychiatrist's need to be more knowledgeable about genetic issues in our field. However, one problem in acquiring this knowledge, at this time, is the lack of clarity as to what are the actual recurrence risks for many of the common psychiatric illnesses we treat. An example illustrating this problem is the estimated risk for bipolar disorder quoted[2] in this survey (in Table 2 of the article by Finn and colleagues[1]), i.e., 4% to 18% in a first-degree relative of the proband.

There would appear to be 2 issues with this quoted risk. First, an upper estimate of risk (18%) that is greater than 4-fold the lower estimate (4%) leaves the clinician with rather imprecise data to use in the genetic counseling process. Better, controlled studies are necessary to help make our task in this process more accurate and, I dare say, more creditable to our patients.

Second, the authors of the survey did not point out that this risk range reflects the risk of only bipolar illness to relatives of bipolar patients. In point of fact, such relatives are at risk for all forms of affective illness, thus making the relative risk to first-degree relatives clearly greater than that stated in the survey. The review by Smoller and Finn[2] reports that there is an additional 6% to 22% risk for unipolar illness in first-degree relatives of bipolar probands; the weighted average risk for any affective illness to a first-degree relative of a bipolar proband is approximately 23%. This latter number is similar to that estimated in other prior reviews.[3–5] Regardless of the lack of preciseness of the existing data, it is important for clinicians not to underestimate the potential risk of illness in their discussions with patients and families.

Dr. Feinberg reports no financial or other relationship relevant to the subject of this letter.

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Sir: I found the article by Finn et al. in the July 2005 issue[1] to be a penetrating look at how psychiatrists approach and avoid genetic issues, given limited scientific expertise in this area. Advising patients about things we do not know much about ought to give us pause. We risk imposing our values on our patients. We are on soft moral ground when we do.

I was struck by the responses to the pregnancy scenario (question 5 of the survey included in that study), in which respondents tackled the imaginary situation in which a fetus ran a quantifiable risk of developing various psychiatric conditions. Respondents then offered either nondirective counsel or advice to continue or terminate the pregnancy. With the exception of anencephaly, about 70% opted for nondirective information. I was surprised that psychiatrists recommended terminations in cases of autism (20%), Down syndrome (19%), schizophrenia (12%), and antisocial personality disorder (10%) as often as they did. Acknowledging the hypothetical nature of this scenario, it still is remarkable that these percentages are so high. This suggests to me that psychiatrists may be quicker to recommend termination than perhaps their patients and/or other physicians might suspect. Without question, these disorders can be profoundly distressing, disabling, and burdensome to those afflicted and those around them. Nevertheless, recommending termination of pregnancy in such cases is to equate it with anencephaly, a condition with a much more uniformly bleak prognosis.

The scenario does not address whether these doctors were to consider this a consultation with people who were not already their patients. I would suggest that directive information may be more easily made when there is no previous doctor-patient relationship. Clearly, this was a minority of respondents dealing with a circumstance that may never come to pass and can only be answered in the abstract. Some psychiatrists' experiences with these disorders could lead them to recommend termination out of compassion. That is a position worthy of respect, although physicians need to be particularly careful about using their professional authority in value-laden decisions.

I am not aware of any recent data concerning psychiatrists' attitudes toward abortion in general or in situations such as those the study attempts to explore. I speculate that psychiatrists tend to be more politically liberal and less religious than the general population. It may also be true that, as advocates for our own patients burdened by such a pregnancy in the context of mental illness, we may see termination as the better choice sometimes. The issue here is not about one's politics or one's religion; rather, it is about being honest about whether or not our recommendations are based on medical knowledge.

Dr. Moldawsky reports no financial or other relationship relevant to this letter.

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Dr. Finn and Colleagues Reply

Sir: We thank Drs. Feinberg and Moldawsky for their comments and agree with their cautions regarding the communication of genetic risks to patients and their families. As Dr. Feinberg notes, empirical recurrence risk estimates available from family studies of psychiatric illnesses lack precision. Of course, this is a problem that applies to many complex disorders,

but is a particular issue in psychiatry, where diagnostic criteria and their implementation can have a significant impact on rates. The familial risks cited in our article reflected a range of estimates reported in the literature; we used a range to avoid being overly stringent in evaluating the accuracy of risks estimated by respondents to our survey. There are, as Dr. Feinberg points out, additional risks that might be relevant in an actual clinical setting (e.g., the risk of unipolar disorder in relatives of bipolar probands or the risk of comorbid disorders in relatives of patients with comorbidities). Several references are available for mental health clinicians who would like to learn more about genetic risks and communication of risks for psychiatric disorders.[1–4] Also, Web-based resources for locating updated genetic information (e.g., Online Mendelian Inheritance in Man [OMIM], http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM; Genetics Resources on the Web [GROW], http://www.geneticsresources.org/) may be of interest. In addition, the National Coalition for Health Professional Education in Genetics (NCHPEG, http://www.nchpeg.org) has developed educational materials for physicians, including a tutorial on the genetics of major psychiatric disorders. Finally, consultation with genetics professionals can be a valuable resource for clinicians and their patients.

Dr. Moldawsky notes that a substantial minority of respondents to our survey indicated they would provide directive counseling in response to a hypothetical scenario involving prenatal genetic testing. He expresses concern that, in some cases, counseling may be influenced by factors other than medical knowledge. We concur that psychiatrists should be aware, in all clinical encounters, of the limitations of their knowledge and ways that practice may be inappropriately influenced by personal biases. As he points out, the counseling scenario presented in our survey involving a highly predictive prenatal test may never become a clinical reality for many psychiatric disorders. Nevertheless, we believe our study highlights several issues that deserve attention if advances in genetics are to inform psychiatric practice. At a minimum, increased education of psychiatrists about genetics, including the complexities and limitations of our current understanding, will be important in the coming years.

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Electroencephalographic Abnormalities Associated With Antidepressant Treatment: A Comparison of Mirtazapine, Venlafaxine, Citalopram, Reboxetine, and Amitriptyline

Sir: Abnormalities in electroencephalography (EEG) recordings may occur during treatment not only with antipsychotics, but also with antidepressants.[1,2] Mirtazapine and venlafaxine, 2 potent novel antidepressants that are regarded as being safer in terms of neurotoxic side effects compared to tricyclic antidepressants (TCAs), have recently been associated with a proconvulsant action.[3,4] To compare the occurrence of EEG abnormalities during mirtazapine and venlafaxine treatment with EEG changes during treatment with antidepressants of other substance classes, including TCAs, we retrospectively analyzed EEG recordings of 255 patients undergoing antidepressant monotherapy with mirtazapine, venlafaxine, citalopram, reboxetine, or amitriptyline.

Method. Patients were diagnosed according to the *International Classification of Diseases*, 10th Revision (ICD-10), criteria (some patients had more than 1 diagnosis): 188 with a major depressive episode (ICD-10: F 31/32/33.xx); 39 with anxiety, obsessive-compulsive, adjustment/acute distress, or somatoform disorders (F 40/41/42/43/45.xx); 19 with schizophrenia or schizoaffective disorder (F 20/25.xx); 9 with dysthymia (F 34.1x); and 9 with personality disorders (F 60.xx). Digital EEGs recorded at wakeful resting states (≥ 20 minutes, including hyperventilation, no sleep tracings) were tracked using a Brain Vision Database (Version 0.93, Brain Products, Munich, Germany) and visually interpreted independently by 2 experienced raters (A.S., O.P.), one of whom was blind to medication, dosage, and diagnosis (A.S.). The findings were classified as normal or abnormal, i.e., with or without intermittent slow waves, slow posterior dominant rhythm, exaggerated response to hyperventilation, and epileptiform activity, as previously reported.[5]

Results. Demographic characteristics of patients and the mean dosage of antidepressants are presented in Table 1. Six patients in the mirtazapine group, 9 in the venlafaxine group, 4 in the citalopram group, none in the reboxetine group, and 5 in the amitriptyline group had abnormal EEG findings (Table 1). Abnormal EEG patterns were intermittent slow waves (mirtazapine, citalopram, venlafaxine, and amitriptyline), slow posterior dominant rhythm (amitriptyline and mirtazapine), and exaggerated response to hyperventilation (amitriptyline, venlafaxine, and mirtazapine). No epileptiform activity was observed in any patient. The frequency of EEG abnormalities varied but was generally low (0% to 18%) and not statistically significantly different among groups ($\chi^2 = 7.54$, df = 4, p = .11; N = 225). Patients with abnormal and patients with normal EEG patterns did not significantly differ by dosage. Only in the mirtazapine group was a statistical trend toward higher dosages in patients with EEG abnormalities found (p = .064).

In contrast to the extensive body of literature on the action of tricyclics and first-generation selective serotonin reuptake inhibitors (SSRIs) on EEG activity,[6,7] mirtazapine, venlafaxine, second-generation SSRIs, and reboxetine are less well studied in this respect.[8] Recently, mirtazapine was found to induce EEG abnormalities with epileptiform patterns in both healthy volunteers and depressed subjects at therapeutic levels,[3] and venlafaxine has been reported to provoke seizures in overdose (≥ 900 mg) at a higher rate than TCAs.[4] In the present study, intermittent slow-wave activity during treatment with venlafaxine, mir-

Table 1. Demographic Characteristics, Mean Dosage of Antidepressants, and Results of Visual Assessments of Electroencephalographic (EEG) Recordings in 255 Patients

Variable	Amitriptyline (N = 45)	Citalopram (N = 58)	Venlafaxine (N = 50)	Mirtazapine (N = 80)	Reboxetine (N = 22)	p Value
Sex, F/M, N	33/12	31/27	26/24	49/31	11/11	.17[a]
Age, mean ± SD, y	50.02 ± 14.12[b]	40.57 ± 15.87[b]	45.90 ± 14.27	49.35 ± 15.49[b]	44.32 ± 15.67	< .01[b]
Daily dose of medication, mg						
Mean ± SD	86.00 ± 49.70	30.17 ± 15.84	151.25 ± 71.94	36.66 ± 13.23	6.18 ± 2.38	
Range	10–250	10–60	37.5–350	15–60	2–8	
EEG findings						
Normal EEG, N (%)	40 (88.9)	54 (93.1)	41 (82.0)	74 (92.5)	22 (100)	
Abnormal EEG, N (%)	5 (11.1)	4 (6.9)	9 (18.0)	6 (7.5)	0 (0)	.11[c]
ISW, N	4	4	9	5	0	
With ERH	1	0	4	3	0	
SPDR, N	1	0	0	1	0	
With ERH	0	0	0	0	0	
With ISW	0	0	0	1	0	
EA, N	0	0	0	0	0	

[a] $\chi^2 = 6.47$, df = 4, p = .17; N = 255.
[b] One-way analysis of variance: significant difference between groups (F = 3.7, df = 4,250; p < .01): amitriptyline- and mirtazapine-treated patients were significantly older than citalopram-treated patients (Scheffé test, p = .045 and p = .025, respectively).
[c] $\chi^2 = 7.54$, df = 4, p = .11; N = 255.
Abbreviations: EA = epileptiform activity, ERH = exaggerated response to hyperventilation, ISW = intermittent slow waves, SPDR = slow posterior dominant rhythm.

tazapine, and citalopram was observed, but no epileptiform patterns occurred. Descriptively, there were clear differences in the frequency of EEG alterations between groups; however, these differences did not reach statistical significance. The retrospective design and moderate sample sizes limit a further interpretation of the data in this respect. It is remarkable that no EEG abnormalities were observed during reboxetine treatment. This observation converges with previous findings suggesting a favorable action of reboxetine on cognitive and psychomotor functions.[9,10]

In conclusion, the current study supports the safety of mirtazapine and venlafaxine in contrast to recent reports of epileptogenic activity. Prospective studies in larger sample sizes including at-risk patients, e.g., patients with cerebral disorders, are now needed to further assess the safety of antidepressants regarding their potential to induce EEG abnormalities.

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

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Panic Attacks Associated With Topiramate

Sir: Although topiramate is not registered in Switzerland for the treatment of bipolar disorder, it is widely prescribed for this disorder, especially in patients suffering from comorbid conditions such as weight gain.[1] We report a patient who experienced panic attacks associated with topiramate treatment.

Case report. Ms. A, a 27-year-old woman with bipolar II disorder (according to the Structured Clinical Interview for DSM-IV Axis I Disorders[2]), had, in 2004, been stabilized for 3 months with lithium, 1200 mg/day. A weight gain justified a

switch to topiramate. In view of the clinical experience of one of the authors (S.W.) in using topiramate for bipolar disorders, we proposed to stabilize the patient at 150 mg/day using a graded regimen with an initial dose of 25 mg/day, increasing by 25 mg weekly.

During topiramate treatment, the patient remained euthymic and lost 3 kg over 4 weeks. However, when 150 mg/day was reached, she experienced panic attacks that included shortness of breath, increased heart rate, and muscle tightness. She had no history of panic attacks before introduction of topiramate. The panic attacks stopped entirely 2 weeks after discontinuation of topiramate, and the patient refused further mood-stabilizing drugs. Two months after topiramate discontinuation, she experienced a hypomanic episode (DSM-IV criteria) without psychotic symptoms, which necessitated hospitalization. With the patient's compliance, topiramate was reintroduced by a psychiatrist who was skeptical about the association between panic attacks and topiramate. When the topiramate dose was increased from 100 to 150 mg/day (same dosing protocol), the patient again experienced panic attacks. The panic attacks disappeared 1 week after switching from topiramate to lamotrigine, 15 mg/day. The patient has remained euthymic since introduction of lamotrigine (4 months) and has experienced no further panic attacks. A detailed patient history allowed us to exclude interactions with other medication as an explanation of the panic attacks.

In a systematic review of the MEDLINE and Cochrane Library databases (range of years: 1970–2005; languages: English, French, and German; keywords: *panic attack*, *topiramate*, and *anxiety*), we found only 1 other case report of panic attacks associated with topiramate,[3] concerning a 24-year-old woman with bipolar II disorder. Panic attacks occurred when 50 mg/day of topiramate was added to treatment with 100 mg/day of lamotrigine; the panic attacks disappeared 2 weeks after discontinuation of topiramate, while treatment with lamotrigine monotherapy continued. A prospective study researching the prevalence of adverse psychiatric events in 103 patients with epilepsy treated with topiramate revealed that 10.7% of patients had affective disorders; 3.7%, psychotic disorders; 5.6%, aggressive behavior; and 3.9%, other behavior abnormalities such as agitated behavior, anger, or anxiety.[4]

The carbonic anhydrase properties of topiramate could theoretically lead to CO_2 retention and trigger the occurrence of panic attacks in patients with a specific vulnerability.[5] Considering the elevated comorbidity of panic disorder associated with bipolar disorders, clinicians who treat patients with topiramate should pay special attention to the possibility of induction or exacerbation of panic attacks. More studies are warranted to elucidate individual differences between patients concerning the influence of topiramate on anxiety level, as well as differences in the neurobiological bases underlying individual anxiety disorders.

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Ziprasidone-Induced Acute Dystonic Reactions in Patients With Bipolar Disorder

Sir: We have recently observed 2 cases of acute dystonic reactions in ziprasidone-treated patients with bipolar disorder. Although characterized by relatively high dopamine-2 (D_2) binding, ziprasidone has been associated with a low rate of extrapyramidal symptoms and dystonia.[1,2] Of 4 early clinical trials with ziprasidone,[3–6] only 1 trial, in patients with schizophrenia and schizoaffective disorder, has reported any dystonia.[3] That 3-week trial of intramuscular and oral ziprasidone[3] noted a 3.7% incidence in 425 patients, but was unclear as to how dystonia was defined. Three studies of ziprasidone that together included 187 patients with bipolar disorder, and 21 patients with schizoaffective disorder, failed to report any dystonic reactions in these subjects.[5,7,8]

Four published case reports describe single episodes of dystonia in ziprasidone-treated patients across several diagnoses. An 11-year-old boy diagnosed with attention-deficit/hyperactivity disorder and developmental delay experienced an oculogyric crisis after receiving 40 mg/day of ziprasidone for 6 weeks. Symptoms rapidly resolved with diphenhydramine.[9] A 31-year-old woman with psychotic symptoms developed torticollis after receiving 80 mg/day of ziprasidone for only 2 days. Symptoms resolved with a combination of benztropine and diphenhydramine.[10] Pisa syndrome was observed in a 38-year-old woman who had received 80 mg/day of ziprasidone for 2 weeks. Symptoms resolved only gradually, over 3 weeks.[11] A 53-year-old schizophrenic man who received 160 mg/day of ziprasidone for 3 days developed a dystonic reaction that was also successfully treated with diphenhydramine. The authors suggested that rapid dose escalation may have contributed to this episode.[12]

Case 1. Mr. A, a 27-year-old African American man, was hospitalized in March 2005 with manic symptoms including irritability with labile affect, rapid speech, disorganized thoughts, and mood-congruent delusions and hallucinations. After a full evaluation, including collateral history from his family and a Structured Clinical Interview for DSM-IV (SCID),[13] he was diagnosed with a first episode of bipolar mania. He had never received psychotropic medications prior to beginning ziprasidone, which was rapidly titrated to 100 mg b.i.d. over 3 days. Within 1 day of reaching the target ziprasidone dose of 200 mg daily, the patient experienced an episode of torticollis, which rapidly resolved with 50 mg of IM diphen-

hydramine. His medication was changed to olanzapine, and symptoms did not recur.

Case 2. Ms. B, a 20-year-old African American woman, was hospitalized in August 2004 with irritability, disorganized thought, decreased need for sleep, increased energy, and mood-congruent delusions. She had been seen briefly in the past by the psychiatric emergency services of the University Hospital, but had not received sustained treatment since being diagnosed with bipolar disorder 2 years prior to her current presentation. Ziprasidone was started at 80 mg b.i.d. and continued for 2 days, until the patient was observed to have dystonia of her jaw and mouth. She received 2 mg of benztropine, with rapid resolution of symptoms. The patient was restarted on ziprasidone, without recurrence of her dystonic symptoms, and discharged. She was later readmitted with subsequent mood episodes, confirming her bipolar diagnosis.

A MEDLINE search using the keywords *ziprasidone* and *dystonia* revealed no previous reports of dystonic reactions in bipolar patients, either as single case reports or as part of a larger study, despite some previous observations of increased incidences of dystonia and extrapyramidal symptoms in patients with affective disorders.[14,15] Our observation of 2 incidents of an acute dystonic reaction in bipolar patients during just 1 year suggests that dystonia may be underdiagnosed or at least underreported in affective, particularly manic, patients. Both of these cases occurred within a few days of rapid dose titration, as did 2 previously reported cases.[10,12] Clinicians prescribing ziprasidone should be vigilant for dystonia in bipolar patients, particularly with rapid dose escalation.

Dr. Adler has received research support from AstraZeneca and Janssen and has served as a consultant for AstraZeneca and Eli Lilly. Dr. Strakowski has been a consultant for Pfizer, Ortho-McNeil, Janssen, and Eli Lilly; has received grant/research support from Janssen, Eli Lilly, AstraZeneca, and Forest; has received honoraria from Pfizer, Ortho-McNeil, Janssen, Eli Lilly, and AstraZeneca; and has served on the speakers or advisory boards for Pfizer, Ortho-McNeil, Janssen, Eli Lilly, AstraZeneca, and Bristol-Myers Squibb. Ms. Weinstein reports no financial or other relationship relevant to the subject of this letter.

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Monosymptomatic Hypochondriacal Psychosis or Tardive Dystonia?

Sir: We read with interest the letter to the editor by Chand et al.[1] The case inspired us to remember a patient presented with the clinical picture of monosymptomatic hypochondriacal psychosis (MHP) who died in our department 11 years ago. He was in his forties, and his earliest complaints were weakness, tiredness, stomach "butterflies," and poor sleep. He was treated with benzodiazepines, promazine, and antidepressants. Shortly after that, he started to complain of having a lump in his throat that prevented him from swallowing food or even liquids. He was evaluated by multiple medical specialists and underwent endoscopy, laryngoscopy, barium swallow, chest x-ray, and blood tests. No test revealed abnormalities. He was severely constipated, and he experienced profound weight loss. He was hospitalized and diagnosed as having MHP, and treatment with fluphenazine was tried. His health deteriorated progressively, and although we repeated diagnostic tests and increased the dosage of fluphenazine up to 15 mg/day and added biperiden (due to postural tremor), 6 mg/day, and promazine, 300 mg/day, he became anergic and died from aspiration pneumonia.

Later analysis of the case reminded us that we did not take into account the possibility of monosymptomatic tardive dystonia caused by fluphenazine, or even earlier by antiemetics or antidepressants, that might have had the same presentation. Eleven years ago we were unable to try treatment with atypical antipsychotics, which could have been effective. Tardive dystonia might be rare, but is a serious complication of antipsychotics and even of antidepressants or antiemetics.[2]

Chand and colleagues stressed their point regarding the successful use of olanzapine and did not, probably because of space shortage, extensively explain the beginning of the patient's illness and the first encounter of the patient with neurotropic drugs.

In conclusion, because MPH patients represent a complex and difficult-to-treat patient population, ongoing assessment of differential diagnosis is critical. Tardive dystonia should be considered in the differential diagnosis of such a presentation of MHP.

The authors report no financial affiliation or other relationship relevant to the subject of this letter.

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Dr. Chand and Colleagues Reply

Sir: We read the letter by Drs. Aukst-Margetić and Margetić in response to our case report published in the June 2005 issue.[1] In their letter, the authors describe a patient suspected of having tardive dystonia of the esophagus. Their patient had initially presented with nonspecific complaints of weakness, poor sleep, and stomach "butterflies" and had been treated with dopamine-blocking drugs and antidepressants, following which he started complaining of a lump in his throat and inability to swallow. He later had worsening following treatment with typical antipsychotics and had an unfortunate death due to aspiration pneumonia.

Although the case that we reported shares some common features with the case described by Drs. Aukst-Margetić and Margetić, the onset and course of illness in our patient were different. His complaint at the onset of illness, 5 years back, was that he had cancer of the esophagus and hence had difficulty in swallowing. He had partial improvement with typical neuroleptics but had discontinued treatment, leading to worsening. He showed good response to olanzapine and later had a relapse after he discontinued the medication, with subsequent improvement after restarting olanzapine.

The evolution of symptoms, the delusion that he had cancer of the esophagus, his response to neuroleptic treatment, and the amelioration rather than worsening of symptoms on neuroleptic reinstitution goes against the possibility of tardive dystonia of the esophagus in the case that we described. Drug-induced dystonia could be hypothesized to have caused the deterioration of the patient described by Aukst-Margetić and Margetić. However, it seems doubtful whether the term *tardive* can be used in their case, as the patient's dysphagia is mentioned to have developed "shortly" after treatment with dopamine-blocking agents. Tardive syndromes typically develop after prolonged exposure to dopamine-blocking agents.[2]

Nevertheless, we do agree that tardive dystonia of the esophagus should be kept as a differential diagnosis in a patient presenting with complaints of a lump in the esophagus, especially if dysphagia had developed after prolonged treatment with antipsychotics.

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