Letters to the Editor

Valproate-Induced Parkinsonism in a Demented Elderly Patient

Sir: Valproate is an antiepileptic drug used for the management of aggressive and violent behavior in elderly patients with dementia. Among the various drugs used, valproate is an effective drug that is well tolerated in elderly patients with dementia.[1,2] A recent report by Lindenmayer and Kotsaftis[3] found that the most frequent diagnoses in nonbipolar patients with aggressive and violent behavior to whom valproate was administered were dementia, organic brain syndrome, and mental retardation. Sedation, drowsiness, and confusion are believed to be the common side effects of valproate. Development of reversible, valproate-induced parkinsonism is one of the insidious side effects found with chronic use of valproate.[4] However, valproate-induced acute and reversible parkinsonism in elderly demented patients has not hitherto been reported.

I recently encountered a case of acute parkinsonism during valproate administration in a patient with dementia accompanied by aggressive and violent behavior.

Case report. Mr. A, at the age of 76 years, had no history of movement disorders or parkinsonism but developed DSM-IV dementia of the Alzheimer's type. Valproate was introduced when he was 77 years of age because of exacerbation in aggressive and violent behaviors. His only concomitant medication was aniracetam, and no antipsychotics were being administered at that time. The valproate dose was gradually increased to 300 mg/day, at which a blood level of 11 μg/mL was established (50–100 μg/mL being the therapeutic range for anticonvulsant activity). However, the patient began to display signs of parkinsonism such as resting tremors, rigidity, gait disturbance, and bradykinesis after 1 week of treatment with valproate. His score on the Unified Parkinson's Disease Rating Scale (UPDRS)[5] increased from 18 at admission (he had cognitive decline and disturbances of activity of daily living due to dementia) to 59 after the administration of valproate. Since the signs of parkinsonism did not change in severity over the next 2 weeks, the administration of valproate was discontinued. These signs of parkinsonism gradually disappeared, and no relapses of symptoms were observed in the following days. Brain computed tomography revealed moderate cerebral atrophy and ventricular dilatation without remarkable vascular lesions. An electroencephalogram showed a normal amplitude of 9 Hz background activity during waking, albeit with normal blocking reaction.

This case is, to my knowledge, the first report of valproate-induced acute parkinsonism in an elderly patient with dementia, in which extrapyramidal effects were encountered on short-term therapy with a low dose of valproate yielding a low serum level. Although the mechanism of parkinsonism during valproate treatment is not known, the mechanism might be resulting from the dysfunction of the mitochondrial enzyme NADH CoQ reductase (complex I) of the respiratory chain prompted by valproate, or to excessive activity of γ-aminobutyric acid (GABA) neurons in the globus pallidus externa produced by GABAergic activity of valproate.[4] While the reason why psychotic symptoms did not relapse after the discontinuation of valproate was unclear, valproate might have changed the balance of GABAergic neurotransmission that caused the aggressive and violent behaviors. Coadministration of another psychoactive drug had a small possibility of making extrapyramidal symptoms worse. Because old age increases the risk of developing extrapyramidal symptoms,[4] I expect that this side effect of valproate will be regularly observed in psychogeriatric patients when carefully monitored over time.

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Hyperinsulinemia in Psychiatric Patients Treated With Olanzapine

Sir: We read with great interest the article by Melkersson and colleagues published in the October 2000 edition of the *Journal*.[1] We are involved in a similar study in Toronto, Ontario, Canada, on weight gain and associated health risks in patients receiving antipsychotic treatment.

Impaired glucose homeostasis in patients with schizophrenia and in association with antipsychotic medication treatment is currently a focus of much attention from a clinical and research perspective.[2–7] The finding by Melkersson et al. of fasting hyperinsulinemia in patients treated with olanzapine is particularly important since insulin resistance and consequent hyperinsulinemia may well be the mechanism underlying an apparent increased rate of diabetes in these patients.

In a group of patients in our study (7 men and 4 women) who were on treatment with olanzapine, the mean ± SD age was

34.6 ± 9.2 years, the mean daily dose was 11.6 ± 4.1 mg, and the mean treatment duration was 22.6 ± 10.6 months. In these patients, the mean fasting insulin level was 88.9 ± 52.5 pmol/L (range, 33–196 pmol/L), the mean fasting plasma glucose level was 5.5 ± 0.86 mmol/L (range, 4.5–7.7 mmol/L), the mean fasting triglyceride level was 3.0 ± 1.9 mmol/L (range, 1.17–7.39 mmol/L), and the mean body mass index (BMI) was 30.8 ± 5.9 (range, 22.4–38.7). Four patients (2 men and 2 women) were receiving concurrent medication that could affect body weight and/or glucose homeostasis, including 1 diabetic patient receiving oral antidiabetic medication, 2 patients receiving divalproex sodium, and 1 receiving topiramate.

We measured insulin levels using a commercially available radioimmunoassay kit (Pharmacia Insulin RIA 100, Pharmacia and Upjohn Diagnostics, Sweden). The assay was performed by an experienced laboratory, the Banting and Best Diabetes Centre in Toronto. We understand that Melkersson et al. measured the insulin levels by a similar radioimmunoassay technique using guinea pig antiserum.[8,9] According to Thoren et al.,[10] these 2 assays correlate well ($r = 0.98$) and are comparable. Therefore, we used the suggested conversion formula to calculate the corresponding values for our fasting insulin data.

Although the mean fasting triglyceride levels and mean fasting plasma glucose levels were similar to the findings of Melkersson et al., the mean fasting insulin levels were lower (143 pmol/L vs. 228 pmol/L). Thirty-six percent of our subjects had hyperinsulinemia compared with 71% in the study by Melkersson et al. according to the cutoff point of 144 pmol/L. We were not able to explain the difference between the 2 studies by the use of concurrent medication in our patients (see above), since the mean fasting insulin level was higher in the patients receiving concurrent medication than in the remaining group. Could the difference in insulin levels between the subjects in the study by Melkersson and colleagues and our own subjects be due to differences in measurement, differences in age or ethnicity, the fact that our patients had been receiving olanzapine longer, or differences in BMI?

As we move closer to understanding the mechanisms involved in antipsychotic-induced weight gain and dysregulation of glucose homeostasis, it is important to account for variability of results and clarify issues of measurement.

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No Complications With Risperidone Treatment Before and Throughout Pregnancy and During the Nursing Period

Sir: Most psychiatric disorders among women arise in the childbearing years, particularly in the perinatal period.[1] This presents a dilemma in treatment management. Prenatal exposure of the fetus to psychotropic drugs carries the risk of teratogenicity.[2] However, when medications are not taken or are discontinued during pregnancy, there is evidence that patients may be at high risk for relapse,[3,4] and there is a possible direct effect of maternal illness on the fetus, for example, impaired ability to obtain prenatal care,[5] increased risk of impulsive and/or dangerous behavior,[6] and obstetric complications.[7]

The safety of psychotropic drugs has not been established in human pregnancy; therefore, the risks and benefits of their use have to be carefully considered.[3] Among the typical antipsychotics, an increase in congenital abnormalities has been observed.[8] There is no evidence of teratogenicity for atypical antipsychotics, although the only data available are from a few letters and case reports on the use of clozapine and olanzapine.[8–14]

To the best of our knowledge, these are the first case reports of risperidone used before and throughout pregnancy and during the nursing period.

Case 1. Ms. A, a 39-year-old Afro-Caribbean woman, has a diagnosis of schizophrenia (DSM-IV criteria) with second- and third-person auditory hallucinations and persecutory delusions. She had been taking chlorpromazine, without much symptomatic control, in her home country and until she presented to the U.K. psychiatric services 4 years ago. She was started on risperidone treatment at 2 mg/day, gradually increasing to 4 mg/day over a few weeks when good symptom control was achieved. For no apparent reason, Ms. A was occasionally noncompliant with her medication and at these times she rapidly relapsed. On each occasion of relapse, the same regimen would be instituted and she responded well.

When she became pregnant at the age of 36 years, she was married to a man of the same ethnicity and had been taking risperidone for over 2 years. However, this was her first pregnancy, and she did not tell anyone that she was pregnant until the end of the third month of pregnancy. The decision was made to continue her medication due to the high risk of relapse and because the pregnancy was past the first trimester. However, the team of obstetricians, who managed the prenatal care and delivery, frequently monitored both mother and fetus, particularly with monthly ultrasonography and measurements of alpha-

fetoprotein levels. To ensure Ms. A's cooperation at term, the baby boy, who weighed 8 lb, was delivered by elected cesarean section. At and since birth, a pediatrician has regularly assessed the child every 3 months. No developmental abnormalities have been found after 9 months.

Case 2. Ms. B, a 30-year-old woman of Asian descent, was born in the United Kingdom and married to a man who was also of Asian descent. She was suspicious and talked to herself when she initially presented to our treatment center 4 years ago. She was subsequently diagnosed with schizophrenia (DSM-IV criteria). A mental state examination revealed that she had persecutory delusions, auditory hallucinations in the second and third person, and negative symptoms. She was started on treatment with risperidone at 2 mg/day, and this dose was gradually increased until control of symptoms was attained at 6 mg/day.

When Ms. B became pregnant 3 years later, she told nobody for at least 2 months. However, since there was a strong risk of relapse with this patient, the decision was made to continue risperidone treatment even after she disclosed her pregnancy. Obstetricians and pediatricians delivered the same intensive support to this woman and child as reported in Case 1. A girl was delivered at term by elected cesarean section weighing 5 lb, 13 oz. No developmental abnormalities have been found in the child after over 1 year.

Withholding antipsychotic treatment was considered to increase the risk of exacerbation of psychosis, an outcome that may ultimately have been more dangerous to mother and child than continuation of risperidone. Risperidone combined with psychosocial support allowed both women to cooperate with prenatal care and to manage their child.

These case reports support the findings of a postmarketing study of 7684 patients who were prescribed risperidone.[15] Nine women took risperidone during 10 pregnancies, and of the 10 pregnancies, there were 7 live births and 3 therapeutic terminations of pregnancy. There were no abnormalities reported among the 7 live infants exposed to risperidone in utero. Animal studies have not found risperidone to show direct reproductive toxicity, although some indirect prolactin- and central nervous system–mediated effects have been reported.[16] Although prolactin concentrations and fertility rates were not measured in the women reported here or in the postmarketing study,[15] it is noteworthy that any possible effects of risperidone on prolactin levels or fertility did not prevent pregnancy. In addition, since risperidone and its major metabolite, 9-hydroxyrisperidone, are excreted in breast milk (women are advised not to breastfeed[16]), infants of breastfeeding women should be closely monitored.[17]

We believe these to be the first cases of risperidone used before and throughout pregnancy and during the nursing period. The cases do not imply that risperidone treatment during pregnancy and nursing will not be hazardous. However, they do contribute to the existing knowledge regarding the use of antipsychotics in pregnancy.

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The Clinical Features of Bipolar Depression

Sir: In the article by Mitchell et al.[1] on bipolar depression, in which they compared the major depressive episodes (MDEs) of bipolar I disorder and major depressive disorder (MDD) inpatients and outpatients matched for gender and age, bipolar I patients had significantly more psychomotor-retarded melancholic and atypical features. One atypical feature, hypersomnia, was present in 43.6% of bipolar I versus 18.0% of MDD patients, and bipolar I patients had significantly more psychomotor retardation (71.8% vs. 41.0%). The authors made reference to an article of mine,[2] suggesting that my comparison of MDE in bipolar II versus MDD patients should have been controlled for age. In the following years, I showed that atypical features in bipolar II and MDD are less common with increasing age.[3,4] To test Mitchell and colleagues' suggestion that comparisons should be controlled for age, I made some logistic regressions in my last sample of private practice consecutive MDD (N = 107, mean ± SD age = 47.2 ± 15.8 years, 60.7% were female) and bipolar II (N = 164, mean ± SD age = 41.7 ± 14.3 years, 67.6% were female) MDE outpatients who were free of psychoactive drugs, diagnosed with the Structured Clinical Interview for DSM-IV, Clinician Version.[5] DSM-IV atypical MDE was found in 46.9% of bipolar II patients (in line with the report by Mitchell et al.) and in 17.7% of MDD patients (in line with Mitchell and colleagues' report), a highly significant difference (odds ratio = 4.0, z = 4.7, p = .000).

I next performed a logistic regression controlled for age, and the difference was still highly significant (odds ratio = 3.7, z = 4.3, p = .000), results that contradicted Mitchell and colleagues' statement that bipolar versus MDD comparisons should be controlled for age, and suggested that age may not have an important effect on the difference in prevalence of atypical features between bipolar II and MDD patients. The latter finding may be related to the decrease in prevalence of atypical features in both bipolar II and major depressive disorders as age increases, leading to small changes in atypical features difference.[3,4] Then, I compared DSM-IV melancholic features, which were present in 16.4% of bipolar II and in 19.6% of MDD patients, in line with a previous report in the same setting[6] (low melancholic features prevalence is common in outpatients[7]), a nonsignificant difference (odds ratio = 0.8, z = –0.6, p = .505). When I did logistic regression controlled for age, difference was still nonsignificant (odds ratio = 0.8, z = –0.3, p = .700), again suggesting that age may not have an important effect on clinical differences between MDEs in bipolar II and MDD.

Bipolar I and bipolar II depressions may be distinct disorders, on the basis of different family history of bipolar II, different MDE severity, and diagnostic stability,[8,9] and should be studied separately and in different settings. A recent series of studies and reviews[10–14] showed that atypical features may point to a bipolar II diagnosis, rather than MDD, with high specificity (82.8%; sensitivity, 45.3%). MDE with concurrent hypomanic symptoms (usually irritability, racing thoughts, and distractibility) may also strongly point to bipolar II diagnosis,[15–17] with greater specificity (92.1%; sensitivity, 46.3%) than accounted for by the prevalence of atypical features. These distinguishing clinical features of bipolar II depression may help clinicians suspect bipolar II over simply MDD, leading to better assessment of past hypomania.

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Dr. Mitchell Replies

Sir: I have known for some time of Dr. Benazzi's publications on the phenomenology of bipolar depression and am aware that he shares our intrigue for characterizing the nature of this clinical presentation.

I am delighted that Dr. Benazzi found a persisting greater prevalence of atypical features in his bipolar II depressed subjects after statistically controlling for the effect of age. Since many of the phenomenological characteristics of depression differ in various age groups, controlling for age is the appropriate conservative statistical strategy, thereby strengthening the validity of any persisting between-group differences. Additionally, it is of considerable interest that he reports virtually identical prevalence rates for atypical features in his bipolar II sample to those reported in our bipolar I depressed population.

In contrast to our findings in bipolar I patients, Benazzi reports no difference in melancholic features between his bipolar II and unipolar samples—either with or without controlling for an effect of age. As he suggests, this lack of difference may indicate that while bipolar I and II depressed patients are similar in terms of atypical features, they may differ with respect to melancholic or psychomotor characteristics. I would emphasize again the critical importance of controlling for age, as many studies have indicated that melancholia is of considerably higher prevalence in older depressed patients.

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Hemodialysis in the Treatment of Valproic Acid Overdose

Sir: Valproic acid (VPA) is currently utilized as a mood stabilizer in bipolar disorder.[1] As a result, it is often the medication employed in suicidal attempts in bipolar depression. VPA overdose can cause serious toxicity and, in some cases, death. The clinical symptoms include progressive coma, respiratory depression, hemodynamic instability, and pancytopenia. Until relatively recently, it was assumed that because VPA is 90% to 95% protein bound, hemodialysis would be ineffective in overdose. Previously, the treatment had been largely symptomatic. Gastric lavage, activated charcoal, supportive care, and naloxone administration had been the first-line treatment for VPA overdose. VPA is rapidly absorbed from the gastrointestinal tract; therefore, gastric lavage, oral charcoal, and laxatives are effective only immediately after ingestion of an overdose or

if the patient has used the sustained-release form. Since only 1% of VPA is excreted in the urine, forced diuresis has minimal effect on drug elimination. However, since 1996, product information for divalproex sodium notes that "in overdose situations, the fraction of the drug not bound is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug."[2(p436)] We report a case in which hemodialysis was successfully used to treat severe divalproex overdose.

Case report. Mr. A, a 38-year-old male veteran who had a DSM-IV diagnosis of bipolar disorder and had made several suicidal attempts in the past, presented to the emergency department 1 hour after overdosing on 180 tablets of 250-mg divalproex and an unknown amount of risperidone and bupropion. The patient's initial serum VPA level was 186 μg/mL (therapeutic range, 50–100 μg/mL), but he remained conscious and alert. He received gastric lavage, was given charcoal, and was admitted to the medical unit for supportive care. The patient's condition, however, started deteriorating as his VPA level started rising. At a VPA level of 726 μg/mL, the patient became confused, restless, difficult to rouse, and unable to follow commands. His blood pH eventually fell to a low of 7.25 (normal pH range, 7.35–7.45). He was transferred to the medical intensive care unit and was intubated secondary to respiratory depression. The renal team was consulted, who felt that hemodialysis was indicated since the protein binding of valproate may have been saturated, leaving a significant dialyzable fraction. The patient received two 4-hour hemodialysis treatments on the same day and within several hours had marked improvement in his general condition. He became alert, oriented, and cooperative. His VPA level fell rapidly to 67 μg/mL. He was transferred to the psychiatry service the following day.

Two recent case reports have appeared in medical literature describing successful treatment of overdose with hemodialysis. The first involved a 43-year-old woman with bipolar illness who may have ingested 75 tablets of 250-mg divalproex.[3] Her serum VPA level at the initiation of treatment was 940 μg/mL. Her initial dialysis lasted 6.25 hours, during which time her VPA level fell to 164 μg/mL. After an intervening 5.5 hours, there was a rebound in her VPA level to 240 μg/mL. This prompted a 4-hour second dialysis, which succeeded in reducing her VPA level to 77 μg/mL. After a bout of aspiration pneumonia, the patient recovered and was discharged 10 days later.

The second case involved a 27-year-old man with a history of seizures who presented to the emergency room with coma, hypernatremia, and respiratory failure caused by an overdose of VPA.[4] Much smaller amounts of carbamazepine and clobazam were also found in his blood. At admission, the plasma VPA level was 1414 μg/mL. The anion gap was 26 mm/L (normal range, < 12–14 mm/L), which correlated with his VPA level. The patient received 2 serial treatments employing both hemodialysis and hemoperfusion lasting 3 hours. After the first treatment, the plasma concentration of VPA fell from 980 μg/mL to 356 μg/mL; after the second session, it fell from 340 μg/mL to 145 μg/mL. Protein binding in the plasma was only 32% at the beginning of treatment and 54% at the end. It was felt that hemodialysis was more effective throughout the whole span of the treatment than hemoperfusion, which was limited by saturation of the charcoal column. This patient, however, had a more stormy course and developed severe liver failure and bone marrow suppression along with remaining comatose for 5 days. Nevertheless, he recovered fully.

In both previous case reports cited, it was apparent that saturation of the binding sites on serum albumen by the high levels of VPA present in the overdose was the principal cause of the decreased percentage of bound VPA. A metabolic acidosis may have also contributed to the reduced protein binding of VPA.[5] In all 3 cases, hemodialysis quickly reversed a toxic course that would have incurred an extended stay in the intensive care unit and was potentially lethal. It is important that health care professionals become more aware of the altered protein binding of VPA at high plasma concentrations so that delays in the appropriate use of hemodialysis can be avoided.

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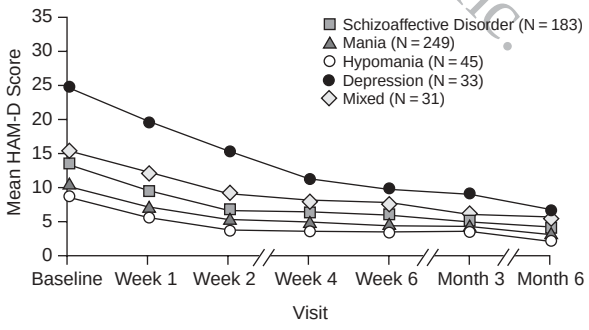
Correction

In the article "Risperidone Safety and Efficacy in the Treatment of Bipolar and Schizoaffective Disorders: Results From a 6-Month, Multicenter, Open Study" by Eduard Vieta, M.D., Ph.D., et al. (J Clin Psychiatry 2001;62:818–825), the symbols for the top and bottom lines in Figure 2 on page 821 were reversed. The corrected Figure 2 is printed below.

The staff regrets this error.

Figure 2. Change in Hamilton Rating Scale for Depression (HAM-D) Scores by Diagnostic Subgroup[a]



[a]$p < .0001$ vs. baseline for all groups at each subsequent visit.