Letters to the Editor

Lack of Association Between Plasma Apolipoprotein E and Suicide Attempts

Sir: Low cholesterol may be associated with increased suicide attempt risk.[1,2] Apolipoprotein E is a plasma protein that serves as a ligand for the low-density lipoprotein receptors and, through its interaction with these receptors, participates in cholesterol transport.[3] No published studies have explored the association between plasma apolipoprotein E and suicide. This study compared plasma apolipoprotein E levels in 298 suicide attempters seen in the emergency room and 258 controls.

The Hospital Ramon y Cajal triages all emergencies in a catchment area of 500,000 persons in Madrid, Spain; all are white.[4] This general hospital of the National Health Service provides free medical coverage to the population. Following the definition recommended by the National Institutes of Health, suicide attempts included those attempts with some evidence that the person intended to kill himself/herself.[5] Suicide attempters were usually assessed during the first 24 hours after the attempt.

Between 1999 and 2001, 298 attempters (190 women and 108 men, mean age = 37.5 years, SD = 14.9 years) were recruited. The Mini-International Neuropsychiatric Interview, version 4.4,[6] a brief structured interview, provided the major Axis I DSM-IV diagnoses (the most frequent diagnoses were major depression, 48%; substance use disorders, 12%; and nonaffective psychosis, 5%). The controls included 258 blood donors (105 women and 153 men, mean age = 35.6 years, SD = 11.7 years) from the same hospital, without personal or familial history of suicide attempts or psychiatric disorders. After complete description of the study to the subjects, written informed consent was obtained.

This study measured plasma cholesterol levels, but only a preliminary analysis has been published.[7] Plasma apolipoprotein E levels were also measured since apolipoprotein E has a crucial role in cholesterol transport[1] and has never been studied before in suicide attempters. The analysis on apolipoprotein E was exploratory and was not the main goal of the study. Thus, if this analysis had been significant it would have required a Bonferroni correction. As all results were negative, a Bonferroni correction was not needed.

There were no significant differences between mean [SD] plasma apolipoprotein E levels in female attempters (3.8 [1.3] mg/dL) versus female controls (3.9 [1.2] mg/dL) ($t = -0.39$, $df = 293$, $p = .46$) or in male attempters (4.0 [1.2] mg/dL) versus male controls (4.2 [1.6] mg/dL) ($t = -1.2$, $df = 259$, $p = .26$). Using Cohen's method, the statistical power for finding medium effect sizes was 99.9% for the female sample and 98% for the male sample.[8]

An analysis of variance (ANOVA) with plasma apolipoprotein E levels as the dependent variable, gender and attempter status (vs. control) as independent variables, and age as a covariate was performed. Although gender was significant ($F = 3.9$, $df = 1$, $p = .48$), neither attempter status nor the interaction between status and gender was significant. In summary, this study with a relatively large sample of representative suicide attempters suggests that plasma apolipoprotein E levels may not be associated with suicide attempts despite low cholesterol levels having been associated with suicide attempts.

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Ribavirin May Be an Important Factor in IFN-Induced Neuropsychiatric Effects

Sir: The recent article by Kraus et al.[1] is of considerable interest since interferon (IFN)-induced neuropsychiatric effects are highly prevalent, but minimally studied, in prospectively designed reports. As reported previously, IFN treatment of chronic hepatitis C resulted in a significant increase in depression, anxiety, and irritability/hostility scores. These neuropsychiatric disturbances frequently necessitate dose reduction and/or treatment discontinuation, an approach that may compromise the treatment of hepatitis C virus (HCV).

We would like to draw attention to another finding in the report by Kraus et al.[1] that was somewhat minimized. The authors reported that patients who were treated with IFN-α_{2b} in combination with ribavirin (1000–1200 mg/day) developed significantly higher scores in depression, anxiety, and irritability/hostility than did patients who were treated with IFN monotherapy. This finding raises the possibility that ribavirin, either alone or in combination with IFN, may be a contributory factor to the induction of depression and other mood disturbances and may therefore have significant clinical implications for the treatment of chronic hepatitis C.

Combined treatment of IFN plus ribavirin results in higher rates of sustained viral remission[2] and has been the standard treatment for hepatitis C since 1998. Ribavirin is a purine nucleoside analogue with antiviral activity against DNA and RNA viruses. Prior reports have suggested that ribavirin might contribute to IFN-α–induced depression. For example, Andreone et al.[3] reported that the combination treatment was associated with higher depression rates during treatment as compared with IFN monotherapy (19.2% vs. 4.2%, respectively). In a report that examined ribavirin in the absence of IFN, Bodenheimer et al.[4] reported that ribavirin lowered aminotransferase levels but was ineffective in lowering HCV-RNA levels. Interestingly, the investigators found that 20.7% of patients in the ribavirin group versus 3.3% in the placebo group acknowledged depression on a "symptom questionnaire." Although both reports suggested a depressogenic effect of ribavirin, the sample sizes in each were small (approximately N = 50), which may have contributed to the lack of significant effects.

If ribavirin is an important contributor to IFN-induced depression or other neuropsychiatric disturbances, attempts should be made to use the lowest effective dose for the shortest possible duration to minimize such side effects. For example, HCV genotype 2 or 3 can be effectively treated with a lower dose of ribavirin (800 mg/day for 24 weeks) while HCV genotype 1 requires a larger dose (1000–1200 mg/day for 48 weeks). It may also be possible to lower the dose of ribavirin if an early viral response occurs without adversely altering the outcome of HCV treatment.[5]

It is worth reminding readers that approximately 20% of severely ill psychiatric patients are positive for HCV.[6] Thus, knowledge of the neuropsychiatric complications resulting from treatment of hepatitis C is critical for appropriate and successful psychiatric care of these patients. Moreover, many gastroenterologists may not be aware of the complexity of these issues and the ramifications of the neuropsychiatric disturbances that accompany ribavirin and/or combination treatment using IFN.

Dr. Asnis serves on the speakers/advisory board for Hoffmann-La Roche, Dr. Miller has received grant/research support from Schering-Plough, and Dr. Raison serves on the speakers/advisory board for Schering-Plough. Dr. De La Garza has no significant financial relationships to report.

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Dr. Kraus and Mr. Schäfer Reply

Sir: In their letter, Asnis et al. comment on a timely and interesting issue concerning neuropsychiatric side effects of interferon-based antiviral therapy. Indeed, there are few data on the potential contribution of ribavirin to interferon-induced adverse events, especially depression.

As pointed out by Asnis and colleagues, in our study,[1] depression and anxiety scores were significantly higher in the subgroup treated with combination therapy (i.e., additionally treated with ribavirin). However, the interpretation of this finding has to be done very carefully.

The antiviral treatment with or without ribavirin was not an independent factor in our study design (hepatitis C patients were not randomly assigned to the respective therapy condition, there was no therapy condition "ribavirin alone," and the change of therapy mode [combination therapy with interferon *and* ribavirin] was not introduced prospectively). In addition, patients in both subgroups differed significantly in the sociodemographic characteristics of age and gender.

Therefore, our findings *might* indicate a contributory role of ribavirin in antiviral therapy–induced psychiatric symptoms in chronic hepatitis C; however, our data do not allow us to determine the exact influence of ribavirin, which would only be possible using a specific study design. Consequently, we mentioned the observed subgroup differences without emphasizing them in the discussion section.

Implications for clinical practice proposed by the authors appear to be somewhat premature. Even given a depressogenic effect of ribavirin, it is not yet clear whether the proposed dose

reductions are suitable for reducing significant therapy-induced depressive symptoms. In addition, ensuring sufficient ribavirin levels is particularly important in the treatment of genotype-1 hepatitis C virus (HCV) infections.[2] Therefore, a decrease of therapy-induced depressive symptoms should, rather, be achieved by an effective antidepressant medication (selective serotonin reuptake inhibitor, e.g., paroxetine or citalopram) than by the strategy of ribavirin dose reduction.[3,4]

Finally, the authors report on the obviously high prevalence of HCV infection among psychiatric patients and possible implications. In this context, we would like to also emphasize that psychiatric patients infected with HCV should be considered potential candidates for combination therapy with interferon alfa and ribavirin when intensive monitoring for psychiatric symptoms is ensured.[5]

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Olanzapine May Cause Delirium in Geriatric Patients

Sir: Olanzapine, a second-generation antipsychotic, is indicated by the U.S. Food and Drug Administration (FDA) for schizophrenia and bipolar I acute mania but has limited evidence for use in elderly patients with these conditions.[1] Olanzapine was FDA-approved in December 2003 for maintenance monotherapy for bipolar disorder. Olanzapine at doses up to 20 mg is recommended to treat schizophrenia and acute mania.[2] The package insert, however, recommends a lower dosage in geriatric patients, based upon studies of elderly with schizophrenia or dementia with psychotic symptoms, not those with acute mania. Recently, however, the package insert for olanzapine has been modified to include a warning for cerebrovascular adverse events in elderly patients with dementia-related psychosis. One recent publication suggested, "Elderly patients with schizophrenia and bipolar disorder have dose requirements that are similar to those of their younger counterparts."[3(p191)] There are limited data for ascertaining this or determining safety and tolerability of full-dose olanzapine in non–cognitively impaired elders. Reduced risk of parkinsonism and tardive dyskinesia may offer theoretical support for the use of olanzapine over other atypical antipsychotics in the elderly. However, we report on an elderly man with bipolar disorder who developed delirium when prescribed olanzapine 20 to 30 mg per day.

Case report. Mr. A, a 76-year-old man diagnosed with bipolar disorder 35 years ago, was initially treated with chlorpromazine and subsequently had trials of haloperidol, risperidone, and olanzapine but was never placed on mood-stabilizer treatment. His community psychiatrist had prescribed olanzapine since 1997, and by the middle of 2002, the patient was receiving olanzapine, 30 mg p.o. q.d., and fluoxetine, 20 mg p.o. q.d. One month later, the patient was hospitalized at another facility because of confusion, gait instability, and falls. His wife reported waxing and waning of consciousness. The community psychiatrist diagnosed delirium but had not attributed it to olanzapine. During that hospitalization, Mr. A wandered, was confused, and was placed on treatment with haloperidol, 2 mg p.o. q.a.m. and 7.5 mg p.o. q.h.s., and benztropine, 2 mg p.o. b.i.d., by house staff. Increasing confusion and family preference led to the transfer of Mr. A to our facility's nursing home unit. At that time, his Mini-Mental State Examination (MMSE)[4] score was 10/30. The patient's intake examination was notable for falling, aggressive outbursts toward staff, profound somnolence, echolalia, clonus, and asterixis. According to DSM-IV criteria, a diagnosis of delirium was made. Results from a complete blood cell count, blood chemistries (CHEM 18), thyroid-stimulating hormone level, vitamin B_{12} level, folate level, urinalysis, and computed tomographic scan of the head revealed no cause for this patient's delirium. The electroencephalogram (EEG) demonstrated diffuse background slowing, which is consistent with delirium. By process of elimination, the delirium was attributed to the patient's psychiatric medications. He was tapered off the haloperidol, benztropine, and olanzapine. Other medications were not changed. The patient became more alert and responded appropriately with staff and wife. His gait improved. His score on a repeated MMSE (1 month later) was 22/30, and results of the repeated EEG (2 months later) had normalized. At discharge in 2002, the patient's MMSE score was 26/30, and he was able to walk out of the hospital unassisted.

Mr. A did well in the community until he experienced a manic episode at the beginning of 2003. His community psychiatrist titrated sodium valproate to 1000 mg p.o. q.h.s. and olanzapine to 20 mg p.o. q.h.s. His wife noted he was "sluggish" weeks later. One month later, at another facility, he underwent spinal surgery, developed a staphylococcus infection postoperatively, and was treated with vancomycin. The patient developed postoperative confusion and was transferred to our facility's nursing home unit. At admission, he was taking olanzapine, 20 mg q.h.s., and sodium valproate, 1000 mg q.d. Due to perseveration and falling asleep mid-sentence, Mr. A was unable to complete the MMSE. A diagnosis of delirium was made according to DSM-IV. The patient had disturbance of consciousness over a short time span. He had already received 2 weeks of intravenous vancomycin, his white blood cell count was within normal limits, and results of blood cultures were negative. An EEG showed "marked diffuse slowing of the background" consistent with delirium. Olanzapine, 20 mg p.o. q.h.s., was discontinued while sodium valproate, 1000 mg, was continued. The patient's delirium resolved, and his MMSE score was 25/30.

This patient developed delirium while taking olanzapine, 20 to 30 mg per day. On both occasions, the delirium resolved after olanzapine discontinuation. Haloperidol and benztropine, as well as the potential interaction between fluoxetine and olanzapine through the cytochrome P450 2D6 metabolic pathway,

could have contributed to the delirium at the first hospitalization. However, according to the patient's wife, confusion occurred while he was taking olanzapine, 30 mg, prior to the addition of haloperidol and benztropine. At the second hospitalization, olanzapine and the staphylococcus infection were associated with delirium. However, the patient's mental state had not improved after 2 weeks of intravenous vancomycin, and the results of his blood cultures were negative. The patient's delirium resolved only after the olanzapine was discontinued.

The safety of olanzapine in elderly patients may be dose related. Olanzapine 5 to 10 mg per day, but not 15 mg per day, was effective in reducing psychosis and behavioral disturbance in demented nursing home elders.[5] The 15-mg/day dose was associated with increased peripheral anticholinergic side effects compared with placebo.[5] An industry-sponsored subanalysis of the safety of olanzapine in Alzheimer's disease patients with psychosis from the aforementioned study[5] found no difference in central anticholinergic effects between placebo and olanzapine at 5-, 10-, or 15-mg doses.[6] This lack of difference in central cholinergic side effects between olanzapine and placebo may be attributable to an increased rate of anticholinergic side effects in the placebo group.

Olanzapine has been used to treat delirium. One trial with doses of 3 to 6 mg per day demonstrated some benefit in patients with hyperactive delirium but was associated with poor outcome, especially in patients with hypoactive delirium, spread of cancer in the central nervous system as the cause of delirium, and age greater than 70 years.[7] In an open-label trial of Parkinson's disease patients treated with olanzapine for 8 weeks, 29% of the subjects dropped out due to severe drowsiness, and over half of the patients developed problems with concentration, memory, dry mouth, and increased sedation.[8] These side effects are consistent with the in vitro muscarinic affinity of olanzapine, although the extent of muscarinic binding may be dependent on whether the cholinergic receptors are of mouse or cloned human origin[9] or the characteristics of the media culture utilized.[10] Delirium can be a side effect of olanzapine's central cholinergic antagonism at high doses. This patient with a mild dementia may have been more susceptible to developing a delirium. However, age alone may predispose to cognitive changes from agents with anticholinergic effects,[11] possibly related to reduced cholinergic activity with aging.[12]

This case demonstrates that olanzapine may cause delirium in elderly patients when used at doses of 20 to 30 mg. Lower doses should be considered for elderly patients with acute mania, and the safety of olanzapine for maintenance of bipolar disorder in the elderly should be questioned. There is a paucity of literature regarding the use of olanzapine in geriatric patients. What may be safe and effective in adult patients may not be safe in geriatric patients given their different pharmacodynamics and physiologies. Data from the use of olanzapine in adult patients cannot always be extrapolated to geriatric patients. More research is required on effectiveness and safety profile of olanzapine in the elderly.

Dr. Samuels has served on the speakers bureau for Janssen and has received honoraria from Novartis. Dr. Fang has no significant financial or other relationships to disclose.

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A Case of Tardive Dystonia Successfully Managed With Quetiapine

Sir: Tardive dystonia is a serious adverse event of neuroleptic medication. Here, we report a case of successful management of tardive dystonia with quetiapine.

Case report. Mr. A, a 31-year-old man with a 7-year history of DSM-IV schizophrenia, had been treated with haloperidol, 2 mg/day, and sulpiride, 400 mg/day. Dystonic movements involving bending and twisting of the trunk were documented in July 2001. Tardive dystonia was suspected, and neuroleptic drugs were discontinued. The patient's dystonic movements progressed, however, with a recurrence of psychotic symptoms. Mr. A was admitted to our hospital in March 2002 for close inspection and treatment.

During the neurologic evaluation performed at admission, muscle contractions of the neck, bending and twisting of the trunk, and sustained hyperextension of both upper and lower extremities were observed. These involuntary movements disabled many of Mr. A's activities of daily life. Secondary dystonias resulting from metabolic disorder, organic disorder, or infection were ruled out. There was no family history of neurologic disorder. The diagnosis of tardive dystonia was made in this case on the basis of the criteria proposed by Burke et al.[1] Mr. A was evaluated using the Marsden-Fahn Scale[2] for the assessment of severity of dystonia and the Positive and Negative Syndrome Scale (PANSS)[3] for the assessment of psychopathol-

ogy. The patient's Marsden-Fahn Scale score was 82/120 on the movement subscale and 15/30 on the disability subscale; the total PANSS score was 82.

Because of ongoing psychotic symptoms and continued tardive dystonia, quetiapine was started in March 2002. Increased dosage of quetiapine, up to 400 mg/day, was accompanied by deterioration of agitation with minimal improvement of tardive dystonia. On reaching a dose of 600 mg/day, tardive dystonia gradually decreased. The patient's involuntary movements responded well to a dose of 800 mg/day, and he became generally able to look after himself. There was, however, minimal change in the patient's psychotic symptoms. In April 2002, Mr. A's Marsden-Fahn Scale score had decreased to 37.5 on the movement subscale and 9 on the disability subscale. His PANSS score was 72. To improve his mental status further, risperidone, 1 mg/day, was added to his regimen. There was no subsequent exacerbation of tardive dystonia, and psychotic symptoms improved. He was discharged in September 2002. During the patient's hospitalization, no antiparkinsonian drugs were used.

The treatment of tardive dystonia is particularly difficult, and several pharmacologic interventions have been tried with varying results.[4,5] Discontinuation of neuroleptics may be the most important factor related to remission of tardive dystonia,[6] but this strategy exposes patients to the risk of psychotic relapse. As far as we know, no studies have been conducted to evaluate the effect of quetiapine on tardive dystonia, but cases of tardive or idiopathic dystonia successfully managed with clozapine, which has pharmacologic similarities to quetiapine, have been reported.[7–10]

The mechanism underlying the efficacy of quetiapine (or clozapine) in tardive dystonia is unknown. In this case, 2 possibilities can be supposed: (1) Improvement of tardive dystonia is the result of a passive mechanism in which dystonic movements ameliorate spontaneously over time in the absence of exposure to the offending agents. (2) Quetiapine may exert a therapeutic (antidystonic) effect on tardive dystonia. Spontaneous remission of tardive dystonia is reported to be rare,[6] and, in this case, tardive dystonia had not improved even after neuroleptic drugs had been discontinued for 6 months. The fact that tardive dystonia in this patient showed rapid and marked improvement within several weeks of starting quetiapine suggests a therapeutic effect of quetiapine.

Although its mechanism of action is still unclear, we certainly recommend trying quetiapine in patients with tardive dystonia who require antipsychotic medication.

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A Rose by Any Other Name

Sir: It was with mixed emotions that I read Dr. Jefferson's recent letter[1] regarding the spelling of "bupopion." On the one hand, it was a relief to know that I am not the only physician who can't spell very well but have been too ashamed to admit it. On the other hand, it's frightening to think that there are many physicians out there who can't spell very well and have been too ashamed to admit it.

I had anxiously hidden my own spelling disability until I confessed to my doctor, who gladly wrote a prescription for "buproprion." The buprenorphine I received greatly relieved my anxiety, and a few other things, but really didn't help my spelling much, especially at higher doses. I next turned to the "spell checker" on my computer. This worked well, or so I thought, until my publications kept coming out in the name "Suture" rather than my actual name "Sutor," perhaps affirming my mother's belief that I should have been a surgeon after all.

As I have now entered middle age, I am increasingly aware that daily 20-mg doses of Proscar or Prozac will help a patient achieve euthymia when properly prescribed—a testament to the fact that nature often has a way of correcting humankind's mistakes. Pharmacists and physicians alike should take comfort in this fact.

More recently I have taken to employing the "smudge vowel" in my handwritten documentation. This useful character stands about the same height as the letter "e" on the written page and resembles all the vowels in general, but none in particular. Sort of. Since I am a doctor, anyone encountering the "smudge vowel" naturally assumes that I know how to spell but that I am just sloppy. Thankfully, my thinking is clearer than my handwriting, and, while I may not be able to spell it, I am certain that the next FDA-approved epilepsy medicine will cure bipolar illness once and for all.

Dr. Sutor has no significant financial or other relationships to disclose.

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