Antipsychotic Medication and Diabetes Mellitus

Sir: Spoelstra and colleagues[1] assert that antipsychotic drugs may worsen metabolic control in type 2 diabetes mellitus and speculate from their pharmacoepidemiologic study that this worsening is probably due to β-cell toxicity. While there is general agreement that exposure to antipsychotic medications (and second-generation agents in particular) may be associated with an increased risk of diabetes mellitus,[2] there are several problems regarding the authors' interpretation of the data.

First, a comparison group of those not taking antipsychotics is probably not comparable to a group taking these medications. The authors acknowledge not having information regarding diagnosis, hence the confound of schizophrenia or bipolar disorder (both associated with increased risk for metabolic problems) could not be accounted for. Cases of worsening of control of diabetes with oral hypoglycemic agents may be influenced more by the diagnosis of a psychotic disorder than by exposure to an antipsychotic per se.

The age of Spoelstra and colleagues' cohort (average of over 60 years) may also be an issue. In another pharmacoepidemiologic study[3] focusing on 11,104 older residents of long-term care institutions in Ontario, Canada (age greater than 65 years), no difference was found by comparing exposure to either first- or second-generation antipsychotics versus exposure to benzodiazepines for risk of association with diabetes mellitus, but a difference was found for patients receiving corticosteroid therapy versus benzodiazepines (adjusted hazard ratio = 2.2, 95% CI = 1.41 to 3.12). Pharmacoepidemiologic studies have largely failed to quantify the risk of association with diabetes mellitus attributable to antipsychotic exposure in the older age group.[4,5]

The theory of β-cell toxicity is not supported by some of the experimental evidence now available. For example, no significant change in insulin response was detected using a hyperglycemic clamp model in healthy volunteers randomly assigned to olanzapine, risperidone, or placebo.[6] Ultimately, there are several different mechanisms that may explain why some patients experience glycemic dyscontrol after exposure to antipsychotics,[2] and these will vary from patient to patient. The bottom line, as the authors suggest, is that glycemic control should be monitored for all patients receiving antipsychotics.

Dr. Citrome has been a consultant for Abbott, Bristol-Myers Squibb, Eli Lilly, and Pfizer; has received grant/research support from Abbott, Bristol-Myers Squibb, Eli Lilly, Janssen, Pfizer, AstraZeneca, and Repligen; has received honoraria from and participated in speakers/advisory boards for Abbott, Bristol-Myers Squibb, Eli Lilly, AstraZeneca, Pfizer, and Novartis; and is a stock shareholder in Bristol-Myers Squibb, Johnson & Johnson, Merck, Eli Lilly, and Pfizer.

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Drs. Cohen and Stolk Reply

Sir: We welcome Dr. Citrome's comments on our research into the relation between exposure to antipsychotics and worsening of type 2 diabetes mellitus. To the existing body of knowledge that antipsychotic drugs cause new-onset diabetes mellitus we add our results, which suggest that antipsychotics cause worsening of glycemic control in patients with existing diabetes. The main result of our research, which is also reflected in the title of the article, is the worsening of existing diabetes due to antipsychotic drugs. Citrome stresses the importance of other potential differences between users and nonusers of antipsychotic medication, such as corticosteroid therapy and schizophrenia or bipolar disorder, that might have distorted our results. We completely agree and adjusted for the available information on potential confounding factors, notably comedication (see Table 2 of the article, p. 677). Seventy-nine percent of patients received fewer than 20 prescriptions of antipsychotic drugs, thereby making the diagnosis of schizophrenia or bipolar disorder very unlikely.

As far as the pathophysiologic mechanism involved in worsening of glycemic control is concerned, our results confirm the reports of others who found evidence of a toxic effect of antipsychotic drugs on β-cell function in susceptible subjects.[1,2] The absence of abnormalities in endocrine parameters in healthy volunteers treated with atypical antipsychotics notwithstanding, we think that the hypothesized β-cell toxicity is at present the best explanation for the observed worsening of metabolic controls, occurring during a relatively short period of treatment and resulting in often drastic, sometimes lethal manifestations of disturbed glucose metabolism that are unaccounted for by any other explanation.

Dr. Cohen has received grant/research support from Janssen-Cilag and has participated in a speakers/advisory board for Bristol-Myers Squibb. Dr. Stolk reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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Increased Efficacy With Addition of Clozapine to Aripiprazole: Alternative Explanations

Sir: I read with interest the letter entitled "Possible Increased Efficacy of Low-Dose Clozapine When Combined With Aripiprazole" by Lim et al.[1] The authors describe 3 cases of individuals suffering from psychotic disorders who apparently responded to combined therapy with clozapine and aripiprazole. In each case, the patient had not responded to therapeutic doses of aripiprazole (15–45 mg per day). As a result of persistent psychotic symptoms, each patient was hospitalized, the patient's aripiprazole dose was adjusted to 15 to 30 mg per day, and modest doses of clozapine were added. Despite total clozapine doses that are considered low, 150 to 200 mg/day (and total serum clozapine levels that ranged from 181–610 ng/mL), each patient demonstrated substantial symptomatic improvement (Brief Psychiatric Rating Scale scores decreased 24%–53%).

As a result of this experience, the authors opine that the clinical improvement they observed was produced by combined clozapine-aripiprazole treatment. They support this assertion by pointing out that clozapine levels were "low," citing prior literature on serum clozapine levels and clinical response.[2–4] The fact that each patient improved after clozapine was added to an established aripiprazole regimen suggests that clozapine, despite use of doses that are considered low, could be responsible for the clinical improvement. The studies the authors cite that investigated serum levels of clozapine describe clinically determined cutoff levels for likely response. These levels are best thought of as "floor" serum levels above which patients have the best possibility of response, not levels required for response. Although the doses utilized by Lim et al. are described as low, they are within the range utilized by European psychiatrists to treat patients with schizophrenia and other psychotic disorders.[5] Therefore, despite the low doses of clozapine utilized in these patients, it is possible that the clinical improvement described was due to clozapine.

Another explanation that must be considered is that the authors' patients may have responded to aripiprazole after it was given enough time to help them. In the first 2 cases, aripiprazole had been in use for only 4 to 8 weeks before clozapine was added. In the third case, although aripiprazole had been used for 4 months, the dose had been increased from 15 to 30 mg/day during this period of time. Chronically ill patients may require more than 4 to 6 weeks of therapy to achieve maximum benefit with an antipsychotic medication.

Although the patients described by Lim et al. appeared to have had a robust response to combined clozapine-aripiprazole, there are alternative explanations that need to be considered in interpreting the authors' observations before endorsing a course of antipsychotic polypharmacy.

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

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Dr. Lim Replies

Sir: We appreciate Dr. DeQuardo's thoughtful comments on our letter. As he suggests, our patients' responses may have been due primarily to the effects of either individual neuroleptic, rather than an actual combined effect. Clozapine alone certainly can produce significant improvement of refractory psychosis. However, in our experience with refractory psychotic inpatients, such doses of clozapine alone have not typically produced similar responses. For those who required higher doses, the side effect burden has sometimes outweighed any therapeutic benefit. In addition, we have not observed such robust responses with aripiprazole monotherapy in the inpatient setting.

We posit that for some refractory psychotic inpatients who cannot tolerate high doses of clozapine, the addition of aripiprazole may permit appropriate symptom management while balancing out the potential negative side effects of clozapine.

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

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Lithium Dosing Schedule and Renal Insufficiency

Sir: Lepkifker et al.[1] performed a valuable service by providing long-term renal follow-up data on a sizable cohort of patients on lithium treatment from 4 to 30 years. Despite the long-standing controversy regarding lithium's effects on renal function, to my knowledge, no study of lithium's renal effects has had 30-year follow-up data. I commend their work. However, I wonder whether their unique cohort could be used to shed further light on more specific questions of how to manage lithium to minimize the risk of renal effects.

Specifically, Plenge et al.[2] and others[3–7] have advanced the idea of dosing lithium once a day to minimize renal effects and provide data showing that certain short-term indices of renal function (e.g., urine volume), as well as possibly the degree of observed renal histological change, improve on a once-daily dosing regimen.[4,5] These authors make an analogy between lithium and other known nephrotoxic drugs such as aminoglycoside antibiotics,[2] for which the need to minimize daily trough levels is well appreciated. Aminoglycosides are now almost universally dosed once daily instead of 3 times a day. However, not all studies of lithium's effects on renal function have observed differences based on dosing regimen,[8] and published studies are limited by the fact that the total dose is frequently not equivalent between the single and multiple daily

dosing regimens.[9] Would Lepkifker et al. be willing to examine the question of what proportion of subjects in the renal insufficiency and non–renal insufficiency groups are on a single daily dosing regimen and for what period of their total lithium exposure? Similarly, is it possible to stratify the cohort into those receiving identical doses (e.g., 900 mg/day, 1200 mg/day) and compare the proportion of cases with renal insufficiency getting the medication once daily versus multiple times per day? This would be of particular interest for the 14 cases of renal insufficiency that occurred without other identified risk factors.

Likewise, some authors have suggested that potassium and lithium may compete in the kidney and that episodes of hypokalemia be avoided.[10] Are data available for this cohort to allow one to determine if potassium levels differed systematically among individuals who developed renal insufficiency and those who did not?

Inquiries such as these would considerably enhance the base of information available to practicing psychiatrists who must decide who to start on lithium treatment and how to best manage the medication once patients start treatment.

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

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Dr. Lepkifker Replies to Dr. Smith

Sir: Dr. Smith raises the important question of how to minimize the risk of renal effects in lithium treatment.

Three approaches have been proposed. First, the possibility was raised that a single dose of lithium per day would allow a reduction of the polyuria and subsequent polydipsia that are bothersome side effects of lithium treatment in an estimated 30% of patients. Four publications from the 1990s have addressed the subject. Bowen and colleagues'[1] cross-sectional study describes a significantly smaller urine volume in patients treated with a single dose as compared with multiple doses of lithium, but not with a twice-daily regimen. Hetmar et al.,[2] in a 20-year follow-up study, report that their single-dose lithium patients had lower urine volumes than those taking multiple daily doses, but the higher-than-normal volumes were maintained even after shifting from multiple to single daily doses. O'Donovan and colleagues'[3] prospective randomized study also indicates that switching from a multiple-dose to a single-dose lithium schedule does not significantly reduce urine output. Finally, a study by Abraham et al.[4] concludes that there is no difference in urinary volumes of lithium-treated patients on a once- versus twice-daily regimen. Therefore, there is no convincing evidence in favor of switching from a multiple-dose to a single-dose schedule, although it is possible that a single-dose schedule from the start might reduce the risk of renal impairment.

From our own series, we cannot contribute any statistical data on that point as almost all of our patients were initially treated with lithium 3 times per day and shifted to a twice per day dosing schedule. It is interesting to note that, of only 4 patients treated on a single-dose schedule, 2 developed symptoms of renal insufficiency—one 56-year-old man treated with lithium carbonate for 31 years and one 58-year-old woman treated with Priadel (Sanofi-Synthelabo S.A., Brussels, Belgium), a slow-release lithium formulation, at doses of 800 mg per day for 14 years and 400 mg per day for 4 more years.

The second approach to minimizing the risk of renal effects is based on the suggestion that potassium supplements could prevent or treat renal complications of long-term lithium treatment. Olesen[5] showed that in rats, a potassium-rich diet reduced lithium-induced polyuria, polydipsia, and hypo-osmolality as well as lithium-induced abnormalities in renal morphology. However, this effect was limited by the length and level of lithium exposure. In humans, too few data are available to draw any conclusion as to the effect of potassium supplementation.[6] Only 1 of our patients exhibited a reduction of serum potassium after about 6 years of lithium treatment. This was corrected by 2 tablets per day of 600 mg of potassium chloride, in a slow-release form. There were no signs of renal insufficiency in this patient.

Finally, the effect of amiloride in lithium-induced diabetes insipidus is worthy of interest. This diuretic medication has been commonly used to reduce urinary output in lithium-induced polyuria. It has a potassium-sparing effect and has been shown to reduce lithium uptake into renal tubular cells. As such, it could reduce the risk of tubular damage,[6] but this assumption remains to be tested in long-term treatment.

We must conclude that, unfortunately, there is still no established way to prevent or treat the renal damage that appears in more than 20% of long-term lithium patients, even if they are carefully treated and closely monitored. We can only emphasize the need, in lithium treatment, to use the lowest effective dosage and to request frequent follow-up examinations that include renal function tests.

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

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Single Versus Multiple Daily Dosing of Lithium: Renal Effects

Sir: I read the recent article by Lepkifker et al.[1] on renal insufficiency in long-term lithium treatment with interest. This retrospective study compared renal functioning (with renal insufficiency operationally defined as blood creatinine levels ≥ 1.5 mg/dL) in 114 subjects with bipolar, major depressive, or schizoaffective disorder on lithium treatment with an age- and sex-matched unmedicated control group of 94 subjects. The duration of lithium treatment ranged from 4 to 30 years (mean = 16.75 years, SD = 7.89). Of those on lithium treatment, a proportion demonstrated "creeping creatinine" phenomenon (progressive increase in creatinine level), and over time 21% developed renal insufficiency. The findings were largely in keeping with other published literature. Renal insufficiency had no association with sex, psychiatric diagnosis, age at onset of diagnosed disorder, duration of lithium therapy, serum lithium concentration, or cumulative lithium dose. Renal insufficiency did show an association with episodes of lithium intoxication and diseases or medicines that could affect glomerular function.

It is unfortunate that the authors did not provide information on the dosing schedule of lithium (specifically, single versus multiple daily dosing). This is of importance, because previous studies (including Danish prospective follow-up studies) have found that both renal dysfunction and structural kidney change show correlation with multiple dose schedules and that single daily dosing may be safer.[2–13] It appears that lithium is more harmful to the kidney when it is administered in a manner leading to a relatively constant serum level of lithium. Conversely, when the schedule of administration produces greater variations in serum lithium levels (between peak and trough levels), the functional and structural changes are less.[2] It has been hypothesized that periods of low lithium concentration permit regenerative processes in the kidney.

The feasibility and effectiveness of single daily dosing of lithium are well known clinically and have been confirmed by many studies. It has also been demonstrated that by dosing lithium once daily, urine volume may be reduced, and, conversely, multiple dosing leads to polyuria more frequently.[3] Perry and associates[4] studied the kinetics of single daily lithium dosing and found that the average steady-state serum lithium concentration was unchanged by conversion to single doses but led to significant decreases in 24-hour urine output. In view of the fact that individuals with a mood disorder who are placed on lithium are often on maintenance treatment for life, or at least on long-term treatment, avoidance of serious side effects carries greater importance. Age itself may lead to changes in renal function with increases in glomerular filtration rate. The functional changes may be reversible early in treatment, but a proportion of patients progress to structural change that becomes irreversible.

Studies suggest that lithium discontinuation, especially in situations requiring rapid cessation, in addition to carrying a risk of relapse, may itself produce treatment refractoriness in bipolar disorder.[14,15] This effect bolsters the need to follow approaches that avoid conditions that necessitate rapid discontinuation of lithium.

There are a number of reasons to consider single daily dosing rather than multiple daily dosing of lithium. These include the facts that it is convenient, easier, and more acceptable for patients; simplifies the drug regimen; may lead to better treatment adherence; and is less likely to cause fatigue and daytime sedation. The total daily dose of lithium tends to be 25% less with single daily dosing compared with multiple daily dosing, and serum lithium levels at therapeutic drug monitoring (12 hours postdose) reflect this. If there are peak-related side effects (such as nausea or other gastrointestinal symptoms), then the dosage could be divided, but preferably still administered in doses loaded later in the day. For example, the dosage could be divided in the following ratio: evening $^1/_3$ and night $^2/_3$, with doses about 4 hours apart rather than 12 hours apart (still requiring relatively less total daily dosage).

Switching to once-daily dosing of lithium may mitigate the risk of renal damage, and it is a simple and straightforward strategy that is easily implemented. Additional strategies for minimizing renal side effects of lithium include avoidance of episodes of renal toxicity, close monitoring of serum levels, monitoring of renal function at least yearly, and seeking medical consultation if serum creatinine rises above 1.5 mg/dL (140 mmol/L).

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

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Dr. Lepkifker Replies to Dr. Shammi

Sir: Dr. Shammi points out affirmatively the advantages of single as opposed to multiple daily dosing of lithium. Indeed, a number of reports concluded that taking lithium in a single dose prevents, or at least limits, the increase in urine output (and the reduction of osmolality) and subsequent thirst.[1] It also would prevent, to a certain degree, the morphological changes of tubular atrophy and interstitial fibrosis.

It is, however, important to note that those favorable effects of a single-dose schedule are tempered by a number of facts. The results of several positive studies indicating a preference for single daily dosing have been questioned because of technical (inadequacy of urine collection) or methodological (randomization, length of lithium exposure prior to measurement, serum levels of lithium) problems.[2] Furthermore, the concomitant use of antipsychotic medication has been reported to be associated with a higher rate of tubular dysfunction.[1] In addition, it is still unclear whether twice a day dosing is as good as once a day dosing or is similar to 3 or 4 doses a day. In some studies,[3,4] twice a day dosing is claimed to be comparable to once a day dosing in preventing polyuria and lithium-induced kidney damage, while in other studies[5] patients treated with a twice a day schedule are grouped with the multiple-dose patients.

Furthermore, and most importantly, the favorable effect of single daily dosing on urine volume and concentration has been shown to be the result of protecting tubular function and structure, conceivably by allowing times of low trough concentration for regeneration of tubular cells.[6] In contrast, the effect of single daily dosing on glomerular function, which is our main focus of concern, is still largely uncharted and remains hypothetical. In a MEDLINE search for publications from Jan. 1, 1999, to Dec. 15, 2004, on renal damage induced by lithium, we found only 1 publication that describes the "surprising" finding of glomerular lesion.[7] Similarly, the potential protective effects of potassium supplementation and of amiloride have been shown on the tubular level, while nothing yet has been described of their actions on the glomerular function and structure.

Finally, it is logical to assume that, to be effective in preventing renal damage, any such means should be used from the start or, at least, early in the course of lithium treatment, before the initial functional impairment develops into irreversible structural damage.[5]

As I already mentioned in my reply to Smith's letter, most of our patients were on a twice a day regimen. Only 4 patients in our series were on long-term once a day lithium treatment. Two of them developed signs of renal insufficiency. Like most of our renal insufficiency patients, they remained free of clinical symptoms.

Notwithstanding the above reservations, I certainly concur with Gitlin's conclusion that "a reasonable current recommendation would be that patients who can tolerate once daily lithium and find it an easier regimen should be allowed to use this regimen since no studies have suggested any benefit from administration of multiple daily doses."[1(p241)]

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

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Cholesterol and Lithium Levels Were Correlated but Serum HDL and Total Cholesterol Levels Were Not Associated With Current Mood State in Bipolar Patients

Sir: In patients with bipolar I disorder, low total serum cholesterol levels have been reported during full remission and manic and depressive episodes.[1,2] Several cohort studies[3–5] assessed the relationship between plasma cholesterol level and depressive symptoms with contradictory results. Studies[6,7] focusing on depressive patients have been more consistent in reporting an association between low total serum cholesterol and major depressive disorder. Some clinical trials also showed that clinical recovery from depression may be associated with a significant increase of total plasma cholesterol.[8] Low serum cholesterol has also been associated with higher suicide attempt risk.[9] Lithium appears to have an antisuicidal effect on bipolar patients during a depressive episode.[10]

In this cross-sectional study, serum high-density lipoprotein (HDL) cholesterol and total serum cholesterol levels were measured in 106 consecutive bipolar outpatients from a lithium clinic at a Spanish general hospital.

Method. The Ramón y Cajal Hospital covers a catchment area of 500,000 persons in Madrid, Spain, most of whom are white.[11] In 1998, 106 consecutive patients with bipolar disorder (73 women and 33 men) were recruited after written informed consent was obtained. The study was approved by the review board of the hospital in which the study was conducted. DSM-IV criteria were used to diagnose the patients and classify their current mood state (24% [25/106] were depressed, 67% [71/106] were in remission without a major depressive or hypo-

manic episode, and 9% [10/106] were hypomanic or manic). HDL, total serum cholesterol, and trough lithium levels were measured from fasting blood samples in the early morning before breakfast.

Results. Mean total serum cholesterol levels (mg/dL) were 204.8 in the depressed group (206.7 in women and 200.0 in men), 205.3 in the remitted group (208.4 in women and 198.5 in men), and 197.7 in the manic group (205.0 in women and 186.8 in men). Mean HDL levels (mg/dL) were 53.9 in the depressed group, 56.9 in the remitted group, and 63.2 in the manic group.

Mean total serum cholesterol and HDL levels were not associated with current mood states (analysis of variance; $F = 0.15$, $df = 2$, $p = .87$, and $F = 0.88$, $df = 2$, $p = .42$, respectively). There was an association between gender and cholesterol levels that was almost significant (multivariate analysis of variance [MANOVA]; $F = 3.947$, $df = 1$, $p = .054$) but became nonsignificant after adjusting for current mood state (MANOVA; $F = 0.06$, $df = 1$, $p = .94$). Mood state was not significantly associated with cholesterol levels in this sample, but other researchers have indicated that it was one of the major confounders that needed to be controlled for.[12]

The correlation between plasma cholesterol and lithium levels was significant (Pearson correlation = –0.20, $p = .04$). The correlation continued to be significant after adjusting for gender and current mood state (partial correlation coefficient = –0.20, $p = .046$). The negative correlation (–0.20) indicates that higher lithium levels were associated with lower serum cholesterol.

In summary, this cross-sectional study including a representative sample of bipolar patients suggested no obvious association of HDL or total serum cholesterol levels with current mood state or gender, but total serum cholesterol levels were significantly correlated to lithium levels. Although there is not complete agreement in all studies, animal and in vitro studies appear to suggest that lithium administration may influence cholesterol levels[13] and increase de novo cholesterol synthesis in some cell lines.[14]

Our study was limited by a lack of suicide behavior assessments. Further research is needed to test the relationship between lithium treatment and serum cholesterol levels in larger bipolar samples using prospective designs. Other studies[1,2,8] have suggested a relationship between mood state and serum cholesterol levels. Therefore, prospective longitudinal studies in the same sample of bipolar individuals may help to establish or rule out this relationship.

Dr. Saiz Ruiz has received grant/research support from Lilly Spain and has been on the speakers/advisory board of Lundbeck. Dr. Baca-Garcia has been on the speakers/advisory board of Sanofi-Synthelabo. In the past 2 years, Dr. de Leon has been on the advisory board of Bristol-Myers Squibb and AstraZeneca, received researcher-initiated grants from Roche Molecular Systems, Inc and from Eli Lilly, and once gave a lecture supported by Eli Lilly. Drs. Diaz-Sastre, Perez-Rodriguez, and Cebollada report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Serious Rash With Lamotrigine After Carbamazepine Discontinuation: A Case Report

Sir: Lamotrigine is an anticonvulsant agent recently approved by the U.S. Food and Drug Administration for maintenance treatment of bipolar illness.[1] Carbamazepine is also an antiepileptic drug commonly used as a mood stabilizer. Rash is frequently associated with both lamotrigine and carbamazepine, ranging from a mild, benign, nonserious rash to a more severe rash in the form of Stevens-Johnson syndrome or even toxic epidermal necrolysis.[2–5]

In premarketing clinical trials of epilepsy, severe or worrisome rash occurred in 1 per 300 cases treated with lamotrigine.[1] However, in bipolar and other mood disorder trials, serious rash occurred in only 1 per 1000 cases.[2] This difference seems to have resulted from the recognition of the importance of a slow titration.[2] Coadministration with valproic acid may increase the risk of rash associated with lamotrigine.[1] Since coadministration with carbamazepine may reduce lamotrigine levels, carba-

mazepine has not been viewed as an agent of concern. Here, we describe a case of serious rash associated with an interaction between lamotrigine and carbamazepine.

Case report. Mr. A, a 63-year-old white man with a past history of bipolar I disorder and no apparent risk factors for rash, first came to our office in a hypomanic state. He was on treatment with lamotrigine and nefazodone for bipolar illness along with clonazepam for restless legs syndrome. Nefazodone was discontinued, lamotrigine was continued at 200 mg daily, and carbamazepine was added at 600 mg per day. Two weeks later, he reported being more euthymic. Lamotrigine was continued, and the patient's carbamazepine dose was increased to 800 mg per day for residual symptoms.

One month later, the patient reported depressive symptoms related to the death of his dog. These were associated with pressured speech and feelings of restlessness and agitation, along with suicidal thoughts. At that time, his carbamazepine dose was further increased to 1000 mg per day. However, 2 weeks later, Mr. A complained of sedation, dizziness, and unsteadiness, although from a psychiatric standpoint he felt more stable. Due to these side effects, he was told to reduce the carbamazepine dose to 600 mg per day, but he instead totally and suddenly discontinued carbamazepine while continuing to take lamotrigine at 200 mg daily. Within 1 week of doing so, he developed a rash surrounding his mouth and on his palms. Mr. A's primary care doctor treated him with prednisone, and he was told to discontinue lamotrigine and carbamazepine. On a subsequent visit to our office 3 weeks later, his rash had disappeared, and he was started on treatment with olanzapine 10 mg/day for bipolar disorder.

The worrisome skin reaction that occurred in this patient is thought to be associated with the sudden discontinuation of carbamazepine and a predictable increase in the level of lamotrigine despite no changes for months in the lamotrigine dose consumed. Carbamazepine is metabolized through the cytochrome P450 enzyme, mainly the 3A4 system.[6] It causes an induction of the cytochrome P450 enzyme, often resulting in an increase in the rate of its own metabolism as well as that of other drugs metabolized by the cytochrome P450 system.[6] In this case, discontinuation of carbamazepine is believed to have resulted in a sudden reduction of enzyme capacity, thus reducing the rate of lamotrigine breakdown and leading to serious rash, as if the lamotrigine dose was increased rapidly. This rash occurred after several months of treatment with a stable dose of lamotrigine, suggesting that the risk for a serious rash may extend beyond the initial 2 months of treatment. Interaction with carbamazepine is a previously unreported way in which lamotrigine may cause worrisome rash and should be considered when treating bipolar patients with this combination.

Dr. El-Mallakh has been on the speakers/advisory boards of Pfizer, Janssen, Eli Lilly, Bristol-Myers Squibb, AstraZeneca, and Glaxo. Dr. Surja and Ms. Brotzge report no financial affiliation or other relationship relevant to the subject matter of this letter.

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Correction

In the BRAINSTORMS installment "Prophylactic Antipsychotics: Do They Keep You From Catching Schizophrenia?" by Stephen M. Stahl, M.D., Ph.D. (November 2004 issue, pp. 1445–1446), reference 6 should be: Woods SE, Breier A, Zipursky RB, et al. Randomized trial of olanzapine vs placebo in the symptomatic acute treatment of patients meeting criteria for the schizophrenia prodrome. Biol Psychiatry 2003;54: 453–464. The online version has been corrected.