Lithium-Associated Psoriasis and Omega-3 Fatty Acids

TO THE EDITOR: Psoriasis is a well-known cutaneous adverse effect of lithium treatment (1). Among the various options for treatment are infusions with omega-3 fatty acids (2, 3). Recently, we participated in a double-blind, placebo-controlled study on the effects of the addition of a maximum of 6 g/day of omega-3 fatty acids containing eicosapentaenoic acid (EPA) ethyl esters to patients with bipolar disorder. In this study, two patients reported a spontaneous reduction of psoriasis, possibly related to taking omega-3 fatty acids.

Ms. A was a woman of 59 years of age with bipolar II disorder, who had been taking lithium for 6 years. After 2 years of lithium treatment, she developed psoriasis on her head, arms, legs, belly, and nails in the form of skin eruptions and scales. In addition to treatment with lithium, carbamazepine, lorazepam, and levothyroxine, she began taking double-blind-study medication because of depression. Initially, she received placebo for 4 months. Because she had not recovered, she was then offered open-label treatment with 6 g/day of omega-3 fatty acids for 4 months, which had no effect on her depression.

After Ms. A started treatment with omega-3 fatty acids, her psoriasis disappeared completely within 4 weeks. When she stopped the medication, the skin problems returned within a week. After another 3 months, she tried another formulation of omega-3 fatty acids from a local drugstore, and it also contained EPA. She took 2 g/day for 4 months but received no positive effects.

Mr. B was a man of 52 years of age with bipolar I disorder. Since his youth, he had also had psoriasis, which had become aggravated, with eruptions on his eyebrows, forehead, and elbows, after he had started taking lithium 13 years ago. In addition to lithium and levothyroxine, he blindly received omega-3 fatty acids because of recurrent depression. Because of adverse effects (diarrhea and nausea), he took varying doses of omega-3 fatty acids, between 2 and 6 g/day, which had no effect on his depression. After the double-blind phase, Mr. B continued treatment with open-label omega-3 fatty acids, at an average dose of 4 g/day, but he stopped taking it after another 2 months because his depression did not improve and he experienced the same adverse effects.

Within 3 weeks after the start of treatment with omega-3 fatty acids, Mr. B recovered totally from his psoriasis. His reddish, scaly skin was transformed. After discontinuing the omega-3 fatty acids, his skin remained stable for 3 months, but then his psoriasis gradually returned.

Our positive findings regarding 4–6 g/day (but not 2 g/day) of omega-3 fatty acids in these two patients with lithium-associated psoriasis are in line with the positive results from recent studies of infusions of omega-3 fatty acids in patients with acute psoriasis (3). In addition to studies in patients with bipolar disorder, we suggest further studies of omega-3 fatty acids in patients with (lithium-associated) psoriasis.

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Side Effects of Ziprasidone

TO THE EDITOR: The following case report pertains to the use and side effects of ziprasidone. In particular, this vignette relates to the prolongation of the QTc interval in the face of abnormal electrolyte levels.

The issue of ziprasidone lengthening the QTc interval has demanded a good deal of attention and created substantial anxiety among clinicians since the drug was recently introduced (1). Considerable scrutiny of ziprasidone's cardiac effects regarding the inception of arrhythmias has been ongoing (2). While thioridazine received a "black box" warning concerning its QTc-interval disturbances, other conventional antipsychotics, such as haloperidol, have also been associated with this risk (3, 4). Glassman and Bigger (1) estimated the rate of occurrence of torsade de pointes with this group of older antipsychotics as "10–15 such events in 10,000 person-years of observation." To our knowledge, no case of torsade de pointes during ziprasidone use has emerged, despite the drug's growing use at doses in excess of 160 mg/day. Moreover, we know of no appearance of arrhythmia in reported cases of intentional overdose (5, 6).

This absence of negative information has not cooled the general fear that, at least in special cases, ziprasidone may yet engender significant arrhythmia, including potentially fatal ventricular disturbances. No study, to our knowledge, has yet addressed either general considerations concerning drug interactions and metabolic interference potentially causing QTc-interval prolongation or specific metabolic inhibitors of aldehyde oxidase, an important mediator of ziprasidone metabolism (7). Recently, Biswas et al. (8) reported a case of cardiac arrhythmia without fatality yet "requiring aggressive cardiac monitoring" in a 17-year-old adolescent who overdosed with ziprasidone and bupropion in combination. Although authors' opinions differ widely (9–13), bupropion in overdose may alone engender cardiotoxicity, including QTc-interval prolongation.

Apart from congenital anomalies, the risk of QTc prolongation increases dramatically in the presence of hypokalemia and hypomagnesemia (14–16). The following case report addresses how ziprasidone behaves in the presence of severe hypokalemia and accompanying hypomagnesemia, significant causes of ventricular abnormalities.

Ms. A was a 52-year-old woman with a lifelong history of severe mood disorder not otherwise specified and borderline personality syndrome. At age 48, she developed a small right cerebrovascular accident secondary to toxic shock syndrome. She had potassium wasting secondary to diuretic treatment, which necessitated her taking exogenous potassium in the form of sustained-release potassium chloride. In addition, she suffered from mild emphy-

sema due to cigarette smoking. For her psychiatric disorders, Ms. A received a medication cocktail consisting of fluoxetine, lamotrigine, amitriptyline, and clonazepam, which brought her significant emotional relief. Of all of the medications Ms. A received, only amitriptyline had potentially destabilizing effects on her myocardium. Nevertheless, she had long used this drug at stable therapeutic levels and obtained multiple serial ECGs without any prior signs of deleterious effects.

Three months before her crisis, Ms. A had received a trial of ziprasidone up to 160 mg/day without ill effect. She then discontinued the drug because of its lack of efficacy in controlling her mood instability and did not receive replacement treatment with another antipsychotic. She did not experience ill effects of any sort during the trial period or during the reduction phase. Her other medications remained unchanged.

About a month after discontinuing ziprasidone, Ms. A inadvertently discontinued her potassium chloride. Soon after, she became confused and ataxic. As a result of her confusion, she began to self-administer ziprasidone in the previous dose for an indeterminate period. A few days before hospital admission, she visited her internist, who, despite her complaints, found her neurologically intact. He ordered magnetic resonance imaging, which showed no change from an earlier reading. He did not perform an ECG or order measures of her electrolyte levels.

Later, after becoming stuporous and repeatedly falling, Ms. A went to an emergency room and was promptly admitted to an intensive care unit because of her abnormal ECG. The ECG showed a markedly lengthened QTc interval, varying from 680 to 720 msec. Her ventricular rate was 75 bpm. Her P-R interval was 166 msec, and her QRS interval was 92. Her cardiac axes were shifted slightly to the right, in keeping with previous readings. Her heart remained in normal sinus rhythm. Her initial potassium level was 1.8 mEq/liter, and her magnesium level was 2.4 mEq/liter. Her potassium oxide level was 74.0 mEq/liter, and her pH was 7.48. Once she received intravenous potassium and magnesium, her QTc interval slowly returned to normal, in close conjunction with improving levels of the two electrolytes.

Our patient's case illustrates ziprasidone's effect on the QTc interval in the presence of a provocative state, severe hypokalemia, and hypomagnesemia. In the present instance, our patient's abnormal electrolyte levels were alone sufficient to account for the prolongation of her QTc interval. While there was evidence to demonstrate the QTc-lengthening effects of ziprasidone, we know of no prior case reports that have discussed its effects under these circumstances. It appears that, at least in this instance, ziprasidone's cardiac action is less dramatic than one might anticipate. These data lend further credibility to the idea that the drug's effect on the myocardium is less dire than is widely feared. Certainly, further investigation into this matter is necessary before one can determine the true margin of safety for ziprasidone use. Unfortunately, such data will have to emerge from fortuitous events. Decisions to use this drug ought to result from our appreciation of the facts, which have so far shown little in the way of significant clinical data regarding cardiac impairment. In the meantime, one ought to remain cautious but not unduly critical of ziprasidone.

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Tourette's-Like Syndrome and Dementia

TO THE EDITOR: Frontal-temporal dementia is associated with a variety of behavioral problems (1). We recently cared for a patient with frontal-temporal dementia who had developed an unusual problem: complex vocal and motor tic-like behavior reminiscent of Tourette's syndrome.

Mr. A, a 79-year-old man with a 5-year history of frontal-temporal dementia, had developed disturbing tic-like behavior, consisting of slapping his forearm while grunting and swearing. This occurred many times per hour, generally without provocation, and was sufficiently disturbing that he and his wife were threatened with eviction by their landlord. He had been unable to tolerate a trial of haloperidol and had not responded to olanzapine or to quetiapine, the latter at 200 mg/day. Other behavioral problems included sexual disinhibition directed exclusively toward his wife and purposeless wandering. There was no evidence of mood disorder or psychosis.

Mr. A's past medical and psychiatric history was unremarkable, and there was no prior history of tics. He had a remote history of moderate alcohol consumption. He was taking no medications. There was no family history of psychiatric or neurological illness. Upon a mental status examination, he exhibited a labile affect with clear *witzelsucht*. He was disoriented and amnestic, but his language was neurologically intact. He performed poorly on a test of controlled word fluency and showed paratonic rigidity bilaterally. A computerized tomography scan showed prominent frontal and anterior temporal atrophy. His sexual disinhibition was treated successfully with paroxetine, 40 mg/day, but this had no effect on his tic-like behavior. He was ultimately treated with clonidine, which was titrated without incident to 0.6 mg/day. This resulted in sustained, almost complete remission of the behavior over the past 5 months.

Tariot (2) espoused the concept of the therapeutic metaphor in the treatment of behavioral problems in dementia, whereby a behavioral syndrome reminiscent of a primary psychiatric illness tends to respond to typical treatment for that illness. Clonidine is known to be effective in the treatment of Tourette's syndrome and proved to be remarkably effective for our patient.

Although changes in the frontal cortex and associated subcortical projections have been implicated in the pathophysiology of Tourette's syndrome (3), a Tourette's-like syndrome in dementia or neurological illness seems rare. Yochelson and David (4) reported a Tourette's-like syndrome in a 16-year-old boy after resection of a left frontal arteriovenous malformation, and the syndrome was also responsive to clonidine. Oelenberg and Pach (5) reported a 52-year-old woman with frontal-temporal dementia who developed a Tourette's-like syndrome that failed to respond to haloperidol or tiapride. Vigilance for a similar behavioral syndrome in individuals "with dementia" is warranted, since clonidine may be an effective treatment option.

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Title Change for DSM-V?

TO THE EDITOR: In a remarkable book, *A Research Agenda for DSM-V* (1), 46 international experts proposed far-reaching research that could eventually lead to diagnoses based more on etiology than on symptom syndromes. I offer a suggestion for improving DSM-V that would require little or no research. I suggest deleting the term "statistical" from the title of the manual, thereby making it the "Diagnostic Manual of Mental Disorders, Fifth Edition." The abbreviation would become DM-V—or, perhaps better—DMMD-V. Here is my rationale for the suggested change.

1. The title of a book should concisely and correctly inform readers about its principal content. The current title misleads readers. DSM-I and DSM-II contain short sections on statistical reporting, but DSM-III and DSM-IV do not. Neither DSM-III nor DSM-IV can correctly be called a "statistical manual."
2. DSM classifications are used for statistical reporting, but they are also used for clinical care, teaching, and research. Including all purposes served by DSM would produce a long and unwieldy title.

This change might puzzle or distress some users who have become accustomed to "DSM." Most users would probably appreciate the need and accept the change; a poll of users could be taken. However, the *American Journal of Insanity* changed its name to the *American Journal of Psychiatry* and continued to prosper.

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Change Diagnosis to "Alcohol Withdrawal Delirium"?

TO THE EDITOR: In 1980 APA replaced the DSM-III diagnosis "delirium tremens" with "alcohol withdrawal delirium." In the following, I describe a study that stemmed from the concern that not only can the term "alcohol withdrawal delirium" be easily confused with "alcohol withdrawal" but the diagnosis "alcohol withdrawal delirium" in general medicine is used indiscriminately, such that other potentially important underlying causes for delirium are often overlooked.

Fifty patient charts from the University of New Mexico Hospital with a discharge diagnosis of "alcohol withdrawal delirium" were randomly selected by a medical records computer for 1994, 1996, and 1998 and were reviewed by me (director of the Psychiatric Consultation and Liaison Service), a trained research assistant, and a medical intern. Data were obtained regarding diagnosis, mental status observations, nursing notes, drinking history from the patient and his or her family, and presence of major medical and surgical problems. A retrospective diagnosis was made by consensus of the two senior clinicians.

The patients were 47 men and three women with a mean age of 42 years (range=29–75). Most (N=34) were treated in medical units, 13 were in surgical units, and three were in the neurology service. They had a mean length of stay of 9.8 days (range=1–83.) The history of recent drinking for three patients was none. Their retrospective diagnoses included 20 with delirium tremens, six with acute intoxication, four with alcohol withdrawal, two with seizures without delirium, and one with alcohol hallucinosis=1. The remaining 17 patients met our criteria for "multifactorial delirium in chronic alcoholics"; that is, these patients with delirium also had serious medical and surgical problems, especially traumatic injuries, which were more

extensive than those ordinarily seen in patients with delirium tremens. There were two deaths; both patients were retrospectively diagnosed as having multifactorial delirium.

The 13 patients without delirium (26.0%) obviously represented considerable diagnostic error. The 17 patients with multifactorial delirium (34.0%) had longer lengths of stay, with a mean stay of 17.5 days, compared to 5.3 days for the patients with delirium tremens. Fourteen of the 20 patients retrospectively diagnosed as having delirium tremens had episodes occurring during a drinking binge, compared to six patients who had episodes occurring during withdrawal.

A history of alcohol abuse influences the diagnosis of patients with delirium, no matter how medically complicated it is. Some of the difficulties may result from diagnostic terminology. I hope this report, despite the well-known problems of chart review, will stimulate interested clinicians to undertake similar retrospective and prospective studies and alert the current DSM-V committee to consider changing the term "alcohol withdrawal delirium" to "delirium tremens" and to consider introducing a new diagnostic term: "multifactorial delirium in chronic alcoholics."

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[Dr. Rosenbaum died May 20, 2003.]

Is *Taijin Kyofusho* a Culture-Bound Syndrome?

TO THE EDITOR: *Taijin kyofusho* is described as a "culturally distinctive phobia in Japan" in DSM-IV. However, in the indigenous Japanese diagnostic system, depending on the content of the patients' fear that they will displease or embarrass others, *taijin kyofusho* is classified into four subtypes: *sekimen-kyofu* (the phobia of blushing), *shubo-kyofu* (the phobia of a deformed body), *jikoshisen-kyofu* (the phobia of eye-to-eye contact), and *jikoshu-kyofu* (the phobia of one's own foul body odor) (1). Of these four subtypes, *sekimen-kyofu* can reasonably be included in the category of social phobia, according to DSM-IV, since the fear of blushing is a common symptom. *Shubo-kyofu* also fulfills the criteria for body dysmorphic disorder in DSM-IV. Thus, at this stage, the notion that *taijin kyofusho* is a culture-bound syndrome cannot be held. Furthermore, although the remaining two subtypes, *jikoshisen-kyofu* and *jikoshu-kyofu*, cannot be adequately assigned to any of the diagnoses in the DSM-IV classification system, a literature review argues against this notion.

For instance, a case has been reported in which an American woman had a fear of embarrassing others by glancing at their genital areas (2). Although the authors gave a diagnosis of *taijin kyofusho* to the patient, a more adequate diagnosis should have been *jikoshisen-kyofu*, according to Japan's classification system. Moreover, it is likely that individuals suffering from *jikoshisen-kyofu* are overlooked in the West because *jikoshisen-kyofu* is a rare condition, and the vast majority of individuals with it do not seek psychiatric services, even in Japan.

As for *jikoshu-kyofu*, a similar condition exists in Western literature (olfactory reference syndrome). Pryse-Phillips (3) introduced the term, describing patients who are preoccupied with the idea that their bodies emit a foul odor that offends others, a feature identical to that of *jikoshu-kyofu*. Therefore, we contend that *jikoshu-kyofu*, as well as the other three subtypes of *taijin kyofusho*, are not culturally distinctive phobias in Japan.

Since there is no properly conducted population-based study of *taijin kyofusho* in Japan or in other countries, to our knowledge, it is difficult to make a firm conclusion as to whether all four subtypes of *taijin kyofusho* are culturally bound or whether some of the subtypes are virtually specific to Japan. It should be recognized, however, that there is a wide gulf between the understanding of *taijin kyofusho* in Japan, since it incorporates diverse clinical entities, and the current stance in DSM-IV. But is *taijin kyofusho* really a culturally distinctive phobia? (Other countries treat it as a specific type of phobia in Japan.) This discrepancy could be due to the erroneous introduction of the concept of *taijin kyofusho* to the West. In future studies, a diagnostic system specifying each subtype of *taijin kyofusho* should be applied, and more clinical attention should be paid to such sufferers.

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Autism and Visual Fixation

TO THE EDITOR: Dr. Klin et al. (1) presented evidence for abnormalities in the visual behavior of autistic subjects in filmed social interactions. They reported that autistic subjects looked more at objects, and when looking at faces, they fixated mostly on mouths instead of eyes. We studied the fixation patterns of autistic children shown faces and objects as well, but in static conditions, and did not find any abnormalities in fixation parameters (2, 3). Dr. Klin et al. suggested that their results were the reflection of a core social deficit. However, we feel that a different interpretation is warranted, given the fact that visual abnormalities were not seen with the static stimuli used in our studies.

Recent models of facial processing have favored a distinction between the perception of static aspects of faces and the perception of changes due to facial movements (4). Structural facial processing is thought to occur mainly in the lateral fusiform gyrus, while dynamic information is processed in the superior temporal sulcus. The lateral fusiform gyrus is located in the ventral object-processing system. There are indications that the superior temporal sulcus receives input from both the ventral and dorsal streams, which carry dynamic information. Therefore, the abnormal fixation patterns of autistic subjects in response to dynamic but not to static faces might reflect abnormal processing in the dorsal stream. There are several indications from studies of motion perception that dorsal-stream functioning is indeed abnormal in subjects with autism.

Because of a problem in dorsal-stream functioning, subjects with autism might be inclined to avoid dynamic stimuli, such as moving faces. The greater focus on the mouth if such subjects look at faces is surprising. However, Dr. Klin et al. reported a positive relationship between social competence and viewing time when subjects focused on mouths. Their suggestion "that by focusing on mouths these individuals with autism might attain some understanding of social situations (perhaps because of greater, focused attention on speech), whereas attention to eyes may not lead to any additional social insights" (p. 906) is interesting. The tendency to focus on mouths might reflect an effort of autistic subjects to overcome a basic perceptual problem. One of the hallmarks of the study by Dr. Klin et al. is a better definition of the phenotype of autism. We want to stress the importance of studying basic perceptual mechanisms in order to improve the chance of finding phenotypic markers.

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Dr. Klin and Colleagues Reply

TO THE EDITOR: In our article, we argued that low orientation to salient social cues embedded in naturalistic social situations is a core deficit in autism. We argued this on the basis of several observations that are not consistent with the suggestions made by Drs. Kemner and van Engeland. Their hypothesis is that individuals with autism exhibit abnormalities in processing moving (versus static) stimuli in general and that the conflict between their findings (van der Geest et al., 2002; J Autism Dev Disord; van der Geest et al., 2002; J Child Psychol Psychiatry) and our results in the *Journal* and elsewhere (1) could be explained in terms of their use of static faces and our use of moving faces.

However, in our experiments, there were several situations in which individuals with autism visually tracked, inspected, and reacted appropriately to moving objects (e.g., a moving glass held by one of the movie protagonists, an opening door, a swinging lamp) as well as movement cues. Figure 6 in our article (p. 903) actually shows that a person with autism reacted more quickly than a typical viewer to a moving cue and with equal accuracy. On the basis of our observations, the scanning patterns of a typical viewer were not different from those of a viewer with autism in their general response to moving stimuli; rather, they differed in specific response to the social components of the stimuli, as opposed to the nonsocial physical aspects (whether static or not). In fact, there were situations in which a face was stationary for as long as 15 seconds and yet the fixation patterns exhibited by the viewer with autism still revealed a preference for the mouth area rather than the facial area (as in Figure 3, p. 900). Although not included in this article, of the time that the viewer with autism looked at faces, he or she spent 14.2% on the eye area and 85.8% on the mouth area, contrasted with 77.8% and 22.2%, respectively, for the typical viewer (χ^2=8.77, df=1, p=0.003). This greater fixation time for mouths was further corroborated in our case-control series (1). Among the various elements of the face, when people are talking the mouth is probably the one that moves the most. In light of this, it is unclear how focus on the mouth, as described in the letter by Drs. Kemner and van Engeland, could reflect an effort by viewers with autism "to overcome a basic perceptual problem," defined as difficulty in processing moving objects.

Finally, we disagree with the suggestion implied in their letter that lack of abnormality in visual fixation patterns in response to static faces signifies intact brain function (involving the lateral fusiform gyrus) underlying "structural facial processing." We (2) and others (3) have shown that intact performance in facial recognition tasks may in fact be associated with abnormal activation patterns of the ventral temporal cortices (specifically, hypoactivation of the fusiform facial area).

In our view, the conflicting findings across the two studies reflect a different but important conceptual point (4). The difference between the studies is that while van der Geest and colleagues presented their subjects with static pictures of faces occupying the entire viewing area, we presented our subjects with scenes intended to recreate a more naturalistic social situation, in which people's faces were embedded in a changing, ongoing context (just as we see people day to day in a way that is necessarily dynamic). While we may encounter static depictions of faces in a magazine, our daily social interactions are inherently contextual and dynamic. In our view, this dynamism is not so much an experimental confound as an integral component of real social scenarios. The main hypothesis put forward in our article was not that individuals with autism are unable to scan faces adequately if instructed to look carefully at them. Our main hypothesis was that they fail to do so in more naturalistic situations when they are trying to make sense of what they see as it is happening. It is in this sense that eye-tracking methods allow us to identify spontaneous visual fixation patterns displayed by individuals with autism, presenting a window into those aspects of the social scene that may have been missed as well as a better understanding of the possible compensatory strategies used to detect meaning in what they see.

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Dr. Horton Replies

TO THE EDITOR: Aaron H. Esman's angry ad hominem denunciation (1) of my review of Breger's *Freud: Darkness in the Midst of Vision* (2) represents a case of shooting the messenger. His argument is with Breger, not with me. Breger contended that Freud, despite not having encountered it personally, used claims of anti-Semitism to his own advantage. This was at a time when

> The Rothschild banking empire [was] well known, yet it was but one of several Viennese banks owned by Jews. In industry, there was Karl Wittgenstein…Austria's largest steel magnate. By the 1880's,…Jews made up one-third of the student body of the University of Vienna…50 percent in medicine and almost 60% in law. All the liberal daily newspapers were owned by Jews and a large proportion of the journalists were Jewish. As the turn of the century approached, the majority of the liberal, educated, intellectual elite of Vienna was Jewish…by 1900 Jewish doctors held the majority of chairs at the University of Vienna Medical School and most of the directorships of the city's hospitals. The emperor's personal physician, the obstetrician to the women in the imperial family, and the surgeon general of the army were all Jewish. Within the university and his chosen field, the fact that Freud came from a Jewish background, far from being a handicap in advancing his career, may well have been an advantage. (3, p. 40–41)

Given these claims and many other statements made by Breger—all of which were cited by page number in my review—about the milieu in which Freud developed his views and about Jewish life, including Jewish life in post–World War I Austria, it is difficult to conclude that anti-Semitism played much of a role, if any, in shaping Freud's *weltanschauung*.

Dr. Esman faults me for not acknowledging the rise of anti-Semitism in the late 1930s. However, while Breger had many things to say about the conditions that might have engendered growing anti-Semitism after World War I, this issue was tangential to his main thesis about the "darkness in the midst" of Freud's vision.

References

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