Posttraumatic Bell's Palsy

TO THE EDITOR: Although Bell's paralysis is common, in many instances its pathogenesis remains unknown. We report on an unusual case with a possible psychological origin.

Mr. A, a 36-year-old train driver, accidentally ran over a suicidal man as the train pulled into a station. Mr. A reacted with horror but continued working. Six weeks later he suddenly noticed two young men standing on the tracks, obviously testing their courage, a few hundred yards in front of his train. No accident occurred, but he was unable to work and called in sick. He felt weak and noticed a prickling on the right side of his face, followed by numbness. The next morning he noticed that his right lip was drooping, saliva was dripping out of the right side of his mouth, and he was unable to blink his right eye. Two days later a neurologist discovered hypoesthesia of his right cheek, Bell's phenomenon on his right side, and a loss of taste on the right side of his tongue; the neurologist diagnosed Bell's paralysis on his right side. Total recovery took 3 weeks. During this period Mr. A did not go to work; he suffered from nightmares and depression and persistently relived the trauma.

Then left facial paralysis appeared. Mr. A was admitted to a university hospital, where peripheral facial palsy on the left side was confirmed. An electrophysiological examination by means of neurography and testing of the orbicularis oculi reflex revealed an incomplete lesion. The results of a lumbar puncture and extensive laboratory tests were negative, as were the results of magnetic resonance imaging. Examinations of serum and CSF provided no evidence of an infectious etiology (e.g., Lyme borreliosis, herpes simplex, varicella-zoster virus, HIV, cytomegalovirus, or Epstein-Barr virus). Recovery took 2 months. In the meantime, posttraumatic stress disorder was diagnosed.

Once during psychotherapy in a rehabilitation clinic, Mr. A was filled with tremendous fear before a treatment session in which he expected to be confronted with what had happened to him. A prickling sensation on the right side of his face reappeared, and according to his and his therapist's reports, temporary right facial paralysis remained for a couple of hours.

To the best of our knowledge, the study by Goldberg and Harte (1) is the only report to systematically focus on emotional factors as a possible cause for Bell's paralysis. The authors reported that facial paralysis resulting from severe emotional trauma might range from a simple conduction block to almost complete neural degeneration. They assumed that such palsy might result from a spasm of the vasa nervorum in the fallopian canal. In cases of otherwise unknown pathogenesis, a past history of severe emotional trauma should be suspected.

Reference

1. Goldberg MJ, Harte S: Emotional factors contributing to facial paralysis. J Am Geriatr Soc 1972; 7:324–329

TORSTEN SIOL, M.D.
MICHAEL HUBER, M.D.
HELMUT BUCHNER, M.D.
Cologne, Germany

Topiramate for Bulimia Nervosa in Epilepsy

TO THE EDITOR: Topiramate is a novel agent approved for the treatment of epilepsy; it has purported effects at voltage-activated sodium channels and γ-aminobutyric acid and glutamate receptors (1). In addition to its anticonvulsant properties, topiramate suppresses appetite, is associated with weight loss (1), and may have mood-stabilizing properties (2). I will describe the history of a patient with partial complex epilepsy and comorbid bulimia nervosa who had complete cessation of her eating disorder with topiramate therapy.

Ms. A was a 34-year-old right-handed woman. Although she did not walk until she was 19 months of age, her intellectual development was considered age-appropriate during her school years. By age 8 she had began to experience a depressed mood, reduced motivation, compulsive overeating, excessive weight gain, and insomnia. She did not receive psychiatric treatment until age 16; that treatment consisted of individual psychotherapy. Despite recurrent depressive and vegetative symptoms, she graduated from high school and college and entered a graduate-level professional school. While in professional school she began to induce vomiting with her fingers or syrup of ipecac. She continued purging several times per week for the next decade. Her bulimic symptoms did not respond to treatment with fluoxetine, sertraline, or venlafaxine.

After graduation from professional school at age 29, Ms. A suffered two losses of consciousness. These were preceded by "altered visual perception" and an intense sensation of thirst. The second loss of consciousness was associated with tonic posturing of all of her extremities. Metabolic derangements secondary to her eating disorder were suspected but could not be confirmed. An EEG revealed left temporal slowing and left anterior temporal sharp waves. The results of computerized tomography and magnetic resonance imaging scans of her brain were unremarkable. She was prescribed phenytoin therapy.

Ms. A's convulsions ceased when she had maintained adequate blood levels of phenytoin for about 5 years. She experienced occasional auras, which often included the sensation of thirst. Phenytoin therapy had no effect on her binge eating or purging. She had recurrent depressive episodes and one episode of self-mutilation with broken glass. After 5 years of phenytoin treatment, the auras began to appear more frequently, and she had a partial complex seizure with clonic movements of the right arm and leg, despite having a serum phenytoin level of 23.4 μg/ml. Topiramate was prescribed and gradually increased to 150 mg/day. Her auras and convulsions disappeared. In addition, she experienced a reduced appetite and a 10-lb weight loss. She became less concerned about her weight and had a reduced desire for binge eating, purging, and self-mutilation. As of this writing, she has remained free of these symptoms for 15 months.

This case is interesting for a number of reasons. Although psychiatric symptoms are commonly reported in patients with epilepsy, the association of epilepsy with eating disorders is less clear. Although the patient's eating disorder predated her clinical epilepsy by several years, the fact that her seizure auras included sensations of thirst suggests that her uncontrolled epileptiform activity could have been related to abnormal appetitive behavior.

The complete resolution of her bulimic symptoms with topiramate therapy also appears to be a novel observation. Selective serotonin reuptake inhibitors are normally prescribed for bulimia nervosa. This practice is supported by a controlled study with fluoxetine (3). Anticonvulsants such as phenytoin (4) and carbamazepine (5) have had limited success in the treatment of bulimia nervosa. This case suggests that the pharmacological actions of topiramate might be useful in the treatment of bulimia nervosa and that controlled trials with this agent are warranted.

References

1. Privitera MD: Topiramate: a new anti-epileptic drug. Ann Pharmacother 1997; 31:1164–1173
2. Marcotte D: Use of topiramate, a new anti-epileptic, as a mood stabilizer. J Affect Disord 1998; 50:245–251
3. Fluoxetine Bulimia Nervosa Study Group: Fluoxetine in the treatment of bulimia nervosa: a multi-center, placebo-controlled, double-blind trial. Arch Gen Psychiatry 1992; 49:139–147
4. Wermuth BM, Davis KL, Hollister LE, Stunkard AJ: Phenytoin treatment of the binge-eating syndrome. Am J Psychiatry 1977; 134:1249–1253
5. Kaplan AS, Garfinkel PE, Darby PL, Garner DM: Carbamazepine in the treatment of bulimia. Am J Psychiatry 1983; 140:1225–1226

MICHAEL B. KNABLE, D.O.
Bethesda, Md.

Thyroid Hormones and Seasonal Mood Change

TO THE EDITOR: Several studies of peripheral thyroid economy in seasonal affective disorder have shown inconsistent results (1). However, measurements of the peripheral thyroid state may not provide a reliable index of the central thyroid state (2).

In contrast to the peripheral tissues, where most of the nuclear-bound triiodothyronine (T_3) is imported from the plasma pool, in the brain the supply of T_3 depends mostly on the cellular uptake and intracellular deiodination of thyroxin by type II 5′-iodothyronine deiodinase (3). The existence of a separate pathway in the brain for thyroxin deiodination suggests that the adult central nervous system has the ability to autoregulate thyroid status (4).

A short photoperiod and low ambient temperature are direct stimuli that could affect type II 5′-iodothyronine deiodinase activity (5). Other effects of temperature and photoperiod (e.g., decreased pituitary and gonadal hormones) could be indirect factors that stimulate type II 5′-iodothyronine deiodinase activity. Thus, seasonal changes in light and temperature may affect the metabolism of brain thyroid hormones.

T_3 may itself be a neurotransmitter, and it may have an antidepressant effect (6). It enhances the effects of norepinephrine (7), serotonin (8), and γ-aminobutyric acid (9). Small alterations of brain thyroid economy, independent of peripheral changes in thyroid status, may produce significant behavioral effects. Therefore, it is reasonable to suggest that brain thyroid hormones might be involved in the mechanisms of seasonal changes in mood and behavior.

References

1. Sher L, Rosenthal NE, Wehr TA: Free thyroxine and thyroid-stimulating hormone levels in patients with seasonal affective disorder and matched controls. J Affect Disord 1999; 56:195–199
2. Esposito S, Prange AJ Jr, Golden RN: The thyroid axis and mood disorders: overview and future prospects. Psychopharmacol Bull 1997; 33:205–217
3. Crantz FR, Silva JE, Larsen PR: An analysis of the sources and quantity of 3,5,5′-triiodothyronine specifically bound to nuclear receptors in rat cerebral cortex and cerebellum. Endocrinology 1982; 110:367–375
4. Dratman M, Crutchfield F, Gordon J, Jennings A: Iodothyronine homeostasis in rat brain during hypo-hyperthyroidism. Am J Physiol 1983; 245:185–193
5. Puig-Domingo M, Guerrero JM, Vaughan MK, Little JC, Reiter RJ: Activation of cerebrocortical type II 5′-deiodinase activity in Syrian hamsters kept under short photoperiod and reduced ambient temperature. Brain Res Bull 1989; 22:975–979
6. Mason GA, Walker CH, Prange AJ Jr: L-Triiodothyronine: is this peripheral hormone a central neurotransmitter? Neuropsychopharmacology 1993; 3:253–258
7. Gordon JT, Martens DA, Tomlinson EE, Greenberg J, Dratman MB: Desmethylimipramine, a potent inhibitor of synaptosomal norepinephrine intake, has diverse effects on thyroid hormone processing in rat brain, II: effect on in vivo 5′-deiodination of [^{125}I]thyroxine. Brain Res 1994; 634:96–104
8. Mason GA, Bondy SC, Nemeroff CB, Walker CH, Prange AJ Jr: The effects of thyroid state on beta-adrenergic and serotonergic receptors in rat brain. Psychoneuroendocrinology 1987; 12:261–270
9. Mason GA, Walker CH, Prange AJ Jr: Modulation of gamma-aminobutyric acid uptake of rat brain synaptosomes by thyroid hormones. Neuropsychopharmacology 1987; 1:63–70

LEO SHER, M.D.
Bethesda, Md.

Thalamic Alterations in Schizophrenia

TO THE EDITOR: Erin A. Hazlett, Ph.D., et al. (1) illustrated anatomic and metabolic alterations in the left anterior and mediodorsal thalamic nuclei in schizophrenic patients. Dorsal thalamic nuclei are smaller and contain fewer neurons in schizophrenic patients than in comparison subjects (2). Andreasen et al. (3) suggested that symptoms and signs of schizophrenia may derive from dysfunction in the thalamus and its circuitry. Infarctions in the anterior tuberothalamic artery region produce clear-cut thalamic lesions and memory impairments (4) resembling those observed in schizophrenic patients (5).

We studied seven patients with strokes in the left anterior thalamus by recording auditory-evoked fields and magnetic spontaneous brain activity (4). Two had delusions at disease onset. Auditory-evoked fields induced by tones delivered at a 2-second interstimulus interval were normal. However, an increase in the length of the interstimulus interval failed to enhance auditory-evoked fields in a fashion observed in comparison subjects. Mismatch fields, elicited by infrequent deviant tones among regular standard tones, were significantly smaller in patients than in comparison subjects. Parieto-occipital spontaneous brain activity was slowed. It is of interest that these electrophysiological alterations resembled those described previously in schizophrenic patients, who have lower mismatch responses (6) and a lower peak frequency of parieto-occipital spontaneous activity (7). A smaller interstimulus interval effect on auditory-evoked responses is implicated by an animal model (8).

Resemblances in findings among patients with thalamic infarctions and patients with schizophrenia support the hypothesis of thalamic alteration in schizophrenia. Further research on correlations of neuropsychological and electrophysiological findings and the severity of alterations in the left anterior thalamus among schizophrenic patients is clearly warranted.

References

1. Hazlett E, Buchsbaum MS, Byne W, Wei TC, Spiegel-Cohen J, Geneve G, Kinderlehrer R, Haznedar MM, Shihabuddin L, Siever LJ: Three-dimensional analysis with MRI and PET of the size, shape, and function of the thalamus in the schizophrenia spectrum. Am J Psychiatry 1999: 156:1190–1199
2. Harrison P: The neuropathology of schizophrenia: a critical review of the data and their interpretation. Brain 1999: 122:593–624
3. Andreasen N, Arndt S, Swayze V, Cizadlo T, Flaum M, O'Leary D, Ehrhardt J, Yuh W: Thalamic abnormalities in schizophrenia visualized through magnetic resonance image averaging. Science 1994: 266:294–298
4. Mäkelä JP, Salmelin R, Kotila M, Salonen O, Laaksonen R, Hokkanen L, Hari R: Left thalamic infarctions modify neuromagnetic cortical signals. Electroencephalogr Clin Neurophysiol 1998: 106:433–443
5. Aleman A, Hijman R, de Haan EH, Kahn RS: Memory impairment in schizophrenia: a meta-analysis. Am J Psychiatry 1999: 156:1358–1366
6. Javitt D, Doneshka P, Grochowski S, Ritter W: Impaired mismatch negativity generation reflects widespread dysfunction of working memory in schizophrenia. Arch Gen Psychiatry 1995: 52:550–558
7. Canive J, Lewine J, Roberts B, Edgar C, Davis J, Orrison WJ: Magnetoencephalographic assessment of spontaneous brain activity in schizophrenia. Psychopharmacol Bull 1996: 32:741–750
8. Jayachandra M, Schroeder C, Lindsley L, Javitt D: Auditory N1 refractoriness in a primate model of schizophrenia. Soc Neurosci Abstracts 1997: 23:557

JYRKI P. MÄKELÄ, M.D., PH.D.
MERVI KOTILA, M.D., PH.D.
MARKUS HENRIKSSON, M.D., PH.D.
Helsinki, Finland

Medication-Free Minors With Schizophrenia

TO THE EDITOR: In their conclusions on schizophrenia research with medication-free minors, Sanjiv Kumra, M.D., F.R.C.P., and colleagues (1) may have underestimated the clinical impact of the speed of tapering neuroleptic medications in children and adolescents, who are usually more sensitive to the adverse effects of psychotropics. The authors stated that the subjects were tapered "over 1 to 2 weeks." Whether or not this schedule conforms to routine clinical practice, common sense and guidelines for the tapering of most psychotropics taken for prolonged periods suggest that this schedule be considered an *abrupt* withdrawal.

And contrary to what the authors implied in their article, the study they cited (2) and another meta-analysis of neuroleptic withdrawal (3, 4) actually show that abrupt withdrawal increases the probability of recurrence of psychotic symptoms. In that light, the "rapid and severe deterioration" of symptoms that followed drug discontinuation in 26% of their subjects points to a withdrawal reaction, as psychotic relapses rarely occur during the first weeks of withdrawal (5). Withdrawal reactions appear to be especially common when atypical neuroleptics are abruptly withdrawn (6, 7). Until the authors provide additional data (e.g., on concomitant medications prescribed and withdrawn, on withdrawal-emergent extrapyramidal symptoms, on speed of response to reinstitution of neuroleptics), their study underscores the clinical need for gradual, patient-centered drug withdrawal and the scientific need to distinguish between neuroleptic withdrawal reactions and psychotic relapses.

References

1. Kumra S, Briguglio C, Lenane M, Goldhar L, Bedwell J, Venuchekov J, Jacobsen LK, Rapoport JL: Including children and adolescents with schizophrenia in medication-free research. Am J Psychiatry 1999; 156:1065–1068
2. Viguera AC, Baldessarini RJ, Hegarty JD, van Kammen DP, Tohen M: Clinical risk following abrupt and gradual withdrawal of maintenance neuroleptic treatment. Arch Gen Psychiatry 1997; 54:49–55
3. Gilbert PL, Harris J, McAdams LA, Jeste DV: Neuroleptic withdrawal in schizophrenic patients: a review of the literature. Arch Gen Psychiatry 1995; 52:173–188
4. Baldessarini RJ, Viguera AC: Neuroleptic withdrawal in schizophrenic patients. Arch Gen Psychiatry 1995; 52:189–192
5. Perenyi A, Frecska E, Bagdy G, Revai K: Changes in mental condition, hyperkinesias and biochemical parameters after withdrawal of chronic neuroleptic treatment. Acta Psychiatr Scand 1985; 72:430–435
6. Shiovitz TM, Welke TL, Tigel PD, Anamd R, Hartman RD, Sramek JJ, Kurtz NM, Cutler NR: Clozapine rebound and rapid onset psychosis following abrupt clozapine withdrawal. Schizophr Bull 1996; 22:591–595
7. Goudie AJ, Smith JA, Robertson A, Cavanagh C: Clozapine as a drug of dependence. Psychopharmacology 1999; 142:369–374

DAVID COHEN, PH.D.
Montreal, Que., Canada

Diagnosing Personality Disorders

TO THE EDITOR: Using a large representative national sample, Mark Zimmerman, M.D., and Jill I. Mattia, Ph.D. (1), attempted to disconfirm a hypothesis my colleagues and I advanced and corroborated (2). I asserted that clinicians do not rely primarily on the direct-question format used in structured interviews to assess personality disorders (e.g., "Have you ever been told that you seemed like a shallow or superficial kind of person?" to assess histrionic personality disorder). Clinicians of all theoretical orientations have reported that they diagnose personality disorder pathology by listening to their patients' narratives about significant interpersonal experiences and observing their behavior in the consulting room.

Drs. Zimmerman and Mattia hypothesized that if clinicians hear the results of structured interviews for borderline personality disorder (including information on particular criteria, such as self-mutilation), this influences their diagnoses—a hypothesis with which no one, myself included, would disagree (unless the clinicians have reason to distrust the data provided by the interviewer). In one-half of their sample, clinicians made diagnoses as they normally would, on the basis of an initial intake interview of unspecified length. In this situation, clinicians diagnosed only 0.4% out of 500 outpatients entering their clinic with borderline personality disorder. In

the other one-half of the sample, researchers conducted structured interviews, then "presented the case to a psychiatrist who reviewed the findings of the evaluation with the patient," and then made a diagnosis. Under these conditions, 27 out of 59 patients diagnosed as having borderline personality disorder by structured interview were diagnosed with borderline personality disorder by a psychiatrist, and seven more were given a rule-out diagnosis of borderline personality disorder.

The investigators largely replicated a well-known psychological finding: that biasing observers with prior information (particularly a label) affects the way they subsequently view a person. What is perhaps more striking is that fewer than one-half of the psychiatrists who were biased in this way gave the patients the borderline personality disorder diagnosis! In the least, from a methodological point of view, the psychiatrist should have been presented with the results of the structured interviews after spending some time with the patients, preferably at least two or three sessions, so that the psychiatrist would have had time to assess the patients' personalities.

The use of intake diagnoses recorded in the patients' charts as an index of the clinician's diagnostic impressions was also an unfortunate methodological choice. The authors report that only two patients out of 500 received an intake diagnosis of borderline personality disorder in the naturalistic condition. This is so far below the norms reported in any study of which I am aware that I agree with the authors' casual observation that "clinicians were very reluctant to diagnose borderline personality disorder during their routine intake diagnostic evaluations" (1, p. 1572). And I applaud the clinicians' reluctance: giving a patient a stigmatizing diagnosis in an official record available to third-party payers after seeing the patient only briefly (presumably spending most of the interview inquiring about axis I diagnoses, suicidality, and other issues relevant to triage) would be inappropriate in most circumstances. In a similar study in which clinicians made anonymous diagnoses (3), Arkowitz-Westen and I found that 14.5% of the patients received a borderline diagnosis.

Finally, the choice to study only one personality disorder, borderline, was unfortunate. As I noted in the article to which the authors were responding (2), borderline personality disorder and antisocial personality disorder are the two diagnoses for which structured interviews have the best validity and reliability data; that is precisely because they are the ones with the most objective behavioral indices (e.g., cutting, suicide attempts, and arrests). A more conservative test of their hypothesis would have been to select a disorder such as narcissistic personality disorder, for which criteria are not so accessible by direct questioning. Whether clinicians would have found diagnoses made after 5–10 minutes of direct questioning by interviewers (some of whom were only bachelor's-level research assistants) compelling enough to accept one-half of the time, as they apparently did with borderline personality disorder, is not so clear.

References

1. Zimmerman M, Mattia JI: Differences between clinical and research practices in diagnosing borderline personality disorder. Am J Psychiatry 1999; 156:1570–1574
2. Westen D: Divergences between clinical and research methods for assessing personality disorders: implications for research and the evolution of axis II. Am J Psychiatry 1997; 154:895–903
3. Westen D, Arkowitz-Westen L: Limitations of axis II in diagnosing personality pathology in clinical practice. Am J Psychiatry 1998; 155:1767–1771

DREW WESTEN, PH.D.
Boston, Mass.

Spontaneous Depression Versus Biphasic Cycling

TO THE EDITOR: The recent randomized study of bipolar depression by L. Trevor Young, M.D., Ph.D., et al. (1), documenting a superior antidepressant response after adding paroxetine rather than a second mood stabilizer to an existing mood stabilizer, addressed a critical and unresolved area of research in the treatment of bipolar disorder. Because studies such as this are scarce, clinical decisions about when to introduce antidepressants for the treatment of bipolar depression remain highly debated (2).

Little attention has been paid in the literature to the distinction between depression that arises spontaneously (i.e., after remission from a prior mania) and depression that arises soon after the resolution of a manic episode (i.e., biphasic). Biphasic episodes of mania followed by depression have been reported to occur in as many as 58% of bipolar disorder patients (3), although even expert clinicians fail to reach consensus on the optimal first-line treatment strategy for depression that occurs immediately after a manic episode (2). Because depression that occurs as part of a biphasic episode could reflect a more cyclical overall disease process than depression that arises spontaneously in the course of bipolar disorder, the utility (and safety) of antidepressants, rather than more aggressive anticycling agents, remains an open issue.

Although the size of the group studied by Dr. Young et al. (1) precluded a definitive subanalysis of spontaneous versus biphasic depression, their data may nonetheless help shed light on this topic by generating hypotheses. Their exclusion of patients with known rapid cycling furthermore makes theirs an ideal group to address this issue, as they are unconfounded by the idiosyncracies of rapid cycling and possible previous antidepressant-induced changes in cycle frequency. In light of other data suggesting that depression that follows manias may portend a more favorable response to lithium treatment than depression that precedes manias (4), it would be a valuable added dimension to their study to provide preliminary observations in this regard.

References

1. Young LT, Joffe RT, Robb JC, MacQueen GM, Marriott M, Patelis-Siotis I: Double-blind comparison of addition of a second mood stabilizer versus an antidepressant to an initial mood stabilizer for treatment of patients with bipolar depression. Am J Psychiatry 2000; 157:124–126
2. Sachs GS, Printz DJ, Kahn DA, Carpenter D, Docherty JP: The Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder 2000. Postgrad Med 2000; special number, pp 1–104
3. Winokur G, Clayton PJ, Reich T: Manic Depressive Illness. St Louis, CV Mosby, 1969

4. Maj M, Pirrozi R, Starace F: Previous pattern of course of the illness as a predictor of response to lithium prophylaxis in bipolar patients. J Affect Disord 1989; 17:237–241

JOSEPH F. GOLDBERG, M.D.
New York, N.Y.

Dr. MacQueen and Colleagues Reply

TO THE EDITOR: Our initial study examined whether bipolar patients who became depressed while taking a mood stabilizer were more likely to improve after the addition of a second mood stabilizer or an antidepressant. In his comment to the editor, Dr. Goldberg questioned whether our data set could be used to assess whether the patients who became depressed after a period of sustained euthymia differed in treatment responsivity from patients who became depressed after a manic episode. As Dr. Goldberg noted, our group size precluded a definitive examination of this issue; however, we were able to determine the preceding mood state for 23 out of 27 subjects in our group. We could not confidently ascertain whether four subjects who had been referred only for participation in the study had been euthymic for the 2 months preceding the onset of depression; therefore, we did not include these subjects in the analyses. We defined the euthymia-depression group as patients who had had no evidence of manic or hypomanic symptoms within the 2 months preceding the onset of the depressive episode. In contrast, the mania-depression patients had been either manic or hypomanic within the 2 months preceding the onset of depression. Of the 14 patients treated with two mood stabilizers, 10 were assigned to the euthymia-depression group, while four were assigned to the mania-depression group. Of nine patients treated with a mood stabilizer plus an antidepressant, four were in the euthymia-depression group, and five were in the mania-depression group.

Analysis of Hamilton Depression Rating Scale scores revealed a significant interaction between week and prior mood state ($F=2.20$, df=6, 114, $p<0.05$); euthymia-depression patients treated with a mood stabilizer plus an antidepressant demonstrated the greatest improvement in Hamilton depression scores across treatment weeks. This differential improvement in euthymia-depression patients treated with a mood stabilizer plus an antidepressant was mirrored in their Global Assessment of Functioning Scale scores ($F=2.27$, df=6, 114, $p<0.03$), which also showed the greatest improvement in the euthymia-depression group.

It is interesting that despite the small group size and post hoc exploratory nature of this analysis, there was a demonstrable difference in improvement for the euthymia-depression group treated with a mood stabilizer plus an antidepressant. Speculatively, Dr. Goldberg might have predicted this pattern of results, as he points out that even non-rapid-cycling patients with mania and depression may have a greater tendency toward cyclicity and be less likely to benefit from antidepressant treatment. As there were no patients in our study who became manic or hypomanic after acute treatment with a mood stabilizer plus an antidepressant, it was not possible for us to comment on the relative safety of antidepressant use in the euthymia-depression group versus the mania-depression group. Nonetheless, our results suggested that prior mood state may influence treatment responsivity in depressed bipolar patients; this clearly warrants further exploration. If the finding is confirmed, determining the illness pattern that precedes the onset of depression in bipolar disorder may help clinicians identify those patients for whom the risk-benefit ratio of antidepressant treatment is most favorable.

GLENDA M. MACQUEEN, M.D., PH.D., F.R.C.PSYCH.
L. TREVOR YOUNG, M.D., PH.D.
MICHAEL J. MARRIOTT, PH.D.
RUSSELL T. JOFFE, M.D.
Hamilton, Ont., Canada

Female Sexual Dysfunction and Antidepressant Use

TO THE EDITOR: David Michelson, M.D., et al. (1) appropriately demonstrated that neither buspirone nor amantadine was more effective than placebo in the treatment of antidepressant-induced sexual dysfunction in women. Their results apparently are not in agreement with those of Landén et al. (2), who showed the superiority of buspirone to placebo for antidepressant-induced sexual dysfunction, particularly in women. However, this discrepancy suggests the possibility that the effects of buspirone on sexual dysfunction might abate with continued treatment, owing to the desensitization of serotonin$_{1A}$ autoreceptors, because Dr. Michelson et al. administered buspirone for a longer period (8 weeks) than Landén et al. (4 weeks).

On the other hand, although the study by Dr. Michelson et al. (1) was not primarily aimed at evaluating the efficacy of the combination of fluoxetine and buspirone in treating affective symptoms, I will comment on this issue. Several case studies and open trials showed the efficacy of buspirone added during antidepressant augmentation (3). In the first controlled, double-blind trial (4), however, buspirone augmentation of a selective serotonin reuptake inhibitor (citalopram or paroxetine) in patients with refractory depression failed to demonstrate any difference in efficacy from placebo augmentation.

The study of Dr. Michelson et al. (1) seems to be a second such study, although most of their patients were almost recovered, as indicated by their Hamilton depression scale scores. Nonetheless, the results of visual analogue scales measuring mood and energy did not indicate their complete recovery. The fact that amantadine added to fluoxetine significantly improved energy levels and approached statistical significance for mood improvement strongly supports the possibility of at least subjectively insufficient recovery of the patients' depression at baseline. The mean mood changes in the visual analogue scales from baseline (higher values represent greater improvement) were 8.7 (amantadine added), 1.4 (buspirone added), and 0.6 (placebo added); the mean energy changes were 9.5, 2.1, and –3.2, respectively. There was no difference between the addition of buspirone and the addition of placebo in mood or energy change, although the addition of amantadine was significantly better than the addition of placebo, particularly in energy change. Also, there was no difference among the groups in changes measured by the Beck Depression Inventory. These findings suggest that buspirone added to fluoxetine cannot improve subjective mood or energy in mild depression.

Although Dr. Michelson et al. (1) did not mention this suggestion because it was not their purpose, I believe that this is important information to note until further placebo-con-

trolled, double-blind studies clarify the role of buspirone in antidepressant augmentation.

References

1. Michelson D, Bancroft J, Targum S, Kim Y, Tepner R: Female sexual dysfunction associated with antidepressant administration: a randomized, placebo-controlled study of pharmacologic intervention. Am J Psychiatry 2000; 157:239–243
2. Landén M, Eriksson E, Ågren H, Fahlén T: Effect of buspirone on sexual dysfunction in depressed patients treated with selective serotonin reuptake inhibitors. J Clin Psychopharmacol 1999; 19:268–271
3. Sussman N: Anxiolytic antidepressant augmentation. J Clin Psychiatry 1998; 59(suppl 5):42–48
4. Landén M, Björling G, Ågren H, Fahlén T: A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. J Clin Psychiatry 1998; 59:664–668

TAKESHI TERAO, M.D., PH.D.
Oxford, U.K.

Dr. Michelson Replies

TO THE EDITOR: We appreciate and note Dr. Terao's comments. With respect to the discrepancy between our results and those of Landén et al. (1999), we note that in addition to differences in length of treatment, their findings derive from a study primarily designed to assess antidepressant efficacy rather than sexual function. The interpretation of their report is, consequently, limited by a number of methodological issues. Conversely, our study was not designed to assess the efficacy of buspirone augmentation of fluoxetine for residual depressive symptoms, and indeed, we selected patients without such symptoms to avoid confounding the analysis of sexual function. In that context, our findings with amantadine were suggestive and consistent with those of several previous reports and merit further investigation. Nonetheless, our study is not a fair assessment of augmentation therapies among patients who have an incomplete response to fluoxetine therapy, nor was it intended to be.

DAVID MICHELSON, M.D.
Indianapolis, Ind.

Detachment and Generalized Social Phobia

TO THE EDITOR: We read with great interest the finding of Aki Laakso, M.D., Ph.D., and colleagues (1) that the personality trait of "detachment" is associated with low dopamine transporter binding in healthy subjects, complementing prior findings of its association with low dopamine D_2 receptor density (2, 3). These results parallel findings in generalized social phobia of low dopamine transporter binding (4) and low D_2 receptor binding (5). The authors suggested that "detachment," as measured by the detachment scale of the Karolinska Scales of Personality (6), relates to a behavioral pattern of withdrawal and aloofness and that the findings may be relevant for schizoid personality disorder. We would caution, however, that "detachment" is also associated with generalized social phobia and may represent social avoidance due to anxiety.

Most of the 10 items of the detachment scale could easily apply to persons who avoid social situations because of fear of embarrassment, rather than aloofness (e.g., "It is [not] easy for me to get close to people"). In an ongoing study in our clinic, 20 patients with generalized social phobia had a mean detachment score of 25.5 (SD=3.8, range=19–35). Nineteen (95%) of the 20 patients had scores exceeding the median score of 19 found among healthy subjects by Dr. Laakso and colleagues (1). The detachment scale therefore may be sensitive to social avoidance related to anxiety in social phobia. Alternatively, the detachment scale may have detected aloofness as an unexpected element (or consequence) of social phobia.

Because social phobia is highly prevalent in the community yet is frequently missed by clinicians, studies recruiting healthy subjects may inadvertently include persons with social phobia unless they are systematically screened out. Because two articles regarding detachment and dopamine (1, 2) did not include the methods used to exclude subjects with psychiatric disorders, some of their subjects with elevated detachment scores may have had social phobia. Future studies of detachment should systematically assess the presence of social phobia among subjects.

References

1. Laakso A, Vilkman H, Kajander J, Bergman J, Haaparanta M, Solin O, Hietala J: Prediction of detached personality in healthy subjects by low dopamine transporter binding. Am J Psychiatry 2000; 157:290–292
2. Farde L, Gustavsson JP, Jonsson E: D_2 dopamine receptors and personality traits (letter). Nature 1997; 385:590
3. Breier A, Kestler L, Adler C, Elman I, Wiesenfeld N, Malhotra A, Pickar D: Dopamine D_2 receptor density and personal detachment in healthy subjects. Am J Psychiatry 1998; 155:1440–1442
4. Tiihonen J, Kuikka J, Bergstrom K, Lepola U, Koponen H, Leinonen E: Dopamine reuptake site densities in patients with social phobia. Am J Psychiatry 1997; 154:239–242
5. Schneier FR, Liebowitz MR, Abi-Dargham A, Zea-Ponce Y, Lin S-H, Laruelle M: Low dopamine D_2 receptor binding potential in social phobia. Am J Psychiatry 2000; 157:457–459
6. Schalling D, Asberg M, Edman G, Oreland L: Markers for vulnerability to psychopathology: temperament traits associated with platelet MAO activity. Acta Psychiatr Scand 1987; 76:172–182

FRANKLIN R. SCHNEIER, M.D.
MICHAEL R. LIEBOWITZ, M.D.
MARC LARUELLE, M.D.
New York, N.Y.

Drs. Laakso and Hietala Reply

TO THE EDITOR: We would like to thank Drs. Schneier, Liebowitz, and Laruelle for their comments regarding our article, which described the association between low dopamine transporter binding and detached personality. Indeed, it may be difficult to discern the psychological basis for avoidant behavior with a self-rating instrument such as the Karolinska Scales of Personality. Patients with either social phobia or schizoid personality disorder do experience discomfort when interacting socially, although this is because of anxiety (often in the presence of a desire to socialize) in the former and more because of a lack of interest in the latter. Although many of the detachment items in the Karolinska Scales of Personality do reflect more aloofness than phobic anxiety about socialization (e.g., "I am [not] deeply moved by other people's misfor-

tunes," "I [do not] want to confide in someone, when I am worried and unhappy"), we agree that the association between detached behavior and low dopaminergic transmission reported by us and others (Farde et al., 1997; Breier et al., 1998) may relate to similar findings on social phobia (Tiihonen et al., 1997; Schneier et al., 2000). However, we also reported a strong positive correlation between scores on the social desirability subscale of the Karolinska Scales of Personality and dopamine transporter binding, which suggests also that motivational aspects of social behavior play a part in the described phenomenon. It is also worth noting that up to 60% of patients with social phobia also fulfill the DSM-IV criteria for avoidant personality disorder (1). This has not been fully addressed in previous studies examining dopaminergic neurotransmission in social phobia (Tiihonen et al. 1997; Schneier et al., 2000).

We feel that it is unlikely that the association we reported could be caused by subjects in our study group with social phobia. First, any direct comparisons of scores on the Karolinska Scales of Personality between diagnostic groups (healthy versus social phobic) from different populations (European versus United States) without normative transformation of the personality data should be made with caution. Second, although social phobia was not excluded with a structured instrument such as the SCID (a thorough clinical interview for axis I diagnoses), a medical history focused on psychiatric and neurologic illness was obtained from healthy volunteers. In addition, the recruitment procedure did not favor subjects with social anxiety. Considering that the point prevalence of social phobia in the general population is between 5% and 10% (2), the risk for including persons with social phobia in our screened group of 18 healthy subjects was low. However, we certainly agree that a detailed psychiatric examination of the subjects is highly important in studies on temperament and character.

References

1. Fahlén T: Personality traits in social phobia, I: comparisons with healthy controls. J Clin Psychiatry 1995; 56:560–568
2. Stein MB: Phenomenology and epidemiology of social phobia. Int Clin Psychopharmacol 1997; 12(suppl 6):S23–S26

AKI LAAKSO, M.D.
JARMO HIETALA, M.D.
Turku, Finland

Lack of Seasonal Mood Change in Icelanders

TO THE EDITOR: The finding of a lack of seasonal affective disorders in Iceland, from a study by Magnusson et al. (1), is striking, especially when compared with findings from other countries of similar latitude. One reason for this finding may be the high content of fish in the Icelandic diet (225 lb per person per year) (2). The authors noted a similar and unexpected previous finding of a low prevalence of seasonal affective disorders in Japan, which also has a high per capita intake of fish (147 lb per person per year) (2). Despite a greater exposure to light in winter, most other countries have higher rates of seasonal affective disorder. Per capita fish intake in pounds per person per year is as follows: Canada, 51; Finland, 72; Netherlands, 25; Sweden, 59; Switzerland, 30; United Kingdom, 41; and the United States, 48 (2). We suggest that the difference in the prevalence of seasonal affective disorders between Icelandic descendants and other citizens in Winnipeg may be due to a cultural tradition of fish consumption, rather than differences in genetic predisposition. Our proposition is consistent with the finding in a cross-national analysis that greater seafood consumption predicted lower prevalence rates of major depression ($r=-0.84$, $p<0.005$) (3).

Seafood is rich in the omega-3 essential fatty acids eicosapentaenoic and docosahexaenoic acids. Docosahexaenoic acid is selectively concentrated in synaptic membranes, where it has a crucial role in maintaining the biophysical properties determining receptor conformation (4). Mechanisms through which eicosapentaenoic and docosahexaenoic acids may diminish depressive symptoms have recently been reviewed (5) and include modulation of serotonin turnover, phosphoinositol-mediated signal transduction, and L-type calcium channel regulation. Depletions of docosahexaenoic acid in RBC phospholipid membranes have been reported in depression (6). A placebo-controlled study in bipolar disorder (7) showed that supplementation with docosahexaenoic and eicosapentaenoic acids had marked mood-stabilizing and antidepressant activity. Thus, high levels of fish consumption should be considered a potential etiology for the finding of a lack of seasonal affective disorder among the Icelandic population.

References

1. Magnusson A, Axelsson J, Karlsson MM, Oskarsson H: Lack of seasonal mood change in the Icelandic population: results of a cross-sectional study. Am J Psychiatry 2000; 157:234–238
2. Fish and Fishery Products: World Apparent Consumption Based on Food Balance Sheets (1961–1993): FAO Fisheries Circular 821, revision 3. Rome, Food and Agriculture Organization of the United Nations, Nov 1996
3. Hibbeln JR: Fish consumption and major depression (letter). Lancet 1998; 351:1213
4. Mitchell DC, Gawrisch K, Litman BJ, Salem N Jr: Why is docosahexaenoic acid essential for nervous system function? Biochem Soc Trans 1998; 26:365–370
5. Hibbeln JR, Umhau JC, George DT, Shoaf SE, Linnoila M, Salem N Jr: Plasma total cholesterol concentrations do not predict cerebrospinal fluid neurotransmitter metabolites: implications for the biophysical role of highly unsaturated fatty acids. Am J Clin Nutr 2000; 71(1 suppl):331S–338S
6. Peet M, Murphy B, Shay J, Horrobin D: Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. Biol Psychiatry 1998; 43:315–319
7. Stoll AL, Severus E, Freeman MP, Rueter S, Zboyan HA, Diamond E, Cress KK, Marangell LB: Omega-3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. Arch Gen Psychiatry 1999; 56:407–412

JERRY COTT, PH.D.
JOSEPH R. HIBBELN, M.D.
Bethesda, Md.

Antidepressant Use Among Elderly Patients

TO THE EDITOR: Muhammad M. Mamdani, Pharm.D., M.A., M.P.H., et al. (1) recently reported that the prevalence of antidepressant use among the elderly population of Ontario increased from 9.3% in 1993 to 11.5% in 1997—a 24% increase from baseline. Annual antidepressant costs in this population increased by 150%, from $10.8 million in 1993 to $27 million in 1997. These increases were mainly accounted for by steady growth in the use of selective serotonin reuptake inhibitors (SSRIs). The authors lauded the increased use of antide-

pressants (on the assumption that more cases of late-life depression are now being treated) but questioned the cost-effectiveness of prescribing SSRIs in favor of the less expensive tricyclic antidepressants. In particular, they argued that there is little evidence from meta-analyses of controlled trials that SSRIs and tricyclic antidepressants differ in efficacy or overall frequency of adverse effects (1).

Unfortunately, the rigor of prescribing tricyclic antidepressants in research studies usually does not carry over to practice in the community. There is abundant evidence that in primary care settings, where most antidepressants are used, tricyclic antidepressants are seldom prescribed at doses that are effective for the treatment of major depression (2, 3). Moreover, the most frequently prescribed tricyclic antidepressants are tertiary amine drugs (3, 4), which are probably least likely to be tolerated by elderly patients (5). In contrast, the vast majority of patients treated with SSRIs receive an effective dose (2, 3). Also, in clinical practice settings, discontinuation rates appear to be lower for SSRIs than for tricyclic antidepressants (4, 6). Thus, there is good reason to believe that a prescription for an SSRI is more likely to result in adequate treatment of depression in elderly patients than is a prescription for a tricyclic antidepressant.

Although the overall frequencies of side effects may be similar for tricyclic antidepressants and SSRIs, there are important differences between these drugs in types of side effects. In particular, SSRIs do not have significant anticholinergic, hypotensive, or cardiac effects, and so, compared with tricyclic antidepressants, there are fewer limitations to their use in the elderly (5). Thus, a broader spectrum of elderly depressed patients can now be treated. Furthermore, persons aged 80 years or older, who are most likely to have medical or neurological conditions that limit the use of tricyclic antidepressants (5), are proportionally the fastest growing segment of the population (7). This suggests that a diminishing percentage of elderly patients will be candidates for tricyclic antidepressants in the years to come.

References

1. Mamdani MM, Parikh SV, Austin PC, Upshur RE: Use of antidepressants among elderly subjects: trends and contributing factors. Am J Psychiatry 2000; 157:360–367
2. Donoghue J: Sub-optimal use of tricyclic antidepressants in primary care. Acta Psychiatr Scand 1998; 98:429–431
3. Donoghue J, Katona C, Tylee A: The treatment of depression: antidepressant prescribing for elderly patients in primary care. Pharmaceut J 1998; 260:500–502
4. Martin RM, Hilton SR, Kerry SM, Richards NM: General practitioners' perceptions of the tolerability of antidepressant drugs: a comparison of selective serotonin reuptake inhibitors and tricyclic antidepressants. Br Med J 1997; 314:646–651
5. Flint AJ: Choosing appropriate antidepressant therapy in the elderly: a risk-benefit assessment of available agents. Drugs Aging 1998; 3:269–280
6. Simon GE, Von Korff M, Heiligenstein JH, Revicki DA, Grothaus L, Katon W, Wagner EH: Initial antidepressant choice in primary care: effectiveness and cost of fluoxetine vs tricyclic antidepressants. JAMA 1996; 275:1897–1902
7. Desjardins B, Dumas J: Population Ageing and the Elderly. Ottawa, Ont, Statistics Canada, 1993

ALASTAIR J. FLINT, M.B., CH.B., F.R.C.P.(C.), F.R.A.N.Z.C.P.
JOSE SILVEIRA, M.D., F.R.C.P.(C.)
Toronto, Ont., Canada

Dr. Mamdani and Colleagues Reply

TO THE EDITOR: Drs. Flint and Silveira have raised several important issues that warrant further consideration. As discussed in our study, the use of tricyclic antidepressants in the elderly should be limited to secondary amine tricyclic antidepressants, such as nortriptyline, given their favorable adverse effect profile relative to tertiary amine tricyclic antidepressants, such as amitriptyline. Unfortunately, findings from studies primarily based on tertiary amine tricyclic antidepressants are often generalized to include secondary amine tricyclic antidepressants, which may not be appropriate. The evidence for inadequate tricyclic antidepressant prescribing, to which Drs. Flint and Silveira refer, is based primarily on tertiary amine tricyclic antidepressants. These conclusions may not be generalizable, since prescribing practices may be much more favorable for secondary amine tricyclic antidepressants (1). Furthermore, numerous studies have demonstrated that treatment with nortriptyline is not associated with a higher dropout rate than with SSRI treatment (2).

Although we concur that SSRIs possess more favorable dosing characteristics and may be more suitable for select groups of patients, such as those with ischemic heart disease (3), much more information is needed to determine the appropriate role of SSRIs and justify such dramatic shifts in prescribing practices. For example, recent evidence suggests that nortriptyline may be significantly more effective than fluoxetine in the treatment of poststroke depression (4). The Danish University Antidepressant Group found better remission rates with tricyclic antidepressants than with SSRIs, raising further questions about the true efficacy of SSRIs versus tricyclic antidepressants (5, 6). Similarly, emerging literature on the superiority of newer agents, such as venlafaxine, to SSRIs has invoked the "dual-mechanisms" explanation that is applicable to many of the tricyclic agents as well (7). With respect to adverse events, SSRI use may be associated with a substantially greater risk of major gastrointestinal bleeding, particularly in those taking nonsteroidal anti-inflammatory drugs (8). Although the frequency of adverse events associated with secondary amine tricyclic antidepressants and SSRIs is well documented, the burden of side effects and their longer-term, clinically relevant implications for patient well-being is poorly understood. Such issues, which may be even more relevant to an elderly population, warrant further consideration and more stringent analyses of the risks, benefits, and costs associated with treatment alternatives, rather than speculative conclusions and strong opinions.

Although clinicians have traditionally ignored the cost of medical treatment, a growing understanding that costs are indeed an important consideration in routine medical decision making is emerging. The allocation of a fixed budget, which must constantly weigh the benefits of newer and often more expensive treatments against the cost of denying other beneficial therapies, makes a strong case for judicious prescribing.

References

1. Jerling M: Dosing of antidepressants: the unknown art. J Clin Psychopharmacol 1995; 15:435–439
2. Roose SP, Suthers KM: Antidepressant response in late-life depression. J Clin Psychiatry 1998; 59(suppl 10):4–8
3. Roose SP, Laghrissi-Thode F, Kennedy JS, Nelson JC, Bigger JT Jr, Pollock BG, Gaffney A, Narayan M, Finkel MS, McCafferty J, Ger-

gel I:. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. JAMA 1998; 279:287–291
4. Robinson RG, Shultz SK, Castillo C, Kopel T, Kosier JT, Newman RM, Curdue K, Petracca G, Starkstein S: Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke: a placebo-controlled, double-blind study. Am J Psychiatry 2000; 157:351–359
5. Danish University Antidepressant Group: Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. J Affect Disorder 1990; 18:289–299
6. Danish University Antidepressant Group: Citalopram: clinical effect profile in comparison with clomipramine: a controlled multicenter study. Psychopharmacology 1986; 90:131–138
7. Ferrier IN: Treatment of major depression: is improvement enough? J Clin Psychiatry 1999; 60(suppl 6):10–14
8. de Abajo FJ, Rodriguez LA, Montero D: Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. Br Med J 1999; 319:1106–1109

MUHAMMAD M. MAMDANI, PHARM.D., M.A., M.P.H.
SAGAR V. PARIKH, M.D.
PETER C. AUSTIN, PH.D.
ROSS E.G. UPSHUR, M.D., M.SC., M.A.
Toronto, Ont., Canada