Aggression in Dementia With Lamotrigine Treatment

Frontal lobe dementia is a presenile condition with an insidious onset; it usually appears with deterioration of personality and behavior. The prominent initial symptoms of frontal lobe dementia are apathy, socially inappropriate behavior, impulsivity, aggression, and disinhibition with relative preservation of memory. It may be difficult to control such symptoms, although a variety of medications have been tried, including β blockers, benzodiazepines, antipsychotics, and mood stabilizers, including lithium and divalproex sodium, at a cost of further deterioration in cognition and other side effects (1, 2). We present a case of frontal lobe dementia with various symptoms in a patient who responded well to lamotrigine but not to other treatments.

Ms. A was a 65-year-old woman with a 12-year history of chronic recurrent episodes of major depression. Before that she had excellent premorbid functioning and worked in accounting. After her husband's suicide when she was 40 years old, she managed to bring up her two sons alone. Treatment of her depression included a variety of antidepressants, which resulted in some improvement that was not sustained. Her last admission was after a 3-month history of repeatedly asking the same questions, picking her nose until it bled, and being verbally and physically aggressive. The episodes of aggression were characterized by hitting, punching, biting, tearing clothes, grunting, barking, screaming, and grimacing—all of which appeared to come on suddenly and involuntarily and were puzzling to her. She had been treated with fluvoxamine, buspirone, lorazepam, vitamin E, thiamine, loxapine, risperidone, and divalproex sodium with little or no improvement.

On admission, in addition to the ongoing problems just listed, Ms. A appeared extremely aggressive and disinhibited, with moderate deterioration in concentration and cognition. Her medications at admission included 1500 mg/day of divalproex sodium (in therapeutic blood concentrations), 2 mg/day of risperidone, and 2–4 mg/day of lorazepam. Preventive measures for aggressive behaviors were applied. However, she convinced the psychiatric trainees and other members of the staff that she would not harm them. The staff believed her, but when approached within an arm's length, she hit two psychiatric residents, a psychiatrist, and a neurologist and left some with facial bruises and black eyes. After neurological examinations, brain scans (computerized tomography and single photon emission computed tomography), and neuropsychological testing, Ms. A was diagnosed with frontal lobe dementia.

There is evidence that excitotoxic damage, apoptotic signals in synapse loss, and neuronal death in neurodegenerative processes involve excessive activation of glutamate receptors and glutamatergic hyperactivity (3, 4). Lamotrigine, an anticonvulsant and possible mood stabilizer, inhibits presynaptic glutamate release, in addition to its other actions (5).

Therefore, Ms. A was initially treated with a dose of 12.5 mg/day of lamotrigine, which was gradually increased to 100 mg/day over 4 weeks, according to clinical response. All of her symptoms dramatically improved, and she was back to her pleasant premorbid mood. She was maintained with this dose of lamotrigine over 6 months with no relapse. No dermatologic or other side effects were reported.

Lamotrigine is suggested for cases such as this. In addition, preventive measures and pharmacological interventions should be considered. This observation has the limitations of a case report. Controlled studies are necessary.

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Optimal Risperidone Dose in Drug-Naive, First-Episode Schizophrenia

An optimal therapeutic dose of a drug should be considered the dose at which a patient has a significant symptom reduction without unwanted side effects. Risperidone, a novel antipsychotic, is marketed with the suggestion of a rapid titration schedule (target dose of 6 mg/day by the third day) (1). However, recently a slower dose increase has been encouraged (1, 2). There is evidence that many patients (i.e., elderly patients, children, drug-naive patients) are sensitive to antipsychotic medication and need low therapeutic doses. To our knowledge, no information exists regarding the optimal risperidone dose in drug-naive, first-episode schizophrenia. The aim of our study was to provide this information.

Our study group consisted of 17 drug-naive patients with first-episode schizophrenia (per DSM-IV criteria): 12 women and five men, with a mean age of 28.6 years (SD=5.6), consecutively admitted to Eginition Hospital, University of Athens, from April 1998 to March 1999. Written informed consent was obtained from the subjects and their relatives.

All patients were openly treated with risperidone, given once daily in the evening, according to standard guidelines. Doses were gradually increased during an 8-week trial period (increased 1 mg/day per week for the first 3 weeks). Diazepam (mean=13.30 mg/day, SD=6.23) was co-administered to nine patients for agitation, anxiety, or insomnia. The patients' psychopathology was assessed at baseline (drug-naive state), biweekly, and at endpoint by using the Positive and Negative Syndrome Scale (3). The optimal risperidone dose was defined as the dose at which either symptoms were reduced (at least 20% from baseline) or extrapyramidal side effects emerged. To assess improvement, we calculated the percentage of symptomatic change on the Positive and Negative Syndrome Scale, adjusted for minimum baseline ratings. The

mean optimal daily risperidone dose was 2.70 mg/day (SD=0.89). All patients reached their optimal dose before developing extrapyramidal side effects. Four patients developed parkinsonism, and one developed akathisia at a mean daily risperidone dose of 5.20 mg/day (SD=1.60). Thirteen patients (76%) achieved an optimal response with a risperidone dose of up to 3 mg/day, with an average 60% (SD=21%) improvement in total Positive and Negative Syndrome Scale score at the end of the 8-week trial period. Four patients (24%) reached an optimal dose of 4–5 mg/day, with a mean 45% (SD=28%) improvement. None of the patients achieved optimal response at doses higher than 6 mg/day.

Although confirmation is needed with the use of larger patient groups, this study's findings suggest that "low and slow" increases of risperidone doses for treating drug-naive patients with first-episode schizophrenia are sufficient to minimize the risk of unwanted extrapyramidal side effects and reduce the risk of noncompliance with treatment.

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Psychiatrists' Attitudes Toward Dissociative Disorders Diagnoses

In our opinion, the article by Harrison G. Pope, Jr., M.D., et al. (1) failed to comport with the level of scholarship usually required for publication in scientific journals. The authors failed to mention two methodologically sound studies (2, 3) showing that favorable attitudes toward dissociative identity disorder are positively correlated with knowledge about the disorder (from reading texts, attending conferences about dissociative identity disorder, etc.). Furthermore, that they did not assess attitudes toward other DSM-IV disorders may have itself introduced bias. This omission also failed to provide a baseline of skepticism from which attitudes toward all disorders might be assessed.

In addition, the authors' methodological and statistical procedures were flawed. Random sampling cannot be achieved by a "prescribed formula." The variables assessed did not appear driven by theory. Thus, while their logistic regression appeared sophisticated, the variables it analyzed were not. The most striking problem concerned their interpretation of the data. They reported that "[the disorders] should be included [in DSM-IV] only with reservations" as the modal response. Nevertheless, a sign test shows no significant differences between this group and the group that opted for inclusion without reservations. Thus, the more reasonable interpretation is that the overwhelming majority of responders indicated acceptance—with or without reservations.

One critically important issue concerns the legal implications of the study for psychiatrists who offer expert testimony in court. In one case, the prosecution convinced a judge to bar the testimony of a psychiatric expert in dissociative disorders from a trial of a criminal defendant said to have a dissociative identity disorder by arguing that the disorder failed to meet the "general acceptance" criterion. Although this decision was reversed by a better-informed appellate court (4), the possibility that the "study" by Dr. Pope et al. could be used to deprive an individual of his or her rights in a court of law is frightening. In this regard, we note that, as of the date of our letter to you, the senior author of this Brief Report is listed as a member of the Scientific and Professional Advisory Board of the False Memory Syndrome Foundation (5).

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In their report, Dr. Pope et al. revealed bias and unfamiliarity regarding the dissociative disorders. They implied a newly attained status of the disorders as of DSM-IV. However, the dissociative disorders have been nosological entities since DSM-II, with published reports extending back to 1791 (1). As DSM-IV work group advisors who considered these disorders, we can assure the authors that these disorders were thoroughly reviewed and discussed with four fellow members who are also on the scientific advisory board of the False Memory Syndrome Foundation.

The study by Dr. Pope et al. might be characterized as promoting an extremely polarized viewpoint, with examples of bias including the following:

1. The authors stated, "Only about one-third of respondents replied that dissociative amnesia and dissociative identity disorder should be included without reservations in DSM-IV.... Only about one-quarter of respondents felt that diagnoses of dissociative amnesia and dissociative identity disorder were supported by strong evidence of scientific validity" (p. 321). Using their own data, the authors could have said that only 9%–15% felt these diagnoses should not be included in DSM-IV and that only one-fifth felt that these diagnoses had little or no scientific validity.
2. No control questions about other dissociative disorder and other nondissociative disorder diagnoses were included in the questionnaire.
3. Four previous studies regarding belief in dissociative identity disorder were ignored (2–4, Hayes and Mitchell,

1994). Belief in dissociative identity disorder has increased to 80% (3).

4. The questionnaire respondent sample appeared biased toward older (55% were at least age 50), male (73%), biological psychiatrists. We would expect these psychiatrists to be biased because of a lack of recent training in dissociation.
5. This study promulgates the political and litigious viewpoint of the False Memory Syndrome Foundation. Two authors (Drs. Pope and Hudson) are on its scientific board. In the article's extremely selective literature review, another two board members (F.H. Frankel and A. Piper) were cited. The False Memory Syndrome Foundation has lobbied against the diagnosis of dissociative identity disorder on the basis of unverified reports of a small number of retractors previously diagnosed with dissociative identity disorder. Although members of the False Memory Syndrome Foundation's scientific advisory board label dissociative identity disorder a controversial diagnosis, they are in the minority. In the scientific literature criticizing dissociative identity disorder, nine past and present board members are responsible for the majority of the criticism, and four regularly write letters to the editor. None has published studies of patients with genuine dissociative disorders in a peer-reviewed journal.
6. The authors appeared to recognize their bias; otherwise, they would not have had a person unknown to the dissociative disorders field distribute their questionnaire.
7. The closure of "several major dissociative disorders treatment units" was cited as evidence of a controversy regarding dissociation. A few have closed because of litigation over therapeutic practices. However, the closure of other units was related to the diminishing rate of reimbursement for inpatient treatment and the rapid rise of managed care. Both general and specialized psychiatric treatment units have closed recently because of marketplace pressures. Presently, several major dissociative or trauma treatment units are flourishing—one at McLean Hospital—where all authors of this article have worked!
8. The authors are mistaken about "sharp shifts" in the diagnostic criteria for dissociative disorders between different versions of DSM. The majority of these shifts have been minor and were supported by the scientific literature.

This discussion should not be interpreted as a wish to stifle the debate concerning dissociative disorders. Informed scientific data serve to hone the accuracy of differential diagnosis. We believe the diagnostic criteria for dissociative identity disorder should reflect its polysymptomatic nature by the inclusion of affective, posttraumatic, and somatoform symptoms in addition to dissociative symptoms (5).

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The article by Dr. Pope et al. contains a serious misconception about the standards for adding new diagnoses to DSM-IV and about the placement of the disorders in appendix B ("Criteria Sets and Axes Provided for Further Study"). A new diagnosis was added to DSM-IV only after a comprehensive review of the literature (and often data reanalysis and field trials) determined that there was sufficient empirical evidence to justify its inclusion (1). The reason that premenstrual dysphoric disorder and binge eating disorder were not added as official categories to DSM-IV was *not* because they "[did] not meet DSM-IV standards for consensus" (p. 321). The empirical evidence supporting their inclusion was simply insufficient. Dissociative disorders that had already been included in earlier versions of DSM (e.g., dissociative amnesia and dissociative identity disorder) were retained in keeping with the conservative approach to DSM-IV, which "opposes the removal of existing categories in the absence of strong evidence recommending either action. The burden of proof generally rests on providing convincing data for either the removal or the addition of categories in preference to keeping the status quo" (1). However, when there are sufficient data indicating a lack of validity, a disorder can be eliminated, as was done with DSM-III-R's idiosyncratic alcohol intoxication criteria. Most problematic is the assumption that a simple vote should be the basis for the inclusion of a new DSM category.

The authors provided no information on the basis for each respondent's vote nor on the extent to which the psychiatrists were fully informed as to the full array of empirical information available on the conditions about which respondents were queried. Nor did the authors note whether the framing of these questions elicited such questions as the extent of evidence needed, whether existing disorders should be held to the same standard as proposed conditions, and the impact of changes in DSM on education and research efforts. In other words, these kinds of clinical or scientific questions should have been answered only through a systematic, evidence-based process.

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In an article by Dr. Pope and colleagues, the authors surveyed 367 board-certified psychiatrists with regard to their opinions about the diagnostic status and scientific validity of the DSM-IV categories of dissociative amnesia and dissociative identify disorder. They randomly selected general psychiatrists from the 1995 edition of *The Official ABMS Directory of*

Board-Certified Medical Specialists. Reviewing the results of this study in Table 1, one could draw a conclusion quite different from that of the authors. With regard to dissociative amnesia, only 9% of those questioned felt that this diagnosis should not be included in DSM-IV in at least some form. If one excludes those who felt this diagnosis should be included only "with reservations" or "as a proposed diagnosis," there is still a 4-to-1 preponderance (35% to 9%) of those who felt this diagnosis should be included without reservations. In addition, 71% of those questioned felt there was at least strong or partial evidence of the scientific validity of dissociative amnesia, compared to only 19% who felt there was little or no evidence.

Also, to further ensure the sample studied was representative, it would be helpful to know if the characteristics of the population studied (73% were men and 55% were older than 50) were consistent with the population of American psychiatrists as a whole. In addition, the authors did not fully explain the formula for selection of the psychiatrists and whether this formula ensured that there was no potential for bias as a result of the authors' familiarity with the names of those selected to complete the questionnaire. The issue of potential bias, even if unintentional, is a significant concern with regard to this study in that at least two of the authors, Drs. Hudson and Pope, are paid substantial fees for legal consultation and appearances as expert witnesses testifying against the scientific validity of the dissociative disorders.

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Dr. Pope and Colleagues Reply

Given space limitations, we focus here on the most important points of the previous letters. To settle one issue, Dr. Pope (but not Dr. Hudson) serves on the scientific advisory board of the False Memory Syndrome Foundation, but neither he nor any of the other authors has ever had any financial involvement with the foundation, nor does the foundation have any influence over our publications.

Turning to more scientific issues, the age and gender distribution of our respondents corresponds almost exactly to the overall population of practicing board-certified psychiatrists listed in *The Official ABMS Directory of Board-Certified Medical Specialists.* This, together with our method of choosing the same-numbered entry from the same-numbered column on each of 406 pages plus the 82% response rate, argues strongly against the possibility of selection bias. We admit that we did not include control questions on the questionnaire, and we limited our sample to U.S. psychiatrists. But we have now collected comparable data on Canadian psychiatrists, showing that they report even higher levels of skepticism about the dissociative disorders than their U.S. counterparts (1).

In short, our article was not an expression of our own opinions but simply a presentation of the opinions of randomly selected others. Some of the letter writers appear unhappy with these opinions, and they may prefer to interpret the glass as half full rather than half empty, but the numbers stand.

The statistical criticisms of Dr. Frankel and Ms. Span appear baseless. For example, the covariates assessed in our regression analysis—age, sex, professional orientation, and professional activities—are objective measures reasonably expected to be associated with attitudes toward the dissociative disorders. Indeed, other letter writers specifically argue that age, sex, and professional orientation may have influenced the responses. As for the sign test, this method assesses whether the median of the difference between matched pairs of observations is zero. It does not apply to differences between unmatched groups and is inappropriately offered by Dr. Frankel and Ms. Span.

The letter writers mention five previous surveys of attitudes toward dissociative identity disorder that we did not cite. Drs. Coons and Chu cite one of these studies (Dunn et al., 1994) as showing that "belief in dissociative identity disorder has increased to 80%." Yet Drs. Coons and Chu fail to note that this study achieved a response rate of only 31%—making it virtually uninterpretable. In the four remaining studies, overall response rates ranged from 43% to 61%—all far below our rate of 82%. In the study that achieved the highest response rate among psychiatrists (Dell, 1988), 80% reported that they had experienced "strong," "severe," or "extreme" skepticism from other professionals regarding dissociative identity disorder.

Finally, regarding the comments of Drs. First and Pincus, we strongly agree that an "evidence-based process" should guide the choice of DSM categories, and indeed, for this reason, we concluded our report by citing reviews of the current evidence. We also agree that a simple vote or a single survey is inadequate for determining the inclusion or exclusion of a disorder in DSM-IV. However, the survey method is an appropriate design to assess whether there exists a consensus regarding a diagnosis. And here, for the two dissociative disorders that we examined, the answer is clearly negative.

We furthermore agree that the rules for the choice of DSM-IV categories, with their emphasis on empirical evidence, are fundamentally sound—although we confess some discomfort with the preference given to "keeping the status quo." If there is fault, then, it lies not so much with DSM-IV itself but with those who cite DSM-IV as evidence for a consensus among psychiatrists regarding the diagnostic status and scientific validity of the dissociative disorders. Our evidence indicates that such a consensus simply does not exist.

This lack of consensus should hardly surprise two of our letter writers. Drs. Coons and Chu claim that "Although members of the False Memory Syndrome Foundation's scientific advisory board label dissociative identity disorder a controversial diagnosis, they are in the minority." Yet Dr. Chu himself has written that "Ever since the introduction of dissociative identity disorder…controversy has swirled around the nature and the validity of this diagnosis" (2). Similarly, Dr. First has coauthored a recent book that refers to dissociative identity disorder as a "new fad diagnosis" (3). Numerous major reviews appearing since the publication of DSM-IV have noted flaws in the evidence claiming to support dissociative amnesia and dissociative identity disorder and have seriously questioned the validity of both of these diagnoses (4–13).

In short, given both the questionable state of the evidence and the lack of consensus for dissociative amnesia and dissociative identity disorder in 1999, the editors of future editions of DSM will need to weigh carefully whether these diagnoses still merit inclusion.

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Cognitive Deficits in Obsessive-Compulsive Disorder

We read with interest a recent article by Sue R. Beers, Ph.D., and colleagues (1) examining neuropsychological functioning in children with obsessive-compulsive disorder (OCD). They found that children with OCD performed normally on a number of measures of executive functioning, including many previously shown to be impaired in adults with OCD. As noted by the authors, previous studies have documented that children with OCD already show abnormalities in frontal and striatal volumes in relation to comparison subjects. One explanation for these findings is that cognitive deficits emerge during the course of development in a manner that parallels the normal maturation of prefrontal systems.

Neuropsychological investigations of adults with OCD show impairment on complex measures of executive functioning and strategic memory. These problems may not be apparent in childhood because normal children do not have fully matured prefrontal networks and, consequently, show less developed executive functioning. Many executive and memory functions, including sustained attention, planning, problem solving, and semantic organization, show the greatest progression after age 12 (2, 3). There is also evidence that cognitive problems secondary to childhood brain injury may not become apparent until adolescence, when these abilities develop in normal children (4).

This concept might also be extended to the clinical phenomenology of OCD in different age groups. Comorbid illnesses, such as Tourette's syndrome and attention deficit hyperactivity disorder, often appear years before the onset of actual OCD symptoms (5). In these cases, the emergence of OCD symptoms closely parallels the normal development of frontal lobe systems and executive functioning. The symptomatic expression of OCD also differs in children and adults, with children showing higher rates of compulsive rituals without clearly delineated obsessions. It is possible that a certain level of frontal system development is actually necessary to manifest some characteristic symptoms of OCD. For example, albeit dysfunctional, the capacity to obsess may require adequate working memory to maintain thoughts continually in awareness.

For these reasons, some neuropsychological and clinical symptoms of OCD may not emerge until critical prefrontal systems mature—perhaps not until adolescence or later. We applaud this interesting work by Dr. Beers and colleagues. Future investigations following such well-characterized cohorts longitudinally may clarify the way in which cognitive deficits and clinical symptoms of OCD evolve over the course of development.

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Dr. Beers and Colleagues Reply

We appreciate the comments on our article by Drs. Savage and Rauch proposing that our null results might be explained by the fact that cognitive abilities dependent on prefrontal function do not develop until later in childhood and, thus, were not apparent at the time of our evaluation of children with OCD. They suggest an emerging deficit in frontal lobe function that mirrors the clinical phenomenology of the illness, noting that the obsessions may not fully develop until frontal lobe processes reach full maturity, sometime after age 12. This is a worthy hypothesis. In a study by Levin and colleagues (1991), healthy older children (ages 13–15 years) showed the expected developmental gains on a measure of verbal fluency and on the Tower of London task (a.k.a. Tower of Hanoi). However, on the Wisconsin Card Sorting Test and the Go–No-Go task, both of which were also included in our study, children performed at the adult level by age 12. Noting that our group was strikingly similar in age to that of the group of Levin et al. (12.3 years [SD=2.9] versus 11.1 years [SD=1.1], respectively), we do not feel that developmental level itself can explain our null results, especially with respect to the Wisconsin Card Sorting Test.

OCD symptoms, even early in the illness, might influence problem-solving efficiency rather than problem-solving accuracy measured within a time limit. A controlled study of adults with OCD (1) demonstrated no between-group differences in number of responses, rate of perseverative responses, and rate of perseverative errors on the Wisconsin Card Sorting Test. However, OCD patients required significantly more time to respond to each trial and to complete the entire test. Careful consideration suggests that within our group of frontal lobe tests, we can make distinctions between those that were timed but brief and highly structured (e.g., Stroop Color/Word Test, Trail Making Test B, Controlled Oral Word Association test) and those that had no obvious time constraints but required deductive reasoning (e.g., Tower of Hanoi, Wisconsin Card Sorting Test). The latter tests emphasize rule acquisition and the problem-solving process, whereas the former require clearly defined responses (e.g., ink color, alternation between numbers and letters) while inhibiting other clearly defined but inappropriate responses. One explanation for our null results may be that we failed to measure problem-solving efficiency during the completion of unstructured problems that require, among other things, the discovery of rules.

Neuroimaging studies have begun to elaborate the structural brain changes associated with OCD in young children. As Drs. Savage and Rauch suggest, it remains for carefully designed longitudinal studies to determine the neuropsychological correlates and functional significance of these brain changes early in the illness and over the course of subsequent development.

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Recurrence of Geriatric Depression

A recent article by Alastair J. Flint, M.B., Ch.B., F.R.C.P.C., F.R.A.N.Z.C.P., and Sandra L. Rifat, Ph.D. (1), describing a naturalistic study of the recurrence of first-episode geriatric depression after the discontinuation of antidepressants, is an important contribution to the literature on the prognosis of depression in elderly subjects. The authors deserve praise for their attempts to control for two prognostic factors (age at onset and number of previous episodes) in the design of this study and to determine the effect of nine other potential prognostic factors (age, sex, duration and severity of index episode, presence of anxiety, cognitive impairment, physical illness, life events and difficulties, and time to response to treatment) in the analysis. Nonetheless, we require more information to clarify the usefulness of their finding of a 61% rate of recurrence or recurrence within 2 years. First, it is necessary to know more about the 21 depressed patients included in the study (e.g., sex, socioeconomic status, living arrangements, and source of referral). Second, it is important to know the number of patients with first-episode, late-onset depression at each stage of the study (i.e., numbers enrolled, responding to treatment, beginning maintenance therapy, and noncompliant or relapsing during maintenance therapy). Third, because the investigators conducting the outcome assessments were not blind to discontinuation, it would be helpful to know if the authors tried to examine or control for potential assessment bias. Finally, it would be useful to know the 95% confidence interval (CI) of the recurrence rate to better judge the merits of arguments for shorter- versus longer-term maintenance therapy in this population.

Reference

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Drs. Flint and Rifat Reply

We thank Dr. Cole for his comments. Our article was published as a Brief Report, so space limitations prevented us from including many of the details that Dr. Cole wants to know. Demographic and clinical characteristics of the 21 patients in the study group were as follows: 13 (61.9%) were women; 21 (100%) were white; seven (33.3%) were married, seven (33.3%) were widowed, five (23.8%) were single, and two (9.5%) were divorced; 17 (81.0%) were living at home and four (19.0%) were living in a retirement facility; and 16 (76.2%) were referred by a family physician, two (9.5%) were referred by a specialist, and three (14.3%) were self-referred. At index assessment, all patients were 60 years or older, and 11 (52.4%) were 75 years or older. Their mean Hamilton Depression Rating Scale score at index assessment was 23.7 (SD=5.1). At the follow-up described in our article (that is, after completion of 2 years of continuation or maintenance antidepressant treatment), the patients had a mean Hamilton depression score of 2.2 (SD=3.1), a mean Mini-Mental State (1) score of 27.9 (SD=2.7), and a low level of medical burden.

With respect to the numbers of patients at each stage of treatment, 52 were treated for an index episode of depression,

and 43 responded. Of the responders, nine (20.9%) had a relapse or recurrence of major depression, and 12 (27.9%) dropped out (five were noncompliant, four developed physical illness, two died, and one moved away) during the 2 years of continuation or maintenance antidepressant treatment. One other patient completed maintenance treatment but was too physically unwell to participate in the follow-up. Thus, the 21 patients reported at follow-up in our article represented 48.8% of the patients who had responded to treatment of an index episode of depression.

With respect to the assessment of outcome, a diagnosis of recurrence was made by the study psychiatrist alone on the basis of a clinical interview and the patient's Hamilton depression score.

Finally, the cumulative probability of a person not having an episode of major depression during the 2 years of follow-up was 0.39. The 95% CI for this survival estimate was 0.17–0.62. Interpretation of this CI is, however, limited by the fact that it is based on a small number of subjects. During the follow-up, 12 patients had a recurrence of depression, three others died (from natural causes), and one moved away. Thus, only five patients were still under observation at 2 years, the time point at which this CI was calculated. The small number of subjects contributed to the wide range of the CI.

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Sex Differences in Cerebral Metabolism Among Abstinent Cocaine Users

In a recent article, Linda Chang, M.D., and colleagues (1) reported that there were sex differences in cerebral metabolism in the frontal lobes of abstinent cocaine users. These data support the findings of a single photon emission computed tomography study (2) and a self-report study (3). The possibility that clinical presentation and symptoms may also be different between male and female cocaine users was not discussed by Dr. Chang et al. (1); therefore, attention is called to reports that give clues as to how sex differences in the effects of cocaine use could translate clinically.

Brady et al. (4) reported higher rates of affective and anxiety disorders in men than in women with cocaine dependence. This finding was at odds with the female-male ratio of people with alcohol dependence and the general population. Others have reported that recent cocaine use in psychiatric inpatients was associated with violent behavior in women but not in men (5). Finally, a study comparing psychiatric emergency room patients with and without urine samples positive for cocaine suggested that recent cocaine use was associated with suicidal behavior in men and with violent behavior in women (6, 7). These three pieces of information suggest that the clinical effects of cocaine use on mood and impulse regulation need to be studied separately in men and women.

The study by Dr. Chang et al. provides exciting new evidence that the neurobiological effects of cocaine differ by sex. Clinical studies suggest an increased risk for mood disturbance in men and violence in women. A caveat is that women with antisocial personality disorder may be overrepresented in groups of cocaine users (4); this may account for an increase in violence. Alternatively, antisocial traits may develop more frequently in women using cocaine than in men. These hypotheses need testing in future studies.

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