Imipramine Toxicity and Terbinafine

TO THE EDITOR: Tricyclic antidepressants are known to be susceptible to drug interactions. We report on a patient who experienced imipramine toxicity due to a probable interaction of the drug with the antifungal agent terbinafine.

Mr. A, a 51-year-old man with bipolar disorder, had been treated over the last 10 years with a combination of lithium carbonate, 1200 mg/day, and imipramine, in doses varying from 150 to 200 mg/day. At these doses his serum imipramine concentrations ranged from 100 to 200 ng/ml. Mr. A's past medical history was notable only for atopic dermatitis, which was treated with topical preparations, and prostate cancer, which had been treated with a total prostatectomy. There was no evidence of liver disease. Mr. A was seen by a local dermatologist for onychomycosis. Oral terbinafine, at a dose of 250 mg/day, was begun as treatment. One week after starting terbinafine treatment, Mr. A complained of a worsening mood, poor concentration, sleep disruption, and anorexia. He was diagnosed with a depressive relapse. Three days later, his imipramine dose was increased from 175 to 200 mg/day.

Approximately 1 week after the dose increase, Mr. A reported an episode of dizziness when he got up at night to urinate, resulting in his falling against the toilet tank and bruising his shoulder. At this time he also reported muscle twitching and excessive oral dryness. His serum imipramine concentration, measured 5 days after the episode of dizziness, was 530 ng/ml. His imipramine dose was gradually reduced to 75 mg/day over a 2-month period. Mr. A's depressive symptoms were alleviated by this dose reduction. A serum level of 229 ng/ml was reached after 10 days at this new dose. His serum aspartate aminotransferase and alanine aminotransferase levels were measured at the same time and were judged within normal limits. His imipramine serum level was measured 3 weeks later and was found to be 213 ng/ml.

To our knowledge, this is only the second case report of toxicity associated with the introduction of terbinafine into current therapy with a tricyclic antidepressant. The only other report we know of is by van der Kuy and Hooymans (1). In that case, an elderly patient had elevated nortriptyline levels and symptoms of tricyclic antidepressant toxicity consisting of vertigo, increased fatigue, and loss of appetite after starting to take terbinafine. The symptoms led to a fall down a flight of stairs. The authors in that report rechallenged their patient with terbinafine after it had been discontinued. The patient's symptoms and increased serum levels of nortriptyline returned on rechallenge. No rechallenge was performed on our patient.

The metabolism of imipramine substantially relies on the cytochrome P-450 enzyme 2D6 (2). Terbinafine has been shown to be a strong inhibitor of that particular enzyme (3). The package label for the U.S. product does not identify tricyclic antidepressants as potentially interacting drugs (4). According to the scale used by Naranjo et al. (5), our patient's symptoms earned a score of 8 out of a possible 12, which is defined as "probable" toxicity. Practitioners who prescribe terbinafine should be aware of this potential interaction and avoid the use of the drug for patients who are taking tricyclic antidepressants.

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Bright Light Therapy for Schizoaffective Disorder

TO THE EDITOR: Schizoaffective disorder is often chronic and disabling. Typical treatment usually consists of antipsychotics and antidepressants (1). Although light therapy is effective in treating winter depression (2), we know of no report of bright light treatment for schizoaffective disorder.

Mr. A, a 50-year-old man, was diagnosed with schizoaffective disorder with recurring depressive episodes in winter. His first episode was in autumn and included symptoms of depression as well as perceptual disturbances, including auditory and visual hallucinations. Subsequently, he experienced depressive symptoms almost every winter. Although he worked for several years in an isolated setting and experienced other periods of productive activity, his course of illness was remarkable for social withdrawal, avolition, consistently disorganized thoughts independent of mood, and highly idiosyncratic—sometimes bizarre—ideation. He intermittently abused marijuana and alcohol. During euthymic, substance-free periods, he experienced months-long periods of hallucinations. Trials with fluoxetine were unsuccessful in treating his depressive episodes. Haloperidol worsened his mood symptoms without improving his withdrawal or avolition. In autumn his seasonal depression was treated with methylphenidate, which proved more effective than other medications. Unfortunately, this psychostimulant exacerbated his thought disorder. In the spring, as his mood improved, Mr. A and his clinician agreed that he would remain medication free throughout the summer.

Mr. A appeared for treatment in an unmedicated condition in the autumn with new onset of a depressive episode and loss of energy, interest, and motivation resulting in functional and occupational impairment. His score on the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (3), was 27 (score of 21 on the 21-item Hamilton depression scale and score of 6 for atypical symptoms), which is consistent with moderate depression (4). He was not experiencing perceptual disturbances but displayed tangentiality, thought derailment, and idiosyn-

cratic thought content. His hygiene and grooming were poor to fair.

In consideration of his pattern of seasonal depression, an empirical home trial of bright light therapy with no additional medication was attempted. He was instructed to use a 10,000-lux SunRay light box (SunBox Company, Gaithersburg, Md.) for daily treatment from 7:00 a.m. to 7:30 a.m. and to glance directly at the unit approximately once every minute. Within 1 week Mr. A's Hamilton depression scale score decreased from 21 to 9, and his atypical depression rating decreased from 6 to 1. Daily treatment with the light box was then increased to 45 minutes, resulting in no adverse effects. Within 1 week Mr. A's Hamilton depression scale score had further decreased to 3; his atypical depression rating remained at 1. His functioning had improved in all dimensions, including grooming and hygiene and the ability to maintain his household and care for his family. Loose associations of speech and idiosyncratic thought remained. A low dose of olanzapine was later added, since his thought disorder continued unabated.

Bright light therapy proved comparable or superior to treatment with previous medications for depression for this patient.

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Continuation of Clozapine After Priapism

TO THE EDITOR: A total of 15%–45% of all cases of priapism are caused by medications, and psychotropic drugs are the most common offenders (1). In addition to trazodone, chlorpromazine, and thioridazine, clozapine has also been cited as a causative agent. Central α_1-adrenergic blockade is the mechanism thought to mediate this side effect. Most patients with priapism, as described in the literature, were not rechallenged with clozapine after experiencing an episode of priapism. However, clozapine is often the treatment of last resort for patients with extremely refractory psychosis; we found in the literature two reports of reexposure to clozapine after occurrence of priapism. One patient had two recurrences of priapism when he began taking lower doses of clozapine (2). The other patient remained free of psychosis and priapism for 2 weeks after clozapine was reinitiated. He then became noncompliant with CBC monitoring, and clozapine was discontinued (3). We report a case of successful, long-term continuation of clozapine for a treatment-resistant schizophrenic patient after an episode of clozapine-related priapism.

Mr. A was a 25-year-old Hispanic man who suffered from unrelenting paranoia, hallucinations, and negative symptoms. Trials of traditional neuroleptics, risperidone, and olanzapine were attempted. Risperidone was discontinued after one episode of priapism and poor response to treatment. Olanzapine was only minimally effective. When he was taking clozapine, 400 mg/day, Mr. A showed remarkable improvement and was able to seek and maintain employment.

Ten months into treatment, Mr. A had a painful, prolonged erection that lasted 33 hours. Nonsurgical methods were unsuccessful in relieving his discomfort. Placement of a cavernosal glandular shunt was required for detumescence. After Mr. A had recovered, various antipsychotic treatment options were offered to him. Both he and his family felt that the benefits of clozapine outweighed the risk of priapism. Given the refractory nature of his illness as well as the severity of his symptoms at decompensation, he continued to take clozapine at one-half the original dose. Except for one episode of noncompliance and subsequent decompensation, Mr. A has continued to do well and has had only residual negative symptoms. The previous episode of priapism resolved, and Mr. A has reported no recurrence of priapism in over a year.

While discontinuation of the causative drug is the usual recommendation for serious side effects such as priapism, patients taking clozapine frequently have severe symptoms not ameliorated by use of other medications. In such cases, a careful risk-benefit assessment involving the patient and significant others may indicate that continuation of the causative agent is the best choice. To our knowledge, this is the first report of successful, sustained clozapine continuation with no recurrence of priapism in a patient with a history of clozapine-associated priapism.

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Olanzapine-Induced Priapism

TO THE EDITOR: Priapism is a condition that has long been associated with use of psychotropic medications. Previous cases of priapism have been reported in association with several antipsychotic drugs, including chlorpromazine, thioridazine, thiothixene, mesoridazine, and perphenazine. The first discussion of priapism associated with administration of atypical antipsychotics, to our knowledge, is a case report from 1992 involving administration of clozapine (1). There have since been reports of priapism in patients receiving the atypical antipsychotics risperidone and olanzapine. We are

aware of only four reports of olanzapine-induced priapism to date (2–5). Recent or concurrent use of other psychotropic agents makes definitive statements regarding the cause of priapism difficult for three of these patients (2–4). The other patient had reversible priapism after olanzapine monotherapy (5). We report here on the first instance, to our knowledge, of olanzapine-induced irreversible priapism in a neuroleptic-naive patient.

Mr. A was a 35-year-old white man who was admitted to a partial hospitalization program for patients with suicidal thoughts and paranoia. He had neither a prior history of mental illness nor a history of psychotropic medication use. Mr. A came in for treatment with paranoid delusions and suicidal thoughts and was diagnosed with schizoaffective disorder. Treatment with 10 mg of olanzapine at bedtime was initiated. Approximately 14 hours after his first and only dose of olanzapine, Mr. A developed a painful erection. He did not report this to anyone at the time and returned to the partial hospitalization program 48 hours later. By this time he was in significant discomfort and acknowledged that his pain was due to an erection that had been present for approximately 2 days. He was immediately taken to the emergency room for a urological consultation.

A urologist attempted evacuation of blood from Mr. A's penis without success. Mr. A was then taken to the operating room, where blood was evacuated and phenylephrine was injected; flaccidity was obtained and lasted for 1 hour before the erection returned. Mr. A was taken back to the operating room, and a corporeal glandular shunt was placed, but this too was unsuccessful in alleviating the erection. He was then transferred to another hospital for possible insertion of a proximal shunt, which was not performed because of the length of time since the onset of priapism. Symptomatic relief was provided with oral analgesics; eventual detumescence of the penis followed. Permanent impotence resulted from Mr. A's prolonged priapism.

Olanzapine can induce priapism because of its α-adrenergic blocking capabilities. While the condition is far from common, clinicians should be aware of olanzapine's ability to induce priapism. Swift recognition is necessary to prevent permanent urological sequelae.

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Venlafaxine- and Trazodone-Induced Serotonin Syndrome

TO THE EDITOR: Serotonin syndrome results from excessive serotonin stimulation and is characterized by confusion, restlessness, myoclonus, hyperreflexia, diaphoresis, and tremor (1). The original descriptions focused on the interaction between monoamine oxidase inhibitors and serotonergic agents. Serotonin syndrome has subsequently been reported to occur with drug combinations involving selective serotonin reuptake inhibitors (SSRIs) and other serotonergic agents (2, 3). In this case, a patient taking venlafaxine and trazodone developed signs of serotonin syndrome.

Mr. A was a 50-year old man with a past history of recurrent depression who was hospitalized for a several-week history of depression characterized by depressed mood, anhedonia, hopelessness, insomnia, and suicidal ideation. He had no psychosis or cognitive impairment. He had a history of opioid dependence since age 19, but his addiction was being treated with methadone. His past medical history was remarkable for his being seropositive for HIV for 10 years (without treatment) and seropositive for hepatitis C for 36 months. The results of laboratory tests at admission were remarkable for mildly elevated hepatic enzyme levels. Two months before admission, Mr. A's CD4 lymphocyte level was 436 cells/μl.

Mr. A began taking extended-release venlafaxine; his dose was increased over 7 days to 225 mg/day. He also received 100 mg of trazodone at bedtime for insomnia, 100 mg t.i.d. of docusate sodium for constipation, and 120 mg/day of methadone. Eighteen days after hospitalization, Mr. A developed disorientation, restlessness, myoclonic jerking, gross tremulousness, and diaphoresis. He was afebrile; his other vital signs were unremarkable. Concurrent results of laboratory tests were not significantly different from those at admission, except for a decreased CO_2 level of 19.1 mmol/liter, an increase in aspartate aminotransferase level to 95 U/liter, and an increase in creatine kinase level to 2277 U/liter. The latter was subsequent to several intramuscular injections given to manage agitation. A computerized tomography scan of his head revealed moderate cerebral atrophy but no acute pathology. After 36 hours, during which Mr. A's condition deteriorated, all medications were discontinued. He was given intravenous hydration. Within 24 hours his clinical status improved dramatically. He began taking methadone and docusate sodium again; he was given mirtazapine for depression. The remainder of his hospitalization was uneventful.

We believe that this was a case of serotonin syndrome that was precipitated by the combination of venlafaxine and trazodone, both of which inhibit the reuptake of serotonin. The clinical features of this episode and their rapid resolution when medication was discontinued support this. Methadone may have been a contributing factor to serotonin syndrome because it increases serotonin synthesis in laboratory animals (4). However, the patient had taken SSRIs in the past while also taking methadone, without ill effects. While venlafaxine and trazodone can be used together in most cases, our patient's chronic medical problems may have made him more vulnerable to effects of the drugs used in combination. Use of this combination requires caution in this population. An agent

without serotonergic effects should be considered if a hypnotic is required in addition to treatment with venlafaxine.

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ECT for Psychotic Depression Associated With a Brain Tumor

TO THE EDITOR: Primary indications for ECT include major depression, mania, and psychosis. ECT may be indicated in the treatment of affective disorders associated with medical illness (1). The APA Task Force on ECT lists space-occupying cerebral lesions under "Situations Associated With Substantial Risk" for ECT; however, there are several case studies on the efficacy of ECT in treating depression in such situations (2). We present the case of a woman with treatment-resistant depression associated with a recurrent brain tumor who experienced rapid remission of her symptoms after ECT.

Ms. A was a 35-year-old woman whose medical history was notable for a left-frontal neurocytoma, two subsequent incomplete resections, and radiation treatment. The neurocytoma was detected during a routine workup for the acute onset of depression. Neurocytomas are a rare, slow-growing type of brain tumor with a high rate of recurrence. Ms. A's subsequent psychiatric illness course was characterized by recurrent hospitalizations for persistent dysphoria, apathy, and hopelessness, including six hospitalizations within 18 months. Trials with more than 10 tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and non-SSRIs produced no definite improvement, while methylphenidate and lorazepam produced transient improvement in her behavior.

Ms. A had been transferred from another hospital, in which she had been hospitalized for 6 weeks after admission for depression and multiple suicide attempts by drowning. After admission to our neuropsychiatry unit, Ms. A remained reclusive, was frequently tearful, stared aimlessly for long periods, and was absent of, or had greatly delayed, verbal and motoric responses. She experienced somatic and religious delusions and expressed a wish to die. The results of a neurological examination revealed mild right-sided weakness and mild transcortical motor aphasia. ECT was considered because of the lack of adequate antidepressant response and increasing suicidality. An ECT workup, including magnetic resonance imaging of Ms. A's brain, revealed a large, complex mass in the left lateral ventricle and left frontal encephalomalacia. A thallium brain scan revealed left frontal hypovascularity but no evidence of tumor recurrence; an EEG showed left hemispheric slowing but no epileptiform activity.

Within 6 hours after right unilateral ECT, Ms. A appeared bright, had improved speech and motoric response, and recalled feeling "bad" and wanting to hurt herself before treatment. Two additional ECT treatments produced full resolution of her dysphoria, hypomotoric state, and delusions. After discharge and withdrawal of antidepressants, Ms. A's mood remained stable over the next 8 months to the point that she pursued a job and driving privileges.

For this patient, who suffered from medication-resistant depression and akinesia secondary to a static brain tumor, ECT proved to be beneficial and without side effects. Unlike in previous cases, our patient experienced a rapid and prolonged antidepressant response and her brain tumor was not a coincidental condition.

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Venlafaxine and Breast-Feeding

TO THE EDITOR: Clinicians treating new mothers for depression require information about the safety of antidepressants if used while the mothers are breast-feeding. In contrast to extensive data on the use of selective serotonin reuptake inhibitor (SSRI) antidepressants by women who are breast-feeding (1–4), we know of only one small case series (N=3) on the use of venlafaxine by breast-feeding mothers (5). In this report, the estimated mean dose the infants received from breast milk was 7.6% of the maternal weight-adjusted dose. No adverse effects were noted in the infants, but the authors cautioned that this dose was high compared to the doses infants are estimated to receive when exposed to other antidepressants through breast milk. To add to the limited available data, we describe results we obtained for two mother-infant pairs in which the mothers were taking venlafaxine while breast-feeding.

Two nursing women taking stable daily doses of venlafaxine provided written informed consent for measurement of their and their infants' serum levels of the drug. The analysis of venlafaxine and its metabolite, *O*-desmethylvenlafaxine, was accomplished by means of high-performance liquid chromatography, which has a detection limit of 10 ng/ml.

At birth, the pair 1 infant weighed 3.3 kg and had a gestational age of 37 weeks. The pair 2 infant weighed 3.9 kg and had a gestational age of 38 weeks at birth. Both infants received breast milk exclusively during their first 6 months. The pair 1 mother began taking venlafaxine (75 mg/day) on the day of delivery, while the pair 2 mother took the medication (150 mg/day) throughout her pregnancy. The pair 1 infant was 3 weeks old and weighed 4.1 kg when the serum testing was performed; the pair 2 infant was 4 weeks old and weighed 4.6 kg. The interval between the time the mother took her oral dose and blood was drawn for serum testing was 3.0 hours for pair 1 and 2.0 hours for pair 2. The mothers' serum medication concentrations were 31.00 and 28.00 ng/ml, respectively, and their serum metabolite concentrations were 148.00 and

230.00 ng/ml. Venlafaxine was not detectable in either infant (0.00 ng/ml in both infants), but the metabolite was present in both children: pair 1 infant, 16.00 ng/ml; pair 2 infant, 21.00 ng/ml. No adverse sequelae, such as changes in sleep, feeding patterns, or behavior, occurred in the infants, as shown by maternal reports and review of pediatric records. In addition, the pediatric records indicated that the children's weight and heights were in the 85th–100th percentiles.

These findings show that the venlafaxine metabolite was present at low but detectable concentrations in infants exposed to venlafaxine while nursing. The presence of the metabolite suggests that these young infants were able to desmethylate the parent drug. It is encouraging that they did not experience adverse effects from venlafaxine exposure through breast milk and that their development over the first year appeared to be normal.

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Psychiatric Pharmacists

TO THE EDITOR: There are currently 352 board-certified psychiatric pharmacists working collaboratively in academic and clinical settings in the United States, Canada, and Australia to optimize the care of patients with psychiatric illnesses. Their number continues to grow as more pharmacists attain this credential. I wish to inform providers of care in the mental health community about the certification process for psychiatric pharmacists so they may better understand the contributions that such pharmacists can make to patient care.

Pharmaceutical specialties are established by the Board of Pharmaceutical Specialties, an independent nongovernmental agency created by the American Pharmaceutical Association in 1976. The pursuit of specialty status for psychiatric pharmacists began in the 1980s. The executive summary of the petition for recognition of psychiatric pharmacy as a specialty was published in 1991 (1); designation as an official specialty occurred in 1992. The first examination for board certification was offered in 1996.

Before specialty status is awarded by the Board of Pharmaceutical Specialties, seven criteria must be met:

1. Evidence to support a significant health demand and need for specially trained pharmacists in the designated area must be provided.
2. The specialty area must include a reasonable number of individuals who devote significant time to practice in the area.
3. Specialized knowledge and skills based on the biological, physical, and behavioral sciences are required for practice in the area.
4. Practitioners must perform specialized functions acquired by education or training beyond those required for licensure.
5. The transmission of knowledge in the area must be accessible through books, journals, symposia, and other formal mechanisms.
6. To be eligible for certification, an applicant must have graduated from an accredited school of pharmacy, have a current active pharmaceutical license, have completed either a residency program in psychiatric pharmacy with 1 additional year of practice, including substantial time in psychiatric pharmacy, or have a minimum of 4 years of practice in psychiatric pharmacy and pass the specialty certification examination.
7. The examination was developed and validated by the Board of Pharmaceutical Specialties Council on Psychiatric Pharmacy in collaboration with a professional testing firm. The examination is based on three domains that assess the pharmacist's ability to collaborate with other health care professionals in pursuing optimal drug therapy for patients with psychiatric illnesses, generate or disseminate knowledge in psychiatric pharmacy, and collaborate with other professionals to recommend, implement, monitor, and modify systems for optimizing pharmacotherapy in patients with psychiatric illnesses. Board-certified psychiatric pharmacists must renew their certifications every 7 years.

This credible process has been implemented to assist the public and health care providers in identifying pharmacists who have the advanced level of knowledge, skills, and abilities required to provide quality health care in an increasingly complex environment. We encourage you to take advantage of the resources that board-certified psychiatric pharmacists have to offer you and your patients. For more information, call the Board of Pharmaceutical Specialties at 202-429-7591 or visit the board's web site at http://www.bpsweb.org.

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End-of-Life Care Content in Textbooks

TO THE EDITOR: The care that physicians provide to terminally ill and end-stage patients has received growing attention. Numerous specialty boards and organizations, including the

Academy of Psychosomatic Medicine, have developed professional standards on end-of-life care for their members (1–3). Although there are several reasons for less than adequate end-of-life care, insufficient training of clinicians in this area is a major concern (4). The textbooks used to train clinicians deserve their fair share of the blame. Our research (5) has identified major deficiencies in the end-of-life content of 50 best-selling medical textbooks, including three top psychiatry textbooks. At first glance, these three textbooks may be praised for scoring significantly higher than other specialty texts. As a group, these textbooks contained helpful information (mean=34.4% of their content) regarding end-of-life care. The textbook with the highest overall score for helpful end-of-life content (44.2%) was a psychiatry textbook. Unfortunately, these figures are praiseworthy only when compared to the paucity of information in texts from other specialties. On their own, these scores call for drastic changes in content.

In the face of such alarming findings, we have led an effort to encourage publishers, editors, and authors to improve their textbooks' content on end-of-life care, including book chapters, cross-referencing, and indexing (6). In following up this effort, we recently surveyed textbook publishers and editors to assess their progress in revising their texts.

We have been encouraged by a very positive response overall. To date, we have received responses to our follow-up survey from 19 publishers and 23 editors (including two of three editors of the psychiatry texts) of the 50 textbooks surveyed. These responses indicate plans to expand the end-of-life care content in the next editions of 22 textbooks, including 17 textbooks with new chapters regarding end-of-life care, 11 with expanded cross-referencing, and 17 with revised indexes. Hence, of the 50 textbooks, over one-third are expanding the end-of-life care content in their next editions. Finally, we have received six personal letters of support from editors and publishers, including a poignant one from an editor who was dying of metastatic melanoma when he wrote to us.

Recently, the Robert Wood Johnson Foundation honored textbook authors, editors, and publishers who have undertaken significant efforts toward making important changes. On Feb. 21, 2001, the Last Acts Project held an awards ceremony for the occasion. The foundation presented awards to the editors of three medical textbooks (*Emergency Medicine,* 5th ed., editor-in-chief, Judith Tintinalli; *Nelson Textbook of Pediatrics,* 16th ed., editors, Richard Behrman, Robert Kliegman, and Hal Jensen; and *Textbook of Primary Care Medicine,* 3rd ed., senior editor, John Noble) and to one medical textbook publisher (Lippincott Williams & Wilkins).

It is unfortunate that there is still much work to be done. Many best-selling textbooks have not yet responded to the suggestions of their specialty boards, the needs of their readers, or the demands of patients and families to improve clinician education in the care of patients at the end of life. We will continue monitoring textbooks over the next several years, and the Robert Wood Johnson Foundation will continue to offer awards to the publishers, editors, and authors who improve the end-of-life content in their books. It is of the utmost importance that current knowledge and ongoing research in palliative care published in this journal quickly find its way into best-selling psychiatry textbooks.

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Psychotherapy by Nonphysicians

TO THE EDITOR: In their otherwise very thoughtful article (1), John O. Beahrs, M.D., and Thomas G. Gutheil, M.D., used the terms "medical" or "medicalized" as necessary parts of their definition of psychotherapy in at least three instances. In the first paragraph, they stated, "It [psychotherapy] stands apart from everyday discourse by the extent to which it is defined as a procedure, i.e., medicalized" (p. 4). They then stated, "It has been ratified as a medical procedure by scientific texts, third-party payers, and the law" (p. 4). To imply that the practice of psychotherapy is somehow the exclusive domain of physicians, which is my interpretation of the quoted statements, is gratuitous and insulting to our nonmedical colleagues.

This interpretation simply is not true. Our community has, as have most others, qualified and talented clinical psychologists, psychiatric social workers, and other mental health professionals who are trained in, and excellent practitioners of, the set of procedures collectively known as psychotherapy. Scientific texts about how to practice psychotherapy and how to measure its effectiveness often include nonmedical practitioners; see the works of Carl Rogers and Lester Luborsky. Third-party payers seem to go out of their way *not* to pay psychiatrists to do psychotherapy, but they often will pay for treatment by nonmedical practitioners. California law recognizes the psychotherapist-patient (or "client") privilege without stating that the psychotherapist has to be a physician. Physicians have no corner on that particular market and no claim of exclusivity to that piece of turf. The issue of informed consent in psychotherapy is just as germane to nonmedical practitioners of psychotherapy as it is to those with medical degrees. Indeed, the opening of our psychoanalytic training institutes to nonphysicians in recent years guarantees that large numbers of nonphysician psychotherapists will be receiving training at its highest level in the future (something that is, unfortunately, disappearing from many psychiatric residencies, which are now turning out some graduates whose training in psychotherapy is woefully deficient).

Had the authors confined themselves to who should be allowed to practice the procedures known collectively as "psy-

chopharmacology" I would have no quarrel with them. Medical training is indeed a necessary prerequisite for the intelligent practice of psychopharmacology, and even here the issue of informed consent requires the kind of analytical thinking that Drs. Beahrs and Gutheil can furnish us.

I hope to see further articles by the authors on this topic, but I hope that they will be written in a more ecumenical spirit, so that they can be read without invidious implication by all who are engaged in the practice of psychotherapy.

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Drs. Beahrs and Gutheil Reply

TO THE EDITOR: We intended to address our article to all practitioners of psychotherapy who work in allied mental health professions.

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Tribute to Lasègue

TO THE EDITOR: A well-deserved tribute was paid to the French psychiatrist Charles Lasègue by Henri Chabrol, M.D., Ph.D., and Jacques Corraze, M.D., Ph.D. (1). The French authors, however, were not overly chauvinistic. They forgot to mention Lasègue's pioneering work in forensic psychiatry, including his seminal papers on exhibitionism and kleptomania. Moreover, they erroneously dated his beautiful psychological description of anorexia nervosa as "5 years after Gull's" (p. 28). As van Deth and I discussed elsewhere (2), Gull's so-called discovery of "hysterical apepsia" in 1868 was his own reinterpretation of a cryptic reference to the disorder that had been made to support his claim for priority in describing the new illness. A careful analysis of the original sources clearly shows that "the modern history of anorexia nervosa commences in 1973 with the independent 'parenthood' shared by Sir William Withey Gull and Dr. Ernest Charles Lasègue" (3, p. 161).

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Drs. Chabrol and Corraze Reply

TO THE EDITOR: We thank Dr. Vandereycken for his savant comment. We agree with his crediting Charles Lasègue priority for his description of anorexia nervosa. Lasègue's article was translated into English (1, 2) before the publication of Gull's article on anorexia nervosa (3). Gull attempted to, and largely did, gain the attribution of the discovery of anorexia nervosa with mentioning his previous quotation of hysterical epepsia as a differential diagnosis for tuberculosis or organic gastrointestinal diseases in cases of severe weight loss (Vandereycken and van Deth, 1989). But the very term he used indicated that he attributed weight loss to the absence of digestion (apepsia) and not to a restrictive diet.

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Psychosocial Treatment for Schizophrenia

TO THE EDITOR: I am concerned as to the validity of the recent review by Juan R. Bustillo, M.D., and colleagues (1) on the psychosocial treatment of schizophrenia. First, this review did not follow the procedures currently considered standard in research synthesis. The authors' literature search appears reasonably comprehensive but may not have been as exhaustive as might be expected in a high-quality journal. For family therapy, for example, the authors failed to mention the trial by Buchkremer et al. (2), which resulted in negative findings. More important, the authors did not appraise—or did not clarify how they appraised—the methodological quality of the individual studies identified; there are so many different ways to proceed, and the validity of the review naturally hinges on which studies the reviewers chose to include (3).

Furthermore, the review did not attempt a meta-analytic pooling of the results. Quantitative synthesis is not a necessary condition for a scientific overview. However, failing to do this in meta-analyses in which it is possible renders the review vulnerable to a selective reporting of results from trials that are consistent with the reviewers' preconceived notions. It also deprives the review of chances to test for heterogeneity and publication bias; this is one of the cardinal requirements of research synthesis in medicine (4).

All this may partly explain my last concern with this review, namely, that the conclusions drawn do not seem to follow logically from the findings in the trials reviewed. In the text, the authors noted the remarkable lack of relapse prevention in the most recent trials of family therapy but recommended it for the "majority of persons suffering from schizophrenia" (1, p. 163). The authors attributed the negative findings of the more recent trials to low event rates, but systematic review over time does not warrant such an interpretation (5). Regarding social skills training, the authors wrote, "There is little evidence that this learning [with use of the basic model] translates into improved social competence in the community" (1, p. 167), and noted only modest benefit, such as in two of six or three of 10 areas of social functioning that they examined, with other, more intensive modes of social skills training. If these statements are true, then how could the authors conclude by writing, "Patients with schizophrenia can clearly improve their social competence with social skills training" (p. 163)?

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Dr. Bustillo and Colleagues Reply

TO THE EDITOR: Dr. Furukawa's letter raises several issues regarding our update on the psychosocial treatment of schizophrenia. His criticisms revolve around our procedures for reviewing the literature and our conclusions. In regard to our methods, he states that in selecting relevant studies, we fell short of what is "currently considered standard in research synthesis." The only example he gives of this is our failure to discuss a report by Buchkremer et al. (1995). As stated in our Method section, we focused on randomized controlled studies that used standardized instruments and were published since the last report in the *Journal* on the psychosocial treatment of schizophrenia by Penn and Mueser (1), in 1996. Dr. Furukawa fails to appreciate that we made explicit the critical questions that informed our review: What is the efficacy for the primary outcome measure? What is the efficacy for other outcomes? Is a particular kind of psychosocial intervention more efficacious for certain outcomes? What evidence exists for effectiveness and transferability? What data exist regarding cost-effectiveness?

Furthermore, we described in our Method section how 167 separate English-language references were identified with computerized literature searches and how, from these, 18 newer studies were selected. A meta-analytic approach to these heterogeneous 18 studies (three studies of family therapy, two of case management, four of social skills training, three of supported employment, five of cognitive behavior therapy, and one of individual therapy, which also had a family therapy arm) might have given some a sense of statistical comfort but would have been problematic. On the other hand, implementation of multiple meta-analyses of all the relevant published studies involving the many different psychosocial treatments for schizophrenia was clearly beyond the scope of our article.

Dr. Furukawa's concerns regarding our conclusions are misplaced. Our article reviewed all of the higher-quality studies published since 1996; however, our conclusions and clinical recommendations were based on an appraisal of all the studies published since 1966. Hence, it is logical that although the three recent studies of family therapy resulted in negative findings, because the broader literature unambiguously supported the efficacy of some forms of family therapy for relapse prevention, we recommended it for most patients residing with their families. We stand by our interpretation that a likely explanation for the negative findings in these studies was their low base rate of relapse (18% for the 1-year study group, 27% for the 2-year group, and only 29% for the 3-year group) and agree with Dr. Furukawa that the majority of studies performed over time do not have such low rates of relapse. Likewise, the large literature on social skills training (which contained only four newer studies) clearly demonstrated that schizophrenia patients can acquire a variety of skills and improve their social competence, as measured in the clinic or in a controlled setting. However, it is not known whether patients will incorporate learned skills and use them in the community, which is a limitation of this therapeutic strategy.

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Research on Women

TO THE EDITOR: I am writing to express my strong disagreement with the tone, nature, and assumptions of the one-sided editorial by Nada Stotland (1). According to studies by Bartlett (2, 3), of all National Institutes of Health (NIH) clinical trials on humans published in the United States between 1966 and 1990, there were 753 studies involving men and 854 involving women. According to Dickersin and Min (4), an analysis of all 293 clinical trials funded by NIH in 1979 revealed that 268 included both men and women, 12 were of men only, and 13 were of women only. Hayunga et al. (5) provided the following statistics for NIH single-sex studies in 1994: there were 219 studies of women and 95 studies of men. In 1997 the figures had reached 740 studies of women and 244 studies of men (6).

But looking now at the broader picture, it is certainly useful to study specific populations: young versus old, tall versus short, Mediterranean versus Anglo-Saxon, Jewish versus Christian, high IQ versus low IQ, active versus inactive, men versus women, and black versus white or Asian. The questions are, How useful is this? and How should we spend precious and diminishing research dollars? When observed in these terms (and while we are being practical, focused, and thoughtful), doing gender-based studies is generally unwarranted, with important exceptions. Far more vital concerns draw our attention, and that's as it should be—unless, of course, one is more interested in a political agenda and willing to sacrifice judgment and good sense trying to substantiate that particular world view.

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Dr. Stotland Replies

TO THE EDITOR: My editorial was based on data, not assumptions. It was data that led the U.S. Public Health Service Task Force on Women's Health to conclude that women's health care had been compromised by the lack of research into women's health. It was those data that convinced the NIH to adopt a policy mandating the inclusion of women in clinical trials, and it was data documenting the failure of researchers to implement that policy that drove the U.S. Congress to enact the policy into law. Fortunately, federal research dollars are not diminishing; there are exciting opportunities to develop new knowledge in the areas opened up by these developments.

In the past, single-sex research on women was nearly always related to the reproductive system, while research performed on men encompassed ailments affecting both genders in the rest of the human body. That research, and trials including both sexes but not analyzed by gender, has been the basis for the care of both men and women. However, women differ from men not only in anatomy and reproductive physiology but also in general disease etiology, symptom profiles, and response to treatment—not to mention crucial psychosocial variables. A world view blind to those differences deprives scientists of fascinating areas of study, physicians of essential knowledge, and women of appropriate care. For example, women's cardiac care has been adversely affected by failure to recognize that myocardial infarction appears differently in women and men, by the relative failure of physicians to take women's symptoms seriously, and by the production of cardiac devices so large that they ruptured women's blood vessels. These are life-and-death issues.

Human beings can be grouped according to a wide variety of parameters, of which gender is but one. Gender differences in the brain are fascinating; sex hormones influence brain development, and brain centers mediate sex differences in the rest of the body. The effects of estrogen on aging are a major focus of investigation. Brain structures such as the corpus callosum differ in size and shape between men and women. Women's language functions are less lateralized than men's, which affects the sequelae of cerebrovascular events. As we discover distinctions that have medical consequences, it becomes our responsibility to address those distinctions, be they distinctions of race, age, size, or factors not yet conceived of. That is why we have geriatrics and pediatrics. Inevitably, as has happened with age- and gender-based biology, our explorations of differences will yield crucial and fascinating scientific insight and improved clinical care for everyone. That is the agenda for medicine.

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Drugs on the Internet

TO THE EDITOR: John H. Halpern, M.D., and Harrison G. Pope, Jr., M.D. (1), drew attention to the immense quantity of information about hallucinogens on the Internet. I would like to add the following comments based on my recent review of many of the same Internet sites (2).

There are a number of hallucinogens not mentioned in the article by Drs. Halpern and Pope that are discussed at Internet drug information sites. These include the lysergic acid amide sources *Ipomoea violacea* and *Argyreia nervosa*, numerous additional botanical sources of dimethyltryptamine (DMT), sources of reversible monoamine oxidase inhibitors (not hallucinogenic per se but used in combination with dimethyltryptamine to make it effective when taken orally, as in ayahuasca), *Amanita muscaria,* nutmeg, ketamine, and dextromethorphan. Anticholinergic agents, which cause hallucinations as a feature of anticholinergic delirium, are also discussed, including a number of nightshade species, dimenhydrinate, and diphenhydramine.

In addition, a number of nonhallucinogenic drugs receive considerable coverage at Internet drug information sites. These include marijuana, 3,4-methylenedioxymethamphetamine (MDMA, or Ecstasy), γ-hydroxybutyric acid (GHB), kava-kava, stimulants (both naturally occurring and synthetic), and nitrous oxide. It is also interesting that certain other widely used drugs receive very little attention on the Internet: alcohol, opiates, sedative-hypnotics other than those mentioned, and inhalants other than nitrous oxide.

Much of the information at the major drug information sites is quite accurate. I reviewed information at three drug information libraries about drug effects, biological sources of psychoactive compounds, and synthesis and extraction procedures. No inaccuracies were found, although some of the synthesis and extraction procedures could not be verified.

I also reviewed the medical literature (MEDLINE, from January 1996 to April 1999) for references to the lesser-known substances discussed at Internet drug information sites. Most of the reports dealt with acute medical problems related to substance use, although a few dealt with long-term misuse. I found no reports of problems involving any of the lesser-known hallucinogens discussed by Drs. Halpern and Pope, although one article discussed the potential for interactions between ayahuasca and selective serotonin reuptake inhibitors. In contrast, there were seven reports dealing with use of GHB, five on dextromethorphan, five on various anticholinergic nightshade species, five regarding nutmeg, three on kava-kava, and one each regarding ketamine, dimenhydrinate, diphenhydramine, 2-CB (a synthetic serotonergic hallucinogen), and absinthe.

These reports shed some light on the extent of acute medical problems but reveal less about abuse and dependence and nothing about the extent of nonproblematic use of any of these substances. Furthermore, existing reports tell us little about the possible role of the Internet in promoting the use of novel substances or well-established substances such as methamphetamine, Ecstasy, and marijuana. Surveys, particularly in high-risk populations such as students, would be a useful next step in determining the prevalence of use, abuse, and dependence for the various novel drugs and to elucidate

the relationship between drug use and exposure to Internet drug information.

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Drs. Halpern and Pope Reply

TO THE EDITOR: We thank Dr. Bogenschutz for supporting our view that the Internet provides a novel window into assessing current and emerging patterns of illicit drug use. As mentioned in our article, no web-based search will yield the same results over time; hence, Dr. Bogenschutz's web search yielded interesting further findings since our survey was conducted in December of 1998. Many of the additional hallucinogens and nonhallucinogens that he mentions were noted by us as well but were edited from our final report for brevity.

The dearth of reports in the medical literature about problems with hallucinogens is perhaps unsurprising, given their long history of apparently safe ritual use in many traditional societies. For example, of the 982,856 drug-related emergency room visits reported in 1998, fewer than 5,000 involved LSD, compared to 172,000 related to cocaine (1). However, use of hallucinogens may continue in the United States and elsewhere in larger numbers than we might think. As one authority has commented, "Large numbers of people, mostly young, male and with high intelligence and creative ability are taking hallucinatory drugs without the medical profession being much aware of it. It is only when something goes wrong that the doctor is involved" (2).

We agree with Dr. Bogenschutz that much of the information posted at Internet drug sites is "quite accurate." Of greater concern is how inadequate our scientific knowledge of these compounds remains. The bulk of the medical literature on hallucinogens is out of date and compromised by multiple methodological limitations. The Internet reveals that there are literally hundreds of drugs with hallucinogenic properties being ingested by humans, most of which have never been medically evaluated for dose range, effect, risk, or abuse liability. Can American psychiatric research continue to remain idle in this area while this "hidden" and ever-expanding pharmacopoeia is disseminated only across public forums like the Internet?

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Adolescents With Schizophrenia

TO THE EDITOR: Barbara Karp, M.D., et al. (1) reported that "adolescents with schizophrenia had a high frequency of neurologic abnormalities. Neurologic signs decreased with age in the healthy comparison subjects but not in the subjects with schizophrenia" (p. 118). The research design of this study did not permit the authors to make these statements because "diagnostic status" was confounded with "level of intellectual functioning" and with "medication/clinical status," both of which could have significant effects on the dependent variable, neurological test performance.

In this study, 21 adolescents with schizophrenia were compared with 27 "healthy age- and sex-matched" (p. 118) normal comparison subjects. The schizophrenia group had a mean full-scale IQ of 77 (range=48–120), while the normal group had a mean full-scale IQ of 121 (range=97–141). Therefore, "diagnostic status" is confounded with "level of intellectual functioning." The neurological abnormalities found in the adolescents with schizophrenia may have reflected poor intellectual functioning, which may or may not have been independent of their diagnosis of early-onset schizophrenia. Furthermore, the schizophrenia subjects "were examined after at least 1 week with no medication," and the examiners were not blind to patient diagnosis "because of active psychotic symptoms in the patients" (p. 119). Consequently, there may have been medication withdrawal effects on neurological test performance, and active psychotic symptoms may have interfered with the subjects' ability to attend to and follow the examiner's instructions. The statement that examiners could not be blind to diagnostic status because of active psychotic symptoms in the adolescents with schizophrenia whose medication had been withdrawn underlines the problem of conducting a neurological assessment under these conditions.

Another problem with this study was the inclusion of four "healthy age- and sex-matched comparison subjects" aged 10 and 11 years, even though there were no 10- or 11-year-old adolescents with schizophrenia to whom they could be matched. According to Figure 1, these additional young normal comparison subjects contributed significantly to the negative correlation between "number of neurologic signs" and "age of subject." Without these subjects, the finding pertaining to abnormal "maturation," which is featured in the title, may have failed to reach the p=0.05 significance level.

A more accurate description of the results of this study might read as follows: "Actively psychotic adolescents with low IQs and early-onset schizophrenia who were withdrawn from medication had a higher frequency of neurologic abnormalities than normal adolescents with normal IQs."

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