Letters to the Editor

Enhancing the Tolerability of Tacrine With Propantheline

TO THE EDITOR: Tacrine, a reversible cholinesterase inhibitor active in both the central and peripheral nervous system, is indicated for the treatment of Alzheimer's disease. Because its peripheral cholinergic activity causes gastrointestinal side effects, including cramping, nausea, vomiting, and diarrhea, only a minority of patients treated with tacrine can tolerate the recommended daily dose of 40 mg q.i.d. We have been able to overcome these problems in four patients with the adjunctive use of propantheline, a peripherally acting anticholinergic medication (1).

Mr. A, 72 years old, had a 4-year history of failing memory, losing objects at home, and neglecting his hygiene and grooming. He had prominent executive dysfunction and impaired memory. A computerized tomography (CT) scan revealed mild brain atrophy, and a single photon emission CT (SPECT) scan showed bilateral temporoparietal, posterior frontal, and right cerebellar hypoperfusion consistent with his clinical diagnosis of probable Alzheimer's disease. He tolerated tacrine up to 120 mg/day without gastrointestinal upset. At 160 mg/day, however, he complained of substantial nausea, which resolved with the addition of propantheline, 7.5 mg, before each 40-mg tacrine dose.

Mr. B was 49 years old when diagnosed with possible Alzheimer's disease. He had progressive memory impairment unexplained by his medical workup, including brain magnetic resonance imaging (MRI). He had a positive response to tacrine, 20 mg q.i.d., without any side effects. A dose increase to 30 mg q.i.d. caused severe nausea and vomiting, necessitating a return to 20 mg q.i.d. Several months later, with the addition of propantheline, 7.5 mg 30 minutes beforehand, he tolerated tacrine, 30 mg q.i.d., without any discomfort.

Mr. C was 49 years old when referred for memory difficulties, which led to his forced retirement as a teacher. He was diagnosed with probable Alzheimer's disease following evidence of memory and executive dysfunctions and bilateral parieto-occipital hypoperfusion on a brain SPECT scan. At referral he was already receiving tacrine, 40 mg q.i.d., and paroxetine, 20 mg/day, but he complained of nausea, gas, and gastrointestinal upset, especially after taking tacrine on an empty stomach. He often skipped his last scheduled tacrine dose because of these side effects. Propantheline, 15 mg 30 minutes before each tacrine dose, controlled all gastrointestinal complaints.

Mr. D was 75 years old when diagnosed with probable Alzheimer's disease following 1 year of cognitive decline and executive dysfunction. His MRI revealed diffuse brain atrophy, and a SPECT scan showed bitemporal and biparietal hypoperfusion. He was treated concurrently with tacrine and propantheline, 15 mg 30 minutes before tacrine. Because of a robust response to tacrine, 20 mg q.i.d., he and his wife refused further dose escalation. They noted that when he omitted the propantheline, he experienced significant nausea and vomiting following each tacrine dose.

On the basis of our experience, we suggest using adjunctive propantheline in patients with untoward gastrointestinal cholinergic effects from tacrine or other cholinesterase inhibitors. Excess propantheline, however, can cause typical anticholinergic effects, including dry mouth, blurred vision, constipation, and difficulty urinating.

REFERENCE

1. Brown JG, Taylor P: Muscarinic receptor agonists and antagonists, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed. Edited by Hardman JG. New York, McGraw-Hill, 1996, pp 141–160

RAYMOND A. FABER, M.D.
San Antonio, Tex.
PAULO J. NEGRO, M.D.
Bethesda, Md.

Sildenafil Citrate for SSRI-Induced Sexual Side Effects

TO THE EDITOR: We present the case of a 42-year-old man with major depression who experienced remission with sertraline but suffered anorgasmia and erectile dysfunction reversed with sildenafil citrate.

Mr. A's first episode of major depression was at age 40, a time of personal stress and bereavement. He and his wife reported that he became anhedonic; slowed mentally; felt sad, hopeless, and fatigued; and experienced a decrease in appetite. He met DSM-IV criteria for major depression, and his score on the Inventory to Diagnose Depression (1) was 38 (a score of 0–10 is normal). A family member had responded to sertraline, so Mr. A was treated similarly, and after 5–6 weeks had a full remission on a dose of 150 mg/day. His scores on repeated administrations of the Inventory to Diagnose Depression ranged from 6 to 11.

Mr. A complained about anorgasmia, which began while he was taking 100 mg/day of sertraline, and erectile dysfunction, which began while he was taking 125–150 mg. Although he reported being "annoyed" at this side effect, he felt it was "tolerable." He then obtained sildenafil from his family doctor.

The patient reported that on four occasions, 50 mg of sildenafil allowed him to have his normal erection and ejaculation with no side effects to date. Without the sildenafil, while taking 150 mg/day of sertraline, he experienced a return of his sexual side effects.

Sildenafil is now best known as a novel, oral treatment for male erectile dysfunction that acts on a subclass of the phos-

phodiesterases, specifically, PDE5 (2). Anorgasmia is a common complaint of both men and women treated with selective serotonin reuptake inhibitors (SSRIs), and any new medication that might enhance compliance should be considered. Sildenafil should be tested systematically for treatment of SSRI-induced anorgasmia and erectile dysfunction.

REFERENCES

1. Zimmerman M, Coryell W: The Inventory to Diagnose Depression (IDD): a self-report scale to diagnose major depressive disorder. J Consult Clin Psychol 1987; 55:55–59
2. Boolell M, Allen MJ, Ballard SA: Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for treatment of penile erectile dysfunction. Int J Impot Res 1996; 8:47–52

JAMES L. SCHALLER, M.D., M.A.R.
West Chester, Pa.
DAVID BEHAR, M.D.
Philadelphia, Pa.

TO THE EDITOR: Sildenafil citrate is a newly approved drug for men with erectile dysfunctions that works through relaxation of the smooth muscle induced by nitric oxide/cyclic guanosine monophosphate (1). Patients receiving selective serotonin reuptake inhibitors (SSRIs) often experience the side effects of impaired desire, erectile dysfunction, and orgasm dysfunctions such as in delay and satisfaction, resulting in distress and SSRI discontinuation (2). I wish to report the cases of two men and one woman who responded to treatment with sildenafil.

Mr. A was a 56-year-old man, otherwise healthy, with a 10-year history of dysthymia who was taking sertraline, 50 mg/day. He had a pre-SSRI history of erectile dysfunction. Since beginning sertraline, he experienced severe orgasm delay and impotence. Sildenafil before masturbation was first prescribed to titrate the dose and foster confidence. One hour after taking sildenafil, 50 mg, Mr. A regained full erections during self-stimulation. Subsequently, following sildenafil administration, he was able to reach orgasm during vaginal intercourse for the first time in a decade. He continued to experience mild orgasm delay despite higher doses.

Mr. B was a 23-year-old man, otherwise healthy, with a 6-year history of bipolar II disorder; he required daily, continual treatment with fluoxetine hydrochloride, 20 mg; gabapentin, 100 mg; diazepam, 5 mg; and dextroamphetamine sulfate, 5 mg. He had a pretreatment history of mild erectile dysfunction. During treatment, he experienced severe impotence and orgasm delay. Sildenafil, 100 mg, provided satisfactory erections about half of the time and enabled penetration during intercourse with unprecedented success, despite continued mild orgasm delay.

Ms. C was a 54-year-old postmenopausal woman in otherwise good health who had been taking fluoxetine first for dysthymia and then for depression for 4 years as well as standard postmenopausal estrogen replacement therapy (medroxyprogesterone acetate 10 mg/day) for 6 years. Fluoxetine doses above 40 mg/day obliterated her ability to reach orgasm, and she required up to 80 mg/day. She reported her first orgasm in more than 18 months during clitoral stimulation after taking sildenafil, 50 mg. She continued to experience impaired orgasm satisfaction and delay, however, even with doses of 50–100 mg. Ms. C complained of flushing, lethargy, and headache for 24 hours after sildenafil administration.

In sum, sildenafil benefited two male patients taking SSRIs who had severe, refractory erectile dysfunctions and one postmenopausal female patient with secondary anorgasmia. Patients were screened for contraindications to sildenafil therapy, such as nitrate therapy, and were advised about sildenafil's side effects and risks (1, 3), including the possibility that lethargy and headache, which are associated with both sildenafil and SSRIs, may be worsened by taking both medications simultaneously. None of the patients experienced untoward effects such as cardiac events.

Disruptions of nitric oxide metabolism have been postulated to mediate SSRI-induced sexual disturbances such as erectile dysfunction (4), and sildenafil may correct the theoretical defects. In addition, some of the SSRI-induced side effects, such as decreased libido and orgasm delay, may be unrelated to nitric oxide metabolism, but sildenafil may enable patients to compensate for these sexual disturbances by improving erections and increasing vasocongestion. Further studies are indicated. Until such time, given the uncertain teratogenic potential, sildenafil should not be prescribed for premenopausal women.

REFERENCES

1. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA: Oral sildenafil in the treatment of erectile dysfunction. N Engl J Med 1998; 338:1397–1404; correction, 339:59
2. Seagraves RT: Treatment-emergent sexual dysfunction in affective disorder: a review and management strategies. J Clin Psychiatry Monograph 1993; 1:57–60
3. Morales A, Gingell C, Collins M, Wicker PA, Osterloh IH: Clinical safety of oral sildenafil citrate (Viagra) in the treatment of erectile dysfunction. Int J Impot Res 1998; 10:69–74
4. Sussman N, Ginsberg D: Rethinking side effects of the selective serotonin reuptake inhibitors: sexual dysfunction and weight gain. Psychiatr Annals 1998; 28:89–97

KENNETH PAUL ROSENBERG, M.D.
New York, N.Y.

Possible Hazard in Use of Priming Dose to Determine Lithium Dosage

TO THE EDITOR: The APA Practice Guideline for the Treatment of Patients With Bipolar Disorder (1) mentioned two methods to initiate lithium treatment and achieve therapeutic serum levels in patients with bipolar disorder. Lithium may be started in low divided doses and the dose titrated upward according to the response and side effects, or, after a single dose of 600 mg the 24-hour lithium serum level may be used as an indicator of required daily dose. The latter method, in which a nomogram is used to predict the appropriate daily dose (2), is sometimes referred to as "Cooper's method."

In our clinic, we started lithium treatment according to Cooper's method in 10 consecutive patients with bipolar disorder. In four of these patients, a 24-hour serum level of 0.08 mmol/liter was observed after administering the 600-mg priming dose. According to the nomogram, these patients should have received a dose of 2700 mg/day of lithium. To avoid toxic side effects, we decided to start with a lower dose than suggested by the nomogram. Eventually, doses of lithium between 1200 and 2000 mg/day proved to render adequate serum levels in these patients (0.5–0.8 mmol/liter).

This observation led to careful review of the reliability of the laboratory test procedures we used for the determination of serum lithium levels. The results of flame atomic emission spectroscopy (3), which is our routine procedure, and the dry chemistry method in a Vitros 950 analyzer (formerly known as Kodak 950) were both in agreement with the results of the atomic absorption reference method (4). Therefore, we concluded that the observed 0.08 mmol/liter after 24 hours was not due to incorrect measurement.

Another approach to the determination of the proper lithium dose is use of the Bayesian technique (5) to calculate patients' individual pharmacokinetic parameters. The results of these analyses in our patients showed that their individual serum values deviated less than one standard deviation from the expected population values.

On the basis of these findings, we conclude that the use of Cooper's method (2) may lead to potentially toxic lithium dose recommendations in a substantial proportion of patients. Especially when very low serum levels are being measured 24 hours after giving the 600-mg priming dose, Cooper's method is probably not a safe method to predict the appropriate daily dose of lithium in patients with bipolar disorder.

REFERENCES

1. American Psychiatric Association: Practice Guideline for the Treatment of Patients With Bipolar Disorder. Am J Psychiatry 1994; 151(Dec suppl)
2. Cooper TB, Bergner P-E, Simpson GM: The 24-hour serum lithium level as a prognosticator of dosage requirements. Am J Psychiatry 1973; 130:601–603
3. Pesce AJ, Kaplan LA: Methods in Clinical Chemistry. St Louis, CV Mosby, 1987
4. Pybus J, Bowers GN: Measurement of serum lithium by atomic absorption spectroscopy. Clin Chem 1970; 16:139–143
5. Taright N, Mentre F, Mallet A, Jouvent R: Nonparametric estimation of population characteristics of the kinetics of lithium from observational and experimental data: individualization of chronic dosing regimen using a new Bayesian approach. Ther Drug Monit 1994:16:258–269

JAN WILLEM PETERSE, M.D.
JOHAN M. HAVENAAR, M.D., PH.D.
HERMAN J.M. VAN RIJN, M.D., PH.D.
Utrecht, The Netherlands

Case Vignette in a Community-Based Study

TO THE EDITOR: We read with interest the article by Shelly F. Greenfield, M.D., M.P.H., et al. (1) regarding the effectiveness of the voluntary screening program for depression. It strikes us that part of the screening was conducted through telephone interview and that it was effective in bringing certain depressed individuals for treatment. Unfortunately, such a program cannot be conducted in a developing country such as Malaysia because the majority of the houses in the rural areas do not have telephones and because there are problems in communication, especially in the remote areas. In such situations, we need to modify the methodology in order to reach the target population. We want to share our experience in conducting a community-based study and treating those who refused psychiatric treatment.

We have been conducting a psychiatric morbidity study to assess the prevalence of major psychiatric disorders in one of the districts in the state of Kelantan, on the east coast of peninsular Malaysia. "Probable cases" were detected through key informants after field workers presented five vignettes portraying mental retardation, acute psychosis, chronic schizophrenia, mania, and depression. At the end of the interview, the informants were asked whether they had observed any person in the village matching the description in the vignettes.

If the informant's answer was convincing, he or she was asked to identify the person. The field workers then contacted each of these individuals ("probable cases") to determine the details of any illness and make appointments with the project psychiatrist for further psychiatric assessment. This part of the study was equivalent with the first stage of the usual two-stage case identification, when the screening instrument to measure symptoms reflecting general psychological distress is administered. Usual instruments, such as the General Health Questionnaire, are not suitable in our situation because a substantial proportion of the target population is illiterate.

In our study, the probable cases were assessed by a psychiatrist using the Structured Clinical Interview for DSM-III-R (SCID) (2) to determine the presence of specific psychiatric disorders. The subjects were diagnosed according to DSM-III-R. The preliminary results revealed that 92 subjects with psychiatric diagnoses had been identified through 34 informants. The majority of the subjects had the diagnosis of schizophrenia. Most of the subjects with psychiatric diagnoses had never received psychiatric treatment, but a small percentage of them had sought traditional treatment. The negative attitude toward psychiatric treatment was reflected by the finding that about one-third of the subjects determined to be probable cases had to be visited in their homes because they refused to come to a nearby clinic, in spite of the fact that we sent a few reminders. Most of the subjects with psychiatric disorders accepted our treatment after a home visit; however, some of them refused to be treated because they did not have confidence in modern Western medicine.

REFERENCES

1. Greenfield SF, Reizes JM, Magruder KM, Muenz LR, Kopans B, Jacobs DG: Effectiveness of community-based screening for depression. Am J Psychiatry 1997; 154:1391–1397
2. Spitzer RL, Williams JBW, Gibbon M, First MB: Structured Clinical Interview for DSM-III-R, Version 1.0 (SCID). Washington, DC, American Psychiatric Press, 1990

S.M. RAZALI, M.D.
A.M. HAMZAH, M.D., M.P.H.
Kelantan, Malaysia

British Experience With High-Dose Olanzapine for Treatment-Refractory Schizophrenia

TO THE EDITOR: We read with interest the letter by Brian B. Sheitman, M.D., and colleagues (1) reporting the use of olanzapine at doses above the recommended upper limit in patients with refractory schizophrenia. Although the maximum recommended dose for olanzapine is 20 mg/day, Reus (2) cited unpublished trials using a higher dose.

During the first 8 months of use of olanzapine at St. Andrew's Hospital, Northampton, U.K., 23 (62%) of 37 patients given olanzapine fulfilled the criteria for treatment-resistant schizophrenia. Eight patients with resistant schizophrenia were difficult to treat within the recommended olanzapine dose range. For these patients, the prescribing con-

sultants felt justified in using a higher maximum dose (60 mg/day), which did not produce any increase in the incidence or severity of side effects. Olanzapine had an acceptable degree of overall tolerability, and there were no cases of treatment-emergent extrapyramidal side effects.

Eleven (48%) of 23 patients with resistant schizophrenia were continued on a regimen of olanzapine because of an appreciable degree of clinical improvement. A greater proportion of the patients who had never taken clozapine demonstrated an improvement in overall symptoms than did those who had previously been treated unsuccessfully with clozapine. There were seven clozapine-naive patients. Six of these patients were continued on a regimen of olanzapine at a mean dose of 33.3 mg/day (range=20–60) and a mean duration of treatment of 4.8 months (range=3–8) by the end of June 1997. Five clozapine-naïve patients improved. In the patients who were started on olanzapine following an unsuccessful trial of clozapine (16 patients), seven patients continued on olanzapine treatment with a mean dose of 31.4 mg/day (range=10–60) and a mean duration of treatment of 7.4 months (range=5–8) by June 1997. Six of these patients exhibited moderate to marked improvement comparable to the improvement of the five clozapine-naïve patients. The remaining nine patients were withdrawn from olanzapine after a mean duration of treatment of 2.2 months (range=0.3–5.7) and a mean dose of 18.9 mg/day (range=10–30) at the time of stopping. Patient refusal to take olanzapine or any other oral antipsychotic medication was a common cause for withdrawal from treatment. This highlights the importance of developing an atypical antipsychotic preparation in depot form to ensure compliance.

REFERENCES

1. Sheitman BB, Lindgren JC, Early J, Sved M: High-dose olanzapine for treatment-refractory schizophrenia (letter). Am J Psychiatry 1997; 154:1626
2. Reus VI: Olanzapine: a novel atypical neuroleptic agent. Lancet 1997; 349:1264–1265

CHRISTOPHER Q. MOUNTJOY, M.B., B.S., F.R.C.PSYCH.
ALEXANDER M. BALDACCHINO, M.D., M.R.C.PSYCH., M.PHIL.
JEAN H. STUBBS, M.SC., M.R.PHARM.S.
Northampton, U.K.

Fluoxetine Versus Phenelzine in Obsessive-Compulsive Disorder

TO THE EDITOR: The article by Michael A. Jenike, M.D., and colleagues (1) reporting the results of a placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder (OCD) contains some serious flaws.

First, although the maximum recommended dose of fluoxetine, 80 mg/day, was administered, the maximum recommended dose of phenelzine, 90 mg/day, was not. Instead, only a dose of 60 mg/day was given. This was probably based on the ease of administering one to four 20-mg doses of fluoxetine and one to four 15-mg doses of phenelzine. In any event, comparing the maximum dose of one drug to a lesser dose of another drug would invalidate any conclusions regarding comparative efficacy. The authors' statement, "Phenelzine was no better than placebo" would be more accurate if it began with the phrase, "Low-dose phenelzine." In our experience and in the literature (2), when phenelzine is used for OCD, doses as high as 105 mg/day may be needed. In addition, measuring the monoamine oxidase (MAO) inhibition level is questionable here because, unlike depression, the level of MAO inhibition required for OCD responsiveness has not been established.

Another problem with the article is that the use of the exclusion criteria was confusing. Initially, the authors stated, "Patients with a history of other significant psychiatric disorders were excluded from the study." Later they say that "none of seven responders in the phenelzine group had a lifetime history of panic or agoraphobia, compared with three of seven responders in the fluoxetine group." Were these conditions excluded or were they regarded as insignificant? It is also difficult to understand why patients with comorbid anxiety disorders would be excluded if the study was attempting to see if OCD patients with high levels of anxiety were preferentially responsive to MAO inhibitors (MAOIs).

As a result of these flaws, the article contributes little. The statement that phenelzine was no better than placebo is misleading and may do harm by discouraging its use as a beneficial second-line agent, especially when OCD and generalized social phobia coexist. MAOIs may be particularly effective in these cases (2).

Further research, including careful head-to-head drug trials, is needed.

REFERENCES

1. Jenike MA, Baer L, Minichiello WE, Rauch SL, Buttolph ML: Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. Am J Psychiatry 1997; 154: 1261–1264
2. Carrasco JL, Hollander E, Schneier FR, Liebowitz MR: Treatment outcome of obsessive compulsive disorder with comorbid social phobia. J Clin Psychiatry 1992; 53:387–391

DANIEL H. GOLWYN, M.D.
CAROL P. SEVLIE, M.S.N., A.R.N.P., C.N.S.
Orlando, Fla.

Dr. Jenike and Colleagues Reply

TO THE EDITOR: Dr. Golwyn and Ms. Sevlie raise questions about our study, a blind comparison of fluoxetine, phenelzine, and placebo in patients with OCD.

First, they state that although we used the maximum recommended dose of fluoxetine, we failed to use the maximum recommended dose of phenelzine, thus biasing our results in favor of fluoxetine. Although many years have passed since this study was conceived and started, the authors' assertion that the maximum dose of phenelzine for OCD is known is unfortunately not accurate. They cite no systematic study demonstrating that 90 mg of phenelzine is better than 60 mg for OCD; to our knowledge, no such study exists. In addition, we often use doses higher than 80 mg for fluoxetine. In a study such as ours, the prudent investigator has to make certain decisions about dose and length of trial without the availability of perfect information.

Their complaints of our measuring MAO inhibition also seem unfounded. This is simply additional evidence that there was significant inhibition according to standards established in studies of depressed patients. Are they arguing that we should not have measured MAO inhibition? How could we use standards for OCD that have not been determined? We would certainly welcome any data the authors may be aware of regarding MAO inhibition in OCD patients that respond to treatment.

The second point made by Dr. Golwyn and Ms. Sevlie about confusing exclusion criteria is valid. Since there had

been a suggestion from the literature that patients with high anxiety or panic disorder or both were particularly responsive to MAOIs (1–3), we hypothesized that there would be a significant correlation between higher baseline anxiety scores and OCD improvement in patients treated with phenelzine; we also hypothesized that this correlation would be stronger in patients treated with phenelzine than in those treated with fluoxetine. Therefore, we excluded patients with psychosis or primary affective disorders but included patients with anxiety disorders.

The conclusion that our article "contributes little" seems harsh. As with any controlled trial, the study simply reports what happened with particular drugs at specific doses. Reasonable clinicians must base treatment decisions on such incomplete data on a daily basis. We do not think that our study would "do harm by discouraging" phenelzine's "use as a beneficial second-line agent." However, the empirical data support the use of selective serotonin reuptake inhibitors before using MAOIs. In fact, we agree with the authors that MAOIs are occasionally useful drugs in patients with OCD (1–4). Perhaps we failed to clarify this point sufficiently, although we did attempt to speculate on which OCD patients may benefit from phenelzine. Finally, who can argue with the authors' closing statement, "Further research, including careful head-to-head drug trials, is needed."

REFERENCES

1. Jenike MA: Rapid response of severe obsessive-compulsive disorder to tranylcypromine. Am J Psychiatry 1981; 138: 1249–1250
2. Jenike MA, Surman OS, Cassem NH, Zusky P, Anderson WH: Monoamine oxidase inhibitors in obsessive-compulsive disorder. J Clin Psychiatry 1983; 44:131–132
3. Jenike MA: MAOIs for obsessive-compulsive disorder (letter). Br J Psychiatry 1982; 140:549
4. Jenike MA, Rauch SL: Managing the patient with treatment resistant obsessive compulsive disorder: current strategies. J Clin Psychiatry 1994; 55(March suppl):11–17

MICHAEL A. JENIKE, M.D.
LEE BAER, PH.D.
WILLIAM E. MINICHIELLO, ED.D.
SCOTT L. RAUCH, M.D.
M. LYNN BUTTOLPH, M.D., PH.D.
Boston, Mass.

Treatment-Refractory Catatonia, ECT, and Parenteral Lorazepam

TO THE EDITOR: I read with interest the Clinical Case Conference by John Boronow, M.D., et al. (1). In the case presented, ECT clearly appeared to be the next reasonable treatment option; however, the patient refused to have ECT administered. The authors noted that a judicial review process exists for involuntary medications, which was used in the case discussed. However, the treatment team's only alternative for involuntary ECT was to ask the family to obtain legal guardianship in order to obtain consent for ECT from a judge. The family refused the request.

In Minnesota, a guardian may not consent to ECT, even under judicial review, for a nonconsenting patient. I believe this is for the best, because, as Dr. Boronow et al. pointed out, it puts the family or guardian in a situation that could have undesired consequences. The family or guardian's relationship with the patient (or with other family members who do not agree with the procedure) could be strained. Instead, in Minnesota, ECT can be petitioned directly to a court if the patient is under a civil commitment. (The case presented certainly could have been considered for a civil commitment on the basis of Minnesota's Commitment and Treatment Act.) In that situation, both parties (the physician or hospital and the patient) may have representation and present their petition(s) to a judge. Any family members could also be part of the testimony if they wish. It appears that this alternative was not available, which was very unfortunate. After reading this case, I wondered what the outcome would have been had this patient lived where I practice.

REFERENCE

1. Boronow J, Stoline A, Sharfstein SS: Refusal of ECT by a patient with recurrent depression, psychosis, and catatonia (case conf). Am J Psychiatry 1997; 154:1285–1291

SCOTT C. ARMSTRONG, M.D.
Willmar, Minn.

TO THE EDITOR: Boronow et al. describe the case of Z, a 36-year-old man who suffered an unremitting course of psychotic depression due to the complication of catatonia. The patient's catatonia, along with the family's reluctance, prevented Z from receiving what the authors felt was the treatment of choice, ECT. Z received courses of oral lorazepam and diazepam and, possibly, intramuscular diazepam, but the report does not mention the use of parenteral lorazepam.

Acute response of catatonia to lorazepam appears to be independent of manner of administration (1–3). Rosebush et al. (1) contended that response to lorazepam in their patients, four of whom were already receiving standing oral doses of benzodiazepines, was due to increased blood levels. Parenteral lorazepam, which produces rapid increases in plasma levels more reliably than other benzodiazepines, might be effective in nonresponders to oral benzodiazepines. We report a series of elderly patients with psychotic depression and catatonia (six men and one woman with a mean age of 73), treated with intramuscular lorazepam alone. All were referred to our geriatric psychiatry inpatient service for involuntary ECT. All had failed to respond to antidepressants with antipsychotics. Six had mutism, three negativism, three withdrawal, and one refusal to eat. A single dose of intramuscular lorazepam (2 mg in six patients, 0.5 mg in one) was given. Relief of catatonia, permitting meaningful conversation, occurred in six of seven patients within 2 hours. Responders were maintained on a regimen of oral lorazepam. Four went on to respond to ECT given on a voluntary basis; one responded to a course of oral risperidone, which his catatonia had previously prevented him from complying with; and one enjoyed a full remission of depression without further intervention. Response was dramatic in our responders.

Z received a course of intramuscular imipramine involuntarily; therefore, intramuscular lorazepam could have been justified on the basis of safety. We acknowledge that Z's length of illness could have decreased the likelihood of response to additional intramuscular lorazepam, but we feel that this intervention may have offered Z another opportunity to actively participate in the ECT consent process. We believe that any patient whose catatonia interferes with assessment or treatment of an underlying serious psychiatric illness, and who refuses or does not respond to oral benzodiazepines, should receive a trial of intravenous lorazepam (3), if safety permits. We refer to this as the "lorazepam challenge test," a term coined by our late mentor, T. George Bidder, M.D.

REFERENCES

1. Rosebush P, Hildebrand A, Furlong B, Mazurek M: Catatonic syndrome in a general inpatient population: frequency, clinical presentation, and response to lorazepam. J Clin Psychiatry 1990; 51:357–362
2. Ungvari GS, Leung CM, Wong MK, Lau J: Benzodiazepines in the treatment of catatonic syndrome. Acta Psychiatr Scand 1994; 89:285–288
3. Bush G, Fink M, Petrides G, Dowling F, Francis A: Catatonia, II: treatment with lorazepam and electroconvulsive therapy. Acta Psychiatr Scand 1996; 93:137–143

RALPH J. KOEK, M.D.
J. RANDY MERVIS, M.D.
Sepulveda, Calif.

Dr. Boronow and Colleagues Reply

TO THE EDITOR: We appreciate the thoughtful comments of Drs. Armstrong, Koek, and Mervis. The Minnesota law that allows direct petitioning of the court for permission to give ECT may well have considerable merit, both as an avenue for expeditious relief of patient suffering and as a check on unacceptable demands being placed on the family.

As it turns out, we have an update to offer the readers on this interesting case. The patient was in fact rehospitalized at our hospital after this article was sent out, and this time a different psychiatrist was able to persuade the guardian, the patient's brother, to go forward with ECT. The patient presented this time with frank catatonic stupor. He received a total of 24 bilateral ECT treatments at the rate of three per week. His response was dramatic, with marked resolution of stupor. Nonetheless, there remained significant residual symptoms (psychomotor slowing, poverty of speech and content, passive oppositionalism). We believe that he received sufficient ECT because he actually became mildly delirious toward the end of the series, suggesting the maximum tolerable amount of ECT had been delivered. The delirium passed in a matter of days, and the patient went back to the residual state described above. At no time did he ever show a glimpse of mania or catatonic excitement. As to the issue of guardianship, it was our experience that the guardian's consenting was due to the unique interaction of the psychiatrist's and guardian's personalities, which were both very strong and shared several important cultural beliefs. It was fortunate that the brother encountered this particular psychiatrist, and it is unlikely that a different psychiatrist would have had the same success in persuading him—another reason for a more predictable judicial process.

As to Drs. Koek and Mervis's suggestion about intramuscular lorazepam, intramuscular diazepam, 10 mg, was given daily for the first 10 days of the second admission. There was no appreciable difference between response to the intramuscular and oral manner of administration in this patient.

Intramuscular diazepam was chosen because we wanted to minimize the number of injections the patient would receive and because we were concerned that intramuscular lorazepam would necessitate multiple daily injections due to its shorter half-life. Unlike chlordiazepoxide, there is good evidence that intramuscular diazepam is adequately absorbed in young men when given in a highly vascular muscle, which it was (1). The possible delay in peak effect was of no consequence because we were not looking for acute sedation but, rather, for consistent delivery over a period of days.

We know of no pharmacokinetic reason that would lead us to conceptualize the intramuscular versus the oral manner of administration as being in any way fundamentally different in terms of mode of action or efficacy, and we have seen several other patients with catatonic schizophrenia show disappointing responses to both manners of administration of either diazepam or lorazepam. Nevertheless, we concur that, acutely, parenteral routes may lead to a more rapid and pronounced peak absorption spike with resulting initial disinhibition, which can then be mobilized in the service of recovery, particularly if there is an "expectation set" for improvement from the staff and milieu, much as what happens in an Amytal interview. We certainly support its use in all such patients.

REFERENCE

1. Divoll M, Greenblatt DJ, Ochs HR: Absolute bioavailability of oral and intramuscular diazepam: effects of age and sex. Anesth Analg 1983; 62:1–8

JOHN J. BORONOW, M.D.
ANNE M. STOLINE, M.D.
STEVEN S. SHARFSTEIN, M.D.
Baltimore, Md.

Reprints of letters to the Editor are not available.

Corrections

In the article "Outcome Assessment and Clinical Improvement in Panic Disorder: Evidence From a Randomized Controlled Trial of Fluoxetine and Placebo" (November 1998, pp. 1570–1577) by David Michelson, M.D., et al., the sentence on the 20th line from the top of page 1576 should begin "The greater relapse among patients receiving 40 mg/day of paroxetine could reflect the presence...."

In the letter "Treatment of Borderline Personality Disorder" (November 1998, pp. 1645–1646), the correct location for authors Edward R. Shapiro, M.D., and Eric M. Plakun, M.D., is the Erikson Institute of the Austen Riggs Center in Stockbridge, Mass.