Letters to the Editor

Interaction of Fluoxetine and Valproic Acid

TO THE EDITOR: The combination of fluoxetine and valproic acid is frequently used for psychiatric patients (i.e., those with bipolar depression). However, there is a growing recognition that the inhibitory effect of fluoxetine on cytochrome P450 may lead to serious adverse reactions (1). We report a drug interaction between fluoxetine and valproic acid.

Ms. A, a 26-year-old obese woman, was referred because of the weekly occurrence of generalized seizures and pseudoseizures. Treatment with valproic acid was initiated, and the dose was titrated up to 2000 mg/day. The patient's valproate serum levels were routinely monitored, and the level (78 mg/liter) was always within the therapeutic range (50–120 mg/liter). She did not receive other drugs. One year later Ms. A developed major depression with binge eating episodes. She was started on fluoxetine, 20 mg/day, and after a week the dose was increased to 40 mg/day. Partial control of symptoms was obtained within 1 month after initiation of fluoxetine, but her valproate serum level (126 mg/liter) had risen above the therapeutic range and remained essentially unchanged (131 mg/liter) 20 days later. The patient was informed about the pharmacological interaction, and she agreed to the withdrawal of fluoxetine. Subsequent serum level monitoring showed a gradual reduction of valproic acid levels (week 2: 105 mg/liter; week 3: 87 mg/liter). The patient continued to take the same dose of valproic acid, achieving good seizure control.

The addition of fluoxetine to an ongoing treatment with valproic acid produced an increase in the steady-state concentrations of valproic acid. Two reports of this interaction (2, 3) have been published in the past few years, but its mechanism remains unknown. Fluoxetine has the potential risk of causing pharmacokinetic interactions with drugs metabolized by cytochrome P450 2D6 and P450 3A4 (1). However, valproic acid is mainly converted to glucuronide by hepatic enzymes, whereas the cytochrome P450-catalyzed formation of the hepatotoxic metabolite accounts for less than 10% of the dose (4). Thus, drugs that affect only cytochrome P450 enzymes are not expected to alter valproic acid clearance appreciably. The most plausible explanation for the raised valproic acid blood levels caused by fluoxetine is impaired glucuronide formation in the liver. While co-ordinate induction of glucuronyl transferases and cytochrome P450 enzymes has been demonstrated (5), we suggest that fluoxetine might inhibit both routes of metabolism. A displacement of valproic acid from plasma protein binding sites is unlikely, as fluoxetine has not been previously found to participate in this type of interaction.

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Ethics in Forensic Psychiatry

TO THE EDITOR: We wish to commend Paul S. Appelbaum, M.D., for his scholarly editorial (1) on the incompatibility of clinical and forensic functions and for his endorsement of the conclusion of Strasburger et al. (2) that the problems which surround a therapist's assumption of the dual role of treater and (forensic) evaluator argue for its avoidance whenever possible.

We take strong issue, however, with Dr. Appelbaum's implying that forensic psychiatrists are necessarily exempt from the canons of ethics embodied in the American Psychiatric Association's *Principles of Medical Ethics, With Annotations Especially Applicable to Psychiatry* (3). Citing his presidential address before the American Academy of Psychiatry and the Law (4) he writes, "Forensic psychiatrists, however, work in an entirely different ethical framework, one built around the legitimate needs of the justice system."

Dr. Appelbaum elsewhere reminds us that forensic psychiatrists who conduct evaluations for legal purposes "do not enter into a physician-patient relationship" and correctly notes that "were forensic psychiatrists to be charged with pursuing subjects' best interests and avoiding harm—like their clinical colleagues—their evaluations would be worthless in the courts" (5). Obviously, on the basis of their training, psychiatrists have more to offer society than a physician-patient relationship. Nonetheless, Dr. Appelbaum overlooks the fact that the sole reason forensic psychiatrists are invited to testify in court is that they are psychiatrists, not administrators of or agents for justice.

Dr. Appelbaum fails to give a necessary warning that there are limits to the overriding goal of the forensic psychiatrist's professional activity to advance the interests of justice. One such limit, we insist, is the mandate of our ethical code that "a psychiatrist should not be a participant in a legally authorized execution" (3, section 1, paragraph 4). It is our conten-

tion that evaluating death row inmates for competency to be executed, given the fact that psychiatric testimony in this regard may prove to be the decisive factor in effectuating the prisoner's death, violates this ethical canon.

Not only forensic psychiatrists, but all psychiatrists, must remain constantly alert to the danger of being drawn into unethical conduct in the service of an elusive and not infrequently unjust "justice." Have we forgotten our condemnation of the Soviet forensic psychiatrists who, in their zeal to advance the interests of "justice," facilitated the unjustified hospitalization of political dissidents?

In articles recently published in the *New York Law School Law Review* (6) and *The Wayne Law Review* (7) we discuss at great length our differences with Dr. Appelbaum's position on what constitutes ethical practice in certain areas of forensic psychiatry.

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Dr. Appelbaum Replies

TO THE EDITOR: Dr. Halpern and colleagues have no problem with the conclusions of my editorial regarding the importance of separating forensic and clinical functions. They wish to argue a broader point, relating to the foundations of ethics in forensic psychiatry. In doing so, however, I am afraid that they both distort my position and misstate the current status of medical ethics as they apply to capital punishment.

To synopsize an argument that I have developed elsewhere (1), it is clear historically and analytically that the basic principles of medical ethics are derived from the physician-patient relationship. In that context, unqualified devotion to the interests of patients—encompassing beneficence and nonmaleficence—is the norm. When physicians venture outside the bounds of that relationship, however, different rules often apply. Clinical researchers, for example, may place the advancement of patients' interests second to the production of generalizable knowledge; use of placebos is an instance of this. With proper informed consent, as part of a scientifically valid study, and with efforts made to minimize risks to subjects, this is an acceptable—even commendable—deviation from the norms of the physician-patient relationship. Indeed, to mark the difference, we are careful to call the persons involved in this different kind of relationship "subjects" rather than "patients."

So, too, for physicians who are performing evaluations for the courts. In the words of the noted medical philosopher Edmund Pellegrino, "The subject-physician relationship [i.e., in the forensic evaluation] does not carry the implication or promise of primacy for the patient's welfare that [is] intrinsic to a true medical relationship" (2). Were it not the case that the evaluation might, if the facts warranted, result in harm to the subject, there would be no point to it at all. Thus, here as well, the ethical ground shifts under the physician, who for the sake of promoting other socially useful objectives (in this case, advancing justice), is no longer focused on benefiting a particular person. That is not to say that no ethical principles exist to guide the work of a physician performing forensic assessments. I have pointed to truth telling and respect for persons as the ethical underpinnings of forensic work (1); subsequent commentators may invoke additional principles.

So, in contrast to the assertions of Dr. Halpern and his colleagues, I do not argue for the exemption of psychiatrists who perform forensic functions from the APA Annotations. However, with but a few exceptions, those Annotations have had little to say about work in the forensic realm. The *Ethical Guidelines for the Practice of Forensic Psychiatry* of the American Academy of Psychiatry and the Law (3) are of much greater relevance. Were APA interested in extending the scope of its Annotations to encompass a broader range of forensic issues, the AAPL guidelines would offer a useful starting point.

Now, to what I suspect is the actual motivation for this letter. Dr. Halpern and colleagues—opponents of the death penalty—have been vociferous advocates of the position that psychiatrists should neither evaluate the competence of prisoners to be executed nor treat those found incompetent. Although I am in agreement with them on the latter, I differ on the former, because I believe that their position reflects a fundamental misconception of the psychiatrist's role (4). As in other forensic settings, psychiatrists are providing information regarding subjects' mental state, with judicial decision makers passing judgment on the implications of those data for the issue at hand. Indeed, one might expect opponents of the death penalty to favor psychiatric involvement, since one of the consequences of psychiatric evaluation may be the postponement, perhaps indefinite, of the sentence of death. Significantly, in contrast to the suggestion in the letter of Halpern et al., both the Ethics Committee of APA (5) and the Council on Ethical and Judicial Affairs of the American Medical Association (6) have ruled that participation in these evaluations is not unethical and does not render the physician a participant in the execution.

These are complex issues, worthy of greater attention than can be afforded them in brief correspondence. I look forward to continuing these discussions in other venues.

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Utilization Management Criteria for Psychiatry

TO THE EDITOR: Ronald L. Goldman, Ph.D., M.P.H., and colleagues (1) reported on the sensitivity and specificity of four psychiatric utilization management criteria sets by comparing them to the consensus of judgments of a panel of expert psychiatrists who reviewed the same cases. Because of differences in the sensitivity and specificity of the instruments when compared to the panel's judgments, the authors concluded that "despite the difficulty of drawing a conclusion from a single study, our findings raise major concerns about the validity of the InterQual ISD [Intensity, Severity, and Discharge] psychiatry criteria. Continued use of these criteria appears questionable until they are modified and evidence of the validity of the revised criteria is presented."

It is true that one goal of utilization management criteria is to mirror current medical utilization practices. This study, however, may mislead some readers into thinking that this goal is the only (or even the most important) goal of these criteria sets. The most difficult task of criteria designers is to strike a balance between current utilization practice and a more efficient utilization practice. By defining validity as equivalent to matching current practice, they will discourage future developers from "pushing the frontier" to challenge practitioners toward a more efficient use of resources.

Goldman et al. noted that "increased stringency in the 1993 InterQual ISD instrument probably led to its decreased sensitivity for continued-stay judgments as compared to the 1992 InterQual ISD Criteria." As they noted, the increased stringency came about because the 1993 InterQual criteria set was the only one to require frequent nursing monitoring, daily psychiatrist contact, and treatments requiring an inpatient setting. Although stringent, these are not unreasonable requirements for continued stay. The purpose of stringent criteria is to create a system for early warning that a patient may be ready for a lower level of care.

The fear expressed in the article that "use of the 1993 InterQual ISD criteria may lead to acutely ill patients having their hospitalizations inappropriately abbreviated" is very unlikely to occur if the system is used as it is designed to operate. Utilization criteria are not designed to unequivocally state that a given patient should be discharged from the hospital, as there are too many factors that need to be taken into account. Instead, they are designed to bring the patient to the attention of the utilization review staff so that a dialogue with the attending physician is started, to determine whether a lower level of care for this patient is appropriate. If there is continued disagreement, the matter should be referred to the physician adviser to resolve.

While I believe that the Goldman et al. article is valuable for fostering new techniques for building physician consensus in review of medical records, its analysis of validity misses the mark. The InterQual criteria are not designed, nor should they be, to validate consensus practice.

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Dr. Goldman and Colleagues Reply

TO THE EDITOR: Dr. Steen questions our use of expert physician panels for testing the validity of utilization management criteria by pointing out that the InterQual criteria were developed to challenge practitioners toward more efficient resource use than is currently practiced. We have several major disagreements with Dr. Steen's letter.

First, we disagree with Dr. Steen's statement that our study defined validity as the matching of current practice. Current practice in our study was represented by the actual care provided according to the medical records studied. We did not compare the judgments of the criteria sets to a standard based on this care; instead, we compared the criteria to the consensus judgments of a panel of psychiatrists, selected by their peers as having special expertise in making judgments regarding the need for acute care. The panelists were instructed to ignore the constraints of actual practice by assuming that all treatment options existed at each Veterans Affairs facility studied and that private-sector psychiatric practice applied to the VA. The panel's consensus judgments were more stringent than the actual practice for 45% of the admissions and continued-stay days we studied; i.e., the panel decided that the patient should be treated on an ambulatory basis rather than as an inpatient. Furthermore, the panel's judgments were frequently more stringent than the assessments based on the InterQual criteria. The criteria indicated that inpatient care was needed while the panel judged that ambulatory care was appropriate for 36% of the discrepancies between the 1993 InterQual criteria and the panel and for 43% of the discrepancies between the 1992 InterQual criteria and the panel.

We also disagree with Dr. Steen's suggestion that to "push the frontier," developers should strive for utilization criteria that are more stringent than expert clinicians' assessments based on the available scientific evidence. His view of criteria development (and, implicitly, of validity testing) is in conflict with the great bulk of the literature on the development of clinical guidelines (e.g., 1–3) and assessment criteria (e.g., 4, 5) and with all prior studies of the validity of utilization criteria of which we are aware (e.g., 6–8). This literature emphasizes expert clinician assessment of scientific evidence in the development and testing of criteria and guidelines. It is our belief that Dr. Steen's more subjective approach to criteria development places too much emphasis on cost reduction and too little on expert clinical judgment and scientific evidence relating to the needs of patients for appropriate care.

Finally, Dr. Steen indicates that the InterQual criteria, even if invalid, will do little harm because they are designed to flag cases for discussion with practitioners and review by physician advisers. However, it is clear from accounts of the utilization management process that the criteria significantly influence these processes (9, 10). Even if the criteria were used only as

warning signals, it clearly would be more conducive to appropriate patient care if they were valid warning signals.

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Reprints of letters to the Editor are not available.

Correction

The title page for the article "Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections: Clinical Description of the First 50 Cases" by Susan E. Swedo, M.D., et al. (February 1998, pp. 264–271) has two errors. The authors should have been listed in the following order: Swedo, Leonard, Garvey, Mittleman, Allen, Perlmutter, Lougee, Dow, Zamkoff, and Dubbert. The correct e-mail address for Dr. Swedo is swedos@irp.nimh.nih.gov.