Suicide Assessment and Terminology

Sir: Elliott et al.[1] (December 1996 issue) presented some extremely interesting and helpful findings. However, I must quibble on two points.

First, the authors report collecting a set of variables including the "presence of an ambivalent emotional reactor [sic] to the suicide attempt," which they assessed by using two closed questions ("Are you glad you survived?" and "Do you wish you would have [sic] died?"). If there is one thing I have learned about interviewing through the decades, it is the value—nay, indispensability—of using open questions, especially when ambivalence is an issue. This technique can very well be literally a matter of life and death when evaluating immediate and future suicide risk in a patient who has just attempted suicide. I ask, "How was it for you when you woke up and found yourself still alive?" and "How do you feel right now about what happened?"

Second, the authors carefully use the term "completed suicide" throughout most of the paper, but lapse (apparently) into writing "successful suicide" in a couple of places. I had thought that the latter wording had long since become a strict "no-no" in our literature!

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Mary N. Smith, M.D.
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Risperidone and Cytochrome P450 3A

Sir: We read with great interest the recent article by Ereshefsky[1] on pharmacokinetics and drug interactions of the new antipsychotics. This work is timely and provides invaluable information for clinicians regarding drug interactions with atypical antipsychotics. In his discussion of cytochrome P450 3A (CYP3A) isoenzyme induction by carbamazepine, Ereshefsky relates that metabolism of certain typical and atypical antipsychotics usually increases when carbamazepine is coadministered. He furthermore relates, in contrast, that risperidone metabolism is unlikely to be affected by carbamazepine coadministration. This stands to reason since risperidone is known to be metabolized by the CYP2D6 isoenzyme and is thought not to be metabolized by the CYP3A. However, we have identified a case example in which carbamazepine induced a greater than twofold decrease in plasma concentration of risperidone in an extensive (normal) metabolizer.

Case report. Mr. A, a hospitalized 22-year-old white nonsmoker with a DSM-III-R diagnosis of chronic schizophrenia, was taking risperidone 4 mg/day and carbamazepine 600 mg/day. An initial plasma concentration of 9-hydroxyrisperidone (9-OH-risperidone) at steady state (with a plasma carbamazepine concentration of 7.9 μg/mL) was less than half the expected 10 μg/L. His risperidone dose was doubled to 8 mg/day. Two weeks later (with a carbamazepine concentration of 7.8 μg/mL), plasma 9-OH-risperidone increased correspondingly to 19 μg/L. Finally, Mr. A's carbamazepine dose was progressively decreased and discontinued. Ten days later, his plasma concentration of 9-OH-risperidone increased more than twofold to 49 μg/L. Mr. A was taking no other cytochrome P450–altering medications and underwent no changes to his medical regimen other than those already noted. Mr. A's CYP2D6 genotype corresponded to an extensive metabolizer (two wild-type alleles).[2]

As Ereshefsky pointed out, the half-life of risperidone in an extensive metabolizer is 3 hours. The equally efficacious metabolite 9-OH-risperidone with a longer half-life of 22 hours is therefore pharmacologically more important in extensive metabolizers. Our serial risperidone samples for the above study were drawn in the morning more than four half-lives after risperidone ingestion. Not unexpectedly, the serial serum concentrations of the parent risperidone compound were all below the 5-μg/L quantifiable threshold of our clinical laboratory.

This case illustrates that carbamazepine can significantly decrease risperidone levels greater than twofold. The role of carbamazepine as an inducer of the CYP3A isoenzyme suggests that CYP3A participates in the metabolism of risperidone and indicates a potential for other potent CYP3A risperidone interactions. More data from additional patients and continued research are needed to clarify the metabolic pathways of risperidone and the clinical significance of the CYP3A isoenzyme.

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Continuing Dialogue on Incentive Bias

Sir: The exchange of Letters to the Editor in the June 1996 (pp. 265–269) issue titled "Incentive Bias?" prompted our response. We have often wondered whether an incentive bias influences the *Journal* not to state in each article printed in a supplement that a pharmaceutical company has provided financial support. This acknowledgment is made on the cover of the supplement, but if reprints of a particular article are distributed, readers have no way of knowing who provided financial support. For example, if we received a reprint of the article by Dr. Nemeroff,[1] we would have no way of knowing that the symposium was sponsored by an unrestricted educational grant from SmithKline Beecham Pharmaceuticals. Incidentally, the content of the article makes it readily apparent that it was not sponsored by an unrestricted educational grant from Pfizer (based on the positioning of sertraline with regard to both dose-response and effect on CYP2D6).

Next, we are aware that manuscripts submitted to the *Journal* itself are peer reviewed, but that does not appear to be the

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case with regard to articles in the supplements. Readers would be better able to assess the quality of supplement articles (most of which are quite high) if they were made aware of the review policy of the *Journal*.

At the time of the symposium in question (March 26, 1994), support for a flat dose-response curve for sertraline was weak. Reports favoring a flat dose-response curve (50 mg/day as the usual effective therapeutic dose) appeared in May 1994[2] and in 1995.[3,4] (It is no surprise that all of them were sponsored by Pfizer, and despite the three references, all of the data appear to be derived from Fabre et al.[3]). It is hardly fair to be critical of Dr. Nemeroff when these data were not at his disposal in March 1994. On the other hand, we would have expected Dr. Nemeroff to have taken these studies into account in his June 1996 Letter to the Editor.[5]

Furthermore, Dr. Nemeroff goes to considerable effort to point out that 50 mg of sertraline is not the dose generally used in clinical trials that allow dose escalation. This hardly seems unusual since *dose escalation studies are designed to escalate dose*. In such a study, the starting dose is never the final dose. For example, Dr. Nemeroff points out in the Aguglia et al. study[6] that the mean daily dose of sertraline was 72 mg. This represents a 44% increase from the starting dose of 50 mg. He did not mention that in the same study the mean daily dose of fluoxetine was 28 mg, which is a 40% increase from the starting dose of 20 mg. Bennie et al.[7] (Pfizer sponsored) compared fluoxetine and sertraline for the treatment of major depression with starting doses of 20 mg and 50 mg daily, respectively. Twenty-four percent of those taking sertraline had the dose doubled to 100 mg—exactly the same percentage of patients taking fluoxetine had the dose doubled to 40 mg daily.

Dr. Nemeroff also makes the point that naturalistic studies suggest that 50 mg of sertraline is not the dose generally used in clinical practice. He refers to Gregor et al.[8] who found a mean starting dose for sertraline of 59 mg (compared with 21 mg for fluoxetine) and a mean dose at the ninth prescription of 117 mg (compared with 25 mg for fluoxetine). The decrease in sample size from 460 patients at first prescription to 38 patients at ninth prescription makes these data difficult to evaluate. In the interest of disclosure, readers should know that while Gregor was from the Center for Pharmaceutical Economics at the University of Arizona, his four coauthors were employed by Lilly, and development of the manuscript was supported, in part, by an educational grant from Lilly. There were similar findings by Fisher et al.[9] in a study with no apparent pharmaceutical company support. Postmarketing surveillance found the mean daily fluoxetine dose to be slightly less than 25 mg (25% higher than the usual 20-mg starting dose) compared with a sertraline mean daily dose of 73.5 mg (47% higher than the usual 50-mg starting dose). A recent study from the Dean Health Plan (supported by a grant from Pfizer) found that for patients receiving their first antidepressant for an episode of depression, the mean daily dose of the fourth prescription was 22.6 mg for fluoxetine (13% above baseline, N = 234) and 70.2 mg for sertraline (40.4% above baseline, N = 41).[10]

It appears that a substantial portion of the literature (controlled clinical trials and naturalistic studies) does not support Dr. Nemeroff's contention that patients treated with sertraline "tend to require doses of at least 100 to 150 mg/day."[1(p10)]

One also wonders how much of the clinical use of sertraline is influenced by a true pharmacologic need for higher than 50-mg doses as opposed to effective counter-marketing by competitors. (We have before us a glossy, two-color folder titled "Fluoxetine vs. Sertraline: When Titration Becomes an Issue," which contains a copy of the Gregor et al. article and was provided compliments of Lilly.)

There are three final points with regard to Dr. Nemeroff's letter. First, he described two studies by Reimherr et al.[11,12] and presented them as separate studies. Since the first report was "one portion of a large multicenter trial," it seems quite possible that the data from the first study are also embedded in the second. Second, the Amin et al.[13] dose-finding study did not find that 200 mg of sertraline was significantly more effective than placebo. There was no significant difference in patient response on the Hamilton Rating Scale for Depression between any dose of sertraline and placebo, and the 200-mg dose of sertraline separated from placebo only on the anxiety/somatization factor. Third, his first mention of the Brown and Harrison study[14] was accurate (fluoxetine nontolerators were switched to sertraline), but his second mention was inaccurate (the study did not evaluate fluoxetine nonresponders). While that study did report a mean final daily dose of 117 mg, it was designed to increase the dose from 50 mg to 100 mg after 2 weeks, to 150 mg after 4 weeks, and to 200 mg after 5 weeks—in effect, it was a dose-escalation study.

In closing, we do not know if 50 mg of sertraline is less effective, more effective, or just as effective as 20 mg of fluoxetine or 20 mg of paroxetine. To resolve this issue, we suggest that Lilly, Pfizer, and SmithKline Beecham form a consortium to support a definitive study—one that compares fixed doses of fluoxetine (20 mg), paroxetine (20 mg), sertraline (50 mg), and placebo in a double-blind, randomized fashion in a sufficiently large patient population—to answer the question once and for all. Finally, it would be foolish to deny that incentive bias exists—it influences everyone, including ourselves. The best one can do is be aware of these subtle and not-so-subtle influences and resist those that are not in the best interests of our patients.

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James W. Jefferson, M.D.
John H. Greist, M.D.
David J. Katzelnick, M.D.
Madison, Wisconsin

Dr. Nemeroff Replies

Sir: There is little doubt that it makes sense and is right for readers of *The Journal of Clinical Psychiatry (JCP)* or for that matter, any journal, to be aware that a journal supplement is supported by an unrestricted educational grant from the pharmaceutical industry. I take no issue with this recommendation and heartily endorse it.

However, I do take issue with several of the other comments made by Jefferson, Greist, and Katzelnick in the space above. In particular, I take strong exception to the implication that my article published in *JCP*[1] was influenced by a pharmaceutical sponsor. This is simply not the case, and frankly I am surprised that such experienced psychopharmacologists as Jefferson and Greist would take such a position. They have published innumerable articles in *JCP* supplements sponsored by the pharmaceutical industry. I have never thought that their writings were influenced by who the pharmaceutical sponsor was.

They criticize my analysis of the sertraline data by suggesting that dose escalation studies are designed to escalate dose. This is certainly the case. Moreover, they criticize the naturalistic studies I cite by suggesting that a decrease in the sample size over time confounds the analysis and, moreover, that coauthors from the Eli Lilly company were not fair in their assessment. Nevertheless, they admit that both the Fisher study and a recent study from their own organization found dose escalation with sertraline at a far greater magnitude (40% above baseline) when compared to fluoxetine (13% above baseline). However, the authors may not be aware of the following data, namely, (1) the National Disease and Therapeutic Index Audit[2] of 2940 office-based U.S. physicians revealed an average prescribed dose of 81 mg/day, and (2) the PCS database[3] of 544,309 patients revealed mean doses for the SSRIs as follows: fluoxetine 26.2 mg, paroxetine 22.8 mg, and sertraline 80.0 mg (though I find their unawareness somewhat surprising because Dr. Greist serves with me on the Eli Lilly Psychiatric Advisory Board, and these data were presented there). A major point I have emphasized in my articles and in previous letters is that 50 mg of sertraline was effective for some, but not all patients, and that the manufacturer of sertraline, Pfizer, has in fact suggested that the acceptable dose range for use in depressed patients is 50–200 mg. What percentage of patients respond optimally to 50 mg of sertraline remains to be determined. This, of course, has a great deal to do with how one defines antidepressant response, and a 50% decline in the Hamilton Rating Scale for Depression score (often used to define response) is certainly quite a different measure than a return to complete euthymia. Thus, 50 mg/day of sertraline may improve mood so that patients are considered responders using one criteria, but such a response may not be optimal. Finally, one must, of course, use the manufacturer's own data, surely something Jefferson et al. would not object to. The recently changed package insert for sertraline states: "The efficacy of Zoloft as a treatment for depression was established in two placebo-controlled studies in adult outpatients meeting DSM-III criteria for major depression. Study 1 was an 8-week study with flexible dosing of Zoloft in a range of 50 to 200 mg/day: the mean dose for completers was 145 mg/day."

In summary, academic Departments of Psychiatry depend on research support from the National Institutes of Health, foundations such as the National Alliance for Research in Schizophrenia and Depression, the Stanley Foundation, and the pharmaceutical industry. My own department's clinical research program receives support from Pfizer, Lilly, SmithKline Beecham, Bristol-Myers Squibb, Solvay, Wyeth-Ayerst, and Abbott Laboratories, as well as Zeneca Pharmaceuticals. Each of these pharmaceutical companies has been generous in its support of the educational mission, as well as the research mission, which is fortunate, particularly in view of the declining clinical revenues brought about by changes in healthcare financing. Little is accomplished by self-righteous declarations of incentive bias on the part of editors or authors. Clear guidelines exist from the FDA and other federal agencies concerning the relationship of the pharmaceutical industry to the support of clinical and basic research. Let's just follow them.

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Charles B. Nemeroff, M.D., Ph.D.
Atlanta, Georgia

The Publishers Reply

We find your suggestion of full disclosure in all articles appearing in Supplements to the *Journal* to be most appropriate. The acknowledgment as to the source for the articles and any educational support, if given for their publication, has always been cited on the inside cover of each Supplement. In addition, the author(s) of each and every article appearing in both the *Journal* and its Supplements must state any source(s) of funding associated with that particular manuscript.

However, from time to time a physician might have an opportunity to read an individual Supplement article apart from the complete publication. When this is the case, the information printed on the inside cover is not readily available. Therefore, in January 1997, we decided to include a brief identification as to the nature of support, if any, for the Supplement on the first page of each article along with the other relevant author/funding information. The addition of this information should dispel any possible confusion that might arise in these circumstances.

The Publishers

Guideline Series Commentary

Sir: The recently published "Expert Consensus Treatment Guidelines for Schizophrenia: A Guide for Patients and Families"[1] is a document that omits one of the most fundamental and important considerations of schizophrenia, namely, cognitive impairment. Thousands of studies have been published delineating the various aspects of intellectual impairment in schizophrenia. Yet the treatment guidelines barely make reference to the fact that schizophrenia is a disorder of cognitive function. The authors simply state that it is a "disorder of the

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brain . . . [that] interferes with the ability to think clearly, know what is real, manage emotions, make decisions, and relate to others" (p. 51). The paper then almost entirely ignores cognitive dysfunction as an important aspect of schizophrenia and concentrates on the DSM-IV definitional symptoms and pharmacologic treatment. It portrays the disorder as if the main problem is treatment compliance, with statements such as "It is very important that patients stay in treatment even after recovering from an acute episode" (p. 53). The guide may be unrealistically optimistic when it states that "Usually patients respond well to treatment of a first episode of schizophrenia, but if there are repeated episodes of schizophrenia, symptoms sometimes persist despite repeated treatment with the standard antipsychotic medications" (p. 53).

There can be little doubt that cognitive deficits are not only a prominent aspect of schizophrenia,[2,3] but also one of the most detrimental and least responsive to treatment. Cognitive deficits are evident in neuroleptic-naive patients with first-episode schizophrenia,[4] and the deficits persist despite symptom relief. Of all the characteristics of schizophrenia, cognitive impairments appear to be the most stable traits of the disorder. Davis has recently noted: "None of the current drugs do anything for the most incapacitating symptom of schizophrenia, the cognitive deficits. Maybe it's time to get off the dopamine merry-go-round we've been on for 40 years" (*Time* [Special Issue] Fall 1996;148[14]:48). Goldberg and Weinberger[5] note that improvements in symptom status have not led to improved quality of life because the majority of cognitive functions remain impaired. They also point out the need for new pharmacologic agents, i.e., nootropics, specifically targeting cognitive dysfunction. I[6] have advocated a model of treatment that emphasizes cognitive deficits rather than psychosis as advantageous in clinical practice because it would lead to greater patient and family acceptance.

We do a disservice to the patients and the families to imply that psychotic symptom suppression is the only relevant treatment goal. Neither does it serve us well to arbitrarily limit the definition to those symptoms that respond to medication, ignoring some of the most persistent and disabling aspects of the disorder.

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Kenneth M. Weiss, Ph.D.
Cleveland, Ohio

Sir: I am writing to encourage an addendum to your "Expert Consensus Guideline Series: Treatment of Bipolar Disorder."[1]

A major and absolute contraindication for the use of valproate was relegated to a tiny editorial footnote (page 36, table 10A). I am referring to the danger of using this drug in sexually active reproductive-age women since it can be a teratogen.

True clinical expertise must be contextualized by the specifics of each patient's life. Since Axis II borderline and impulsive patients are increasingly treated pharmacologically as Axis I bipolar patients, the risks of valproate—when there may be manic promiscuity and intercourse without contraception—become crucial concerns.

It would be a pity if your "expert" guidance in the use of medication omitted substantive psychosocial variables, reinforcing the caricature of psychopharmacologists as reductionistic. Your Guidelines are fastidious in emphasizing cardiac, renal, and CNS side effects. Why not reproductive issues?

Please correct this error. The consequences are dire.

Reference

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Sara Hartley, M.D.
Oakland, California

Dr. Kahn and Colleagues Reply

Sir: We appreciate the thoughtful comments received regarding the Expert Consensus Guidelines for bipolar disorder and schizophrenia. Dr. Weiss makes the important point that cognitive deficits are major determinants of disability in patients with schizophrenia and that we did not address this topic in the first iteration of our project. There are indications that when patients switch from typical to atypical antipsychotics, small improvements occur in certain cognitive domains. Several studies are currently under way to test this question. There are also indications that when schizophrenia is detected early and treated consistently, patients are more likely to maintain gainful employment, a rough measure of cognitive function. Additional studies are exploring this issue by comparing early intervention between typical and atypical antipsychotics.

Dr. Hartley raises crucial questions regarding both management of pregnancy in the patient with bipolar disorder and careful diagnosis to prevent excessive use of medications in women with personality disorders who may be at higher risk of unplanned pregnancy. We understand her concerns and feel that it would be useful for the issue to be addressed in a similar body of work.

Because we based our guidelines on a set of survey questions that was comprehensive for the subject we addressed but not exhaustive of all the possible relevant issues, there are clearly going to be some important topics that we did not cover. As with all practice guidelines, clinicians and patients should always use their own best judgment about the appropriate course of action in any circumstance. We hope to begin work on the second iteration of each guideline in the near future and welcome comments and suggestions regarding areas of interest for the new surveys.

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