Letters to the Editor

Pindolol-Paroxetine Combination

TO THE EDITOR: In an important contribution, Robert M. Berman, M.D., and colleagues (1) concluded that the combination of the selective serotonin reuptake inhibitor (SSRI) fluoxetine with pindolol, a serotonin (5-HT) blocker at 5-HT_{1A} receptors, conveyed no advantage over treatment with fluoxetine alone in either response time or efficacy. The authors' experience differs from earlier open-label studies of the combination (2, 3), which were themselves based on promising studies in rats (4). We have recently completed a randomized, placebo-controlled, double-blind trial in which pindolol was combined with paroxetine in the treatment of major depression (5). The combination demonstrated both a reduction in latency of the antidepressant action and a possible superior efficacy that was sustained for up to 6 months after the trial's completion.

We were struck by some apparent differences between the two studies in the patient groups that were used. For example, we found that the pindolol-paroxetine combination worked less well for men over 35 years of age and for male and female subjects with a chronic history of dysthymia or depression or who were more severely depressed. We specifically excluded subjects who misused substances. It may be relevant that our patients were reviewed twice weekly during the first 2 weeks of the study and weekly thereafter to permit ascertainment of an early medication response.

These methodological issues apart, other possibilities may explain why Berman et al.'s patients did not show positive results. It is becoming clearer that the 5-HT_{1A} receptor is subject to genetic polymorphism (6), and such differences may be highlighted by use of a 5-HT_{1A} receptor blocker. Moreover, the isomer and the mixed enantiomer compositions of pindolol appear to act differently (in rats at any rate [7]) in their activity as partial agonists of 5-HT_{1A} receptors. Thus, it could be that the isomeric composition differed between the two studies. Finally, although we agree with Berman et al. that there are no a priori reasons to suggest that the absence of an effect is due to the choice of fluoxetine, rather than paroxetine or citalopram, perhaps this requires more examination as well.

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Drs. Berman and Charney Reply

TO THE EDITOR: We appreciate the comments of Drs. Isaac and Tomé. Our results suggested that pindolol cotreatment with an SSRI did not hasten antidepressant response, as had been reported in other randomized controlled trials (1, 2). Isaac and Tomé offered multiple reasons to explain this discrepancy, which we will address here.

One important possibility is that differences in the study populations may have led to the discordant results. For example, Drs. Isaac and Tomé suggest that chronicity may be associated with reduced efficacy of a pindolol-SSRI combination. Indeed, our negative results may have been due to the high level of chronicity found in our subjects (the mean duration of current depressive episode was over 5 years). Further work is needed to reliably identify a particularly responsive subset of subjects. Isaac and Tomé also raise the possibility that more frequent mood assessments during the first weeks of medication may have detected a differential response between the pindolol- and placebo-treated groups. This is unlikely to have yielded a clinically meaningful difference in our study, given that we found a statistically insignificant trend that favored the placebo-treated group.

Drs. Isaac and Tomé also suggest that our negative results may be attributable to intergroup 5-HT_{1A} receptor-related genetic variation. Although functionally relevant mutations in these genes can be identified, they are rare (prevalence of less than 2% [3–5]) and, therefore, unlikely to explain discrepant results. Finally, consideration is given to the isomeric composition of pindolol. Our formulation was made by the same manufacturer as that used in Blier and Bergeron's initial positive open-label investigation, which Isaac and Tomé cited, and similar doses were employed.

Although the results from our double-blind, placebo-controlled study do not support the use of pindolol to hasten SSRI treatment response, we still believe that the use of a 5-HT_{1A} antagonist is a compelling pharmacologic strategy in the treatment of depression. Further investigation is merited.

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Bulimia Outcome

TO THE EDITOR: We read with interest the recent article by Pamela K. Keel, A.B., and James E. Mitchell, M.D., on bulimia nervosa outcome (1). However, although the authors were aware that two studies (2, 3) reported findings from a single cohort of 50 bulimia nervosa patients followed for at least 5 years after initial clinical assessment, they appear to be unaware that a subsequent 10-year follow-up (4) also used the same patient cohort. This error has implications for the review's findings. For example, the reported mortality is incorrect, since the one death in the group has consequently been analyzed as two fatalities.

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TO THE EDITOR: Ms. Keel and Dr. Mitchell compared the outcome of subjects with bulimia nervosa who had been in naturalistic outcome studies ("follow-up studies") with that of subjects who had taken part in randomized controlled trials ("treatment outcome studies"). On the basis of differences between the two groups, they concluded that "Treatment interventions may speed eventual recovery but do not appear to alter outcome more than 5 years following presentation." This conclusion is suspect on three grounds.

First, very few studies have followed subjects for as long as 5 years, and Keel and Mitchell misclassified two of them. Second, the conclusion is based on the assumption that subjects who have and have not been exposed to treatment are being compared. This is not the case, since the great majority of subjects in the follow-up studies also would have been exposed to treatment, having been recruited from treatment clinics (i.e., the follow-up studies were mostly studies of clinical course rather than studies of natural history).

Finally, the only study to have directly addressed the issue raised by Keel and Mitchell, namely, the long-term impact of treatment, found that treatment did have a major influence (1). Subjects who had received behavior therapy had an extremely poor long-term outcome, while those who had received either cognitive behavior therapy or interpersonal psychotherapy did comparatively well. It therefore seems premature to draw general conclusions about the long-term impact of treatment in bulimia nervosa.

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Ms. Keel and Dr. Mitchell Reply

TO THE EDITOR: We were aware that the articles cited by Drs. Reiss and Johnson-Sabine reported data for a single cohort. For both the 5- and 10-year follow-up studies, the single death was reported as being due to a car accident in 1983, which we reported and analyzed as a single mortality across all three articles. We did state that for two cohorts death was accidental, but the single fatality from the three studies cited by Reiss and Johnson-Sabine was only the first of these two cohorts. The death in the second cohort was caused by a hypertensive episode due to ingestion of an antacid during the course of phenelzine treatment, which was reported by Fallon et al. (1). The sentence that noted a cohort in which two deaths resulted from traffic accidents was referring to a study by Patton (2).

We would, however, like to acknowledge an error we made with respect to Reiss and Johnson-Sabine's cohort. As Dr. Fairburn advised, we misclassified the cohort as a follow-up study when it should have been considered a treatment study. After having a blind rater review our classifications, we agree that this cohort and the study by Olmsted et al. (3) should be classified as treatment rather than follow-up studies. Because of the potential for this kind of error to significantly alter our conclusions, we reanalyzed the data by using hierarchical loglinear analyses after correcting study type assignment. All significant findings remained significant, and all insignificant findings remained insignificant. Although the statistical analyses did not change substantially, we very much regret the errors in study classification.

In response to Dr. Fairburn, our statement in the abstract was too strong and should have been modified to reflect many of the points made both in his letter and in our discussion section. For example, Fairburn noted that very few studies have followed patients for as long as 5 years. We agree and attempted to address this issue when we stated that "a limited number of studies followed women 5 or more years; thus, longer-term recovery rates rely on sharply decreasing numbers of women."

Fairburn stated that our conclusion assumes that we com-

pared subjects who had and had not been exposed to treatment. This was not our assumption. In fact, we stated as an important limitation to our conclusion that "follow-up studies contained large numbers of treated women."

Fairburn's own study had great influence on the findings of our review in that it was one of very few that contributed data for longer-term outcome. Within this study, treatment clearly influenced outcome. However, our conclusion is based on results across studies. In comparing Fairburn et al.'s study with other studies of comparable follow-up duration, we were struck by the similarity of values that represented full bulimia nervosa and remission 5 or more years after presentation. This convergence of values was all the more striking because of the substantial difference between study types for shorter follow-up periods and because treatment interventions varied greatly across studies.

We would like to make a point that perhaps we did not make strongly enough in the review. The ability of treatment interventions to speed eventual recovery is no small contribution. This effect would decrease the time (perhaps in years) that a person remains symptomatic over the course of the follow-up period. In saying that treatment interventions do not appear to alter long-term outcome, we are not saying that they have no impact. It simply appears to us that women who receive less effective or no treatment catch up over a long follow-up period in terms of recovery. Further data are needed to either support or refute this interpretation.

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Schizophrenia Practice Guideline

TO THE EDITOR: The recent APA "Practice Guideline for the Treatment of Patients With Schizophrenia" (1) conveys the optimism inherent in the development of new medications to treat this devastating disease as well as the appropriate caution about the lack of longer-term data on the newer compounds. We realize that the production of guidelines is a monumental task but believe that the clinical implications of the new neuroleptics' variable effects on prolactin deserve more attention.

Much of the new drug development has focused on minimizing unwanted side effects, notably acute extrapyramidal symptoms and tardive dyskinesia, since patients freed from movement disorders are more likely to be medication compliant, maintain recovery, and benefit from rehabilitation programs. Other side effects have not been the target of drug development. The discomfort and social stigma of extrapyramidal symptoms should not be minimized, but we would like to emphasize the potentially serious side effects of dopamine antagonism in the pituitary gland, namely hyperprolactinemia and its attendant risks of sexual side effects and infertility. Sexual and reproductive functioning are dimensions of human existence that are arguably of as much importance to our patients as neurological movement disorders.

According to its product monograph, risperidone causes higher prolactin elevations than haloperidol. Clozapine (2) and olanzapine (3) cause little or no serum prolactin rise, which is good news. However, clinicians need to be alert to patients, who had been relatively infertile as a result of neuroleptic-induced hyperprolactinemia, becoming not only more sexually active but also fully fertile. The return of menses in women who had been amenorrheic for many years is a common clinical phenomenon of clozapine and olanzapine treatment that is sometimes welcome and sometimes frightening. Pregnancies in women switched from standard antipsychotics to clozapine have been described (4). Family planning programs for these patients are essential.

It is also important for clinicians to be aware of potential long-term consequences of 1) neuroleptic-induced hyperprolactinemia, including the debate about neuroleptics and breast cancer risk, and 2) secondary hypogonadism, with its possible effects on bone mineral density, the cardiovascular system, and immune functioning. Behavioral effects of indirectly lowering gonadal steroids in patients with schizophrenia are currently unknown but may include an impaired sense of well being, depression, and cognitive problems, a set of symptoms that may be mistaken for an exacerbation of "negative" symptoms. This complex area requires more research.

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TO THE EDITOR: The recently published practice guideline for schizophrenia contains a grievous omission for persons with treatment-refractory schizophrenia. While the guideline adequately covered pharmacotherapy for treatment-refractory patients (e.g., the use of clozapine), there was no mention of social learning programs or token economies, which are the best validated and replicated methods of motivating and involving in psychosocial services patients who do not respond to conventional drug and psychosocial treatments (1–5). Patients with treatment-refractory schizophrenia have 1) persisting and intrusive positive psychotic symptoms despite the best efforts of pharmacotherapy and conventional psychosocial services, 2) severe negative symptoms that often interfere with their participation in treatment programs, 3) psychosocial

deficits that make unsupervised community functioning implausible, and 4) intolerable deviant behaviors (e.g., aggression, fire-setting, denudative behavior) that lead to their ejection from community living (6).

The token economy refers to a system in which special coins, chips, cards, or points (tokens) are vested with reward value by requiring their exchange for desired goods, services, and activities (back-up reinforcers). Patients earn tokens for adaptive behavior (e.g., self-care skills, attendance and participation at psychoeducational groups) and lose them for maladaptive behavior (response costs). Token economy systems provide an explicit set of procedures for patients' earning, spending, and losing tokens (contingencies of reinforcement). Emphasis is placed on "shaping" improvements in instrumental, self-care, social, and recreational behavior through abundant and frequent reinforcement of small behavioral improvements (7).

Ethical concerns about withholding privileges and needed services from patients are dealt with in high-quality social learning programs by ensuring that all patients in the institution or day hospital receive the basic level of services and privileges. These basics are then supplemented with additional privileges and rewards for active and adaptive participation in the program. Thus, patients can choose not to participate in a token economy and still receive all their basic treatment needs just as citizens have inalienable rights and access to services, but those who expend greater effort can be promoted up a career ladder or earn more money for a greater spectrum of privileges.

Structured and highly specified inpatient or day hospital programs that have used token economies have been shown to yield shorter hospital stays, longer community tenure, and substantial improvements in symptoms, social functioning, goal attainment, and self-care skills in otherwise treatment-refractory patients. Moreover, these improvements are over-and-above the improvements achieved by antipsychotic medications alone (8–11). As with more treatment-responsive patients, the refractory patient's target problems tend to be "treatment specific." Medications (such as clozapine) are more likely to improve symptoms while token economy or social learning programs are more likely to improve psychosocial functioning. Thus, it is important in designing and evaluating social learning programs to have multilevel assessments in place for ongoing treatment monitoring (6). Social learning systems are thus complementary and additive to antipsychotic medication and can be used concurrently with other efficacious psychosocial treatments, such as social skills training and psychoeducational or behavioral family management (12, 13).

Patients with treatment-refractory schizophrenia are not receiving the full benefits of judicious and validated treatments if they are not participating in a social learning or token economy program. It is incumbent upon psychiatrists, whose training rarely prepares them for establishing and maintaining a high-quality token economy system, to ensure that competent psychological consultation or staff are employed in making this approach available to their patients.

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Dr. Herz and Colleagues Reply

TO THE EDITOR: Drs. Dickson and Seeman are correct in emphasizing the potentially serious side effects of dopamine antagonism on pituitary gland functioning, namely hyperprolactinemia and its accompanying risk of sexual side effects and infertility. Psychiatrists should explore these issues fully with their schizophrenic patients, both to determine the extent of problems with the present medication and the implications of switching to a medication without these side effects. We agree that in deciding which antipsychotic medications to prescribe, psychiatrists should take into account the advantages of using medications that do not raise serum prolactin levels.

We disagree with Dr. Liberman that the topics of social learning and token economy systems were omitted from the practice guideline. On page 33, under "Long-term hospitalization," there is a discussion of long-term hospital treatment programs for refractory patients.

> Studies have suggested that patients with treatment-resistant schizophrenia who require long-term hospitalization profit most from treatment programs that emphasize highly structured behavioral techniques, including a token economy, point systems, and skills training that can improve patients' functioning . . . . Paradoxically, despite its demonstrated efficacy,

> the token economy is not often used in clinical settings . . . . Obstacles to its implementation include resistance by staff who hold tightly to traditional custodial methods, increased costs (for the reinforcers backing up the tokens), lack of support from administrators, and inadequate training of clinical staff."

Admittedly, token economies could be used in day treatment programs for seriously functionally impaired patients with treatment-refractory schizophrenia. However, the use of token economies for better functioning patients can be demeaning for these individuals and thus counterproductive, and little data exist that support their use for these patients.

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