Letters to the Editor

Conventional Psychotropic-Induced Tremor Extinguished by Olanzapine

TO THE EDITOR: We have observed, unexpectedly, the disappearance of prominent, persistent, and troublesome fluphenazine- or haloperidol-induced coarse tremors in three patients within days of initiation of treatment with olanzapine, 10 mg/day p.o., without discontinuance of or decrement in the dose of either fluphenazine or haloperidol. Treatment with diphenhydramine, benztropine, amantadine, and propanolol—tried in cases 1 and 2 only—had provided negligible and transient tremor relief. Our intent, then, was to wean all three patients from fluphenazine or haloperidol while starting olanzapine, but we observed the following responses:

Case 1. Mr. A, a 36-year-old Caucasian man with an 18-year history of recurrent command hallucinations, suicide attempts, paranoid delusions, severe depression, and alcohol dependence, had been in remission for 1 year on a regimen of fluphenazine decanoate, 37.5 mg i.m. every 2 weeks, and nefazodone, 100 mg p.o. at bedtime. The patient experienced coarse truncal and extremity tremors. Four days after the addition of olanzapine, 10 mg/day p.o., to his regimen, his tremors had noticeably diminished; by day 7, they were no longer apparent. Without further medication adjustment, the tremors had not returned after 26 weeks.

Case 2. Ms. B, a 25-year-old African American woman with a 2-year history of recurrent paranoid ideation, violent behavior, psychotic depression, and mania, with intercurrent marijuana, heroin, and "crack" cocaine abuse, had been in remission for 1 year on a regimen of fluphenazine decanote, 25 mg i.m. every 2 weeks; fluphenazine, 7.5 mg p.o. at bedtime; and divalproex sodium, 1000 mg p.o. twice a day. She had developed coarse hand tremors that disappeared within 7 days of the addition of olanzapine, 10 mg p.o.; her tremors had not returned after 21 weeks without other medication changes.

Case 3. Ms. C, a 34-year-old African American woman with a 20-year history of recurring severe thought disorganization or mania, had been in remission for 1 year on a regimen of haloperidol, 20 mg p.o. at bedtime; lithium carbonate, 300 mg p.o. twice a day; and divalproex sodium, 750 mg p.o. twice a day. She had unsightly coarse circumoral and hand tremors, not relieved with lithium discontinuance. Her tremors disappeared 1 week after initiation of treatment with olanzapine, 10 mg/day p.o., without other medication adjustments; her tremors had not returned after 20 weeks.

Olanzapine is active against muscarinic cholinergic receptors (1), a fact that may account for the observed suppression of fluphenazine- and haloperidol-induced tremor. The patients in cases 1 and 2, however, had been treated with benztropine, an antagonist of muscarinic acetylcholine receptors, with little tremor relief, suggesting that olanzapine could suppress tremor by means other than antimuscarinic action.

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Book Review Challenged

TO THE EDITOR: I do not ordinarily respond to psychoanalysts' adverse reviews of my published work; as a persistent critic of psychoanalytic instinct theory over the past 50 years, I have come to take such reviews for granted. Now, however, I find myself compelled to respond to the patent unfairness of Richard Chessick's appraisal (1) of the reissue of the 1968 volume of essays, *Modern Psychoanalysis: New Directions and Perspectives* (2), which I had the privilege of editing. Chessick makes the egregious error of comparing it to new editions of the *Cecil Textbook of Medicine,* as if *Modern Psychoanalysis* were presented as a textbook of psychoanalysis that needed periodic updating. In fact, the volume is a collection of essays by a group of distinguished contributors (many of whom, unhappily, have since died) who shared the conviction that much of psychoanalytic theory lacks a sound scientific basis and needs to be supplanted by newer concepts based on biobehavioral research findings. Because the critical ideas expressed by these authors continue to be highly relevant, Transaction Publishers considered the book worthy of reprinting as a contemporary classic.

The correctness of that decision is dramatically exemplified by Chessick's thinking, which conceals a resurgence of instinct-oriented theorizing clothed in "postmodern" seductive verbiage. Anyone who doubts this should read his article "Archaic Sadism" (2), in which he advances the astounding, totally unscientific, and unprovable thesis that "all humans are born with a primal biological archaic aggressive-destructive drive the gratification of which gives satisfaction just like the sexual drive." If that is representative of the kind of psychoanalytic thinking that he favors, I can say only that it underlines the importance of calling the essays in *Modern Psychoanalysis* to the attention of the psychodynamically oriented members of our profession all over again.

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Dr. Chessick Replies

TO THE EDITOR: This is in response to Dr. Marmor's letter. There is a distinction between "unfairness" and difference of opinion. My review of Dr. Marmor's edited book was in no way unfair; it simply expressed my opinion, which happens to be different from his. I did not, and do not now, think that it was wise to reprint the book as a "classic," since parts of it are obsolete, as I indicated in my review. It would have been much better to re-edit and to update the book as a second edition, rather than to let it stand as it was 30 years ago. I do not think I made any error, egregious or otherwise, and I stand by what I said in the review. I think the error was made by Transaction Publishers.

I was flattered that Dr. Marmor took the trouble to read my essay in the *Journal of the American Academy of Psychoanalysis*. It was not paraded as a "scientific" article but, rather, as an expression of my own view. I was surprised that Dr. Marmor found my thesis "astounding, totally unscientific, and unprovable," since it has been put forth in various forms throughout history: in philosophy from the time of the followers of Confucius; in religion from the time of the ancient Egyptians; and in psychoanalysis, not only by Freud but by many of his followers, including Hartmann and the ego psychology school. I can certainly understand that Dr. Marmor entirely rejects instinct-oriented theorizing, and I respect both him and his opinion; however, there is hardly anything novel or extraordinary about my opinion.

The issue of what makes an opinion unscientific and unprovable has certainly not been decided today; that is why postmodernism and hermeneutics have become important influences in our clinical work. In fact, every interpretation given to a patient represents an opinion. I do not know what Dr. Marmor means by the phrase "postmodern seductive verbiage." I think, as he does, that biobehavioral research is very important; however, I would like to see it supplement and correct, rather than completely replace, current psychoanalytic theory, in a friendly dialectic between our clinical experience and findings from research in various fields of the behavioral sciences and neurobiology. Incidentally, I believe that Freud would have agreed with this approach; after all, he began as a neuroscientist.

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Olanzapine for Primary Negative Symptoms

TO THE EDITOR: A key issue in understanding schizophrenia and in developing better drugs for the disease is whether any improvement in the negative symptoms associated with the use of neuroleptics reflects improvement not only in secondary negative symptoms but in primary negative symptoms as well. On the basis of data from a double-blind, controlled study comparing the effects of olanzapine to those of haloperidol and placebo in exacerbated schizophrenic patients (1), Tollefson and Sanger intended subsequently to determine to what extent the superior total effect on negative symptoms was direct or indirect (2). The authors defined the direct treatment effect of olanzapine as the additional improvement in negative symptoms remaining after they had corrected for changes in positive symptoms, depressive symptoms, and extrapyramidal symptoms. They found that olanzapine had a greater direct effect than placebo and haloperidol on negative symptoms, hypothesizing that this finding represented an improvement in primary negative symptoms. Some comments, however, are warranted.

The original study was designed not for evaluating the effect on primary negative symptoms but for evaluating the effect on positive symptoms. Tollefson and Sanger state that it was not known what the patients' negative symptom histories were; in turn, it was not known whether they had exhibited a chronic deficit state before the index admission (2). The authors ignore this limitation, however, when they state that "it is likely that these results could be generalized to patients in a chronic deficit state who are not in an acute exacerbation of schizophrenia." That the benefits of olanzapine on negative symptoms were replicable in a subgroup of patients with prominent negative symptoms was not surprising because this subgroup of patients was a subset of the study group from which the results to be replicated were generated.

The authors do not mention the issue of dealing with the psychic side effects of haloperidol such as reduced speed of thinking, lack of energy, flat affect, and anhedonia (3). These symptoms are phenomenologically indistinguishable from a range of negative symptoms measured on the Scale for the Assessment of Negative Symptoms, and the number of such symptoms may not necessarily correlate with the number of extrapyramidal side effects. Therefore, the psychic side effects of haloperidol may contribute to the magnitude of the superior direct effect of olanzapine when compared with haloperidol. Improvement in negative symptoms due to changes in positive symptoms not captured by the Brief Psychiatric Rating Scale may be another source of bias.

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Drs. Tollefson and Sanger Reply

TO THE EDITOR: We thank Dr. Licht for his comments. In our opinion, one of the defining characteristics of olanzapine, the improvement of negative symptoms, has been demonstrated in several double-blind, controlled clinical trials against either placebo (1), haloperidol (2, 3), or risperidone (4). As pointed out by Meltzer (5), improved patient outcomes—whether negative symptom treatment advantages are primary or secondary in nature—are of the utmost importance.

However, whether novel antipsychotics, such as olanzapine, are effective in a subgroup of primary negative symptoms is a question of significant academic interest (6). Accord-

ingly, in our recent publication, we employed the well-accepted statistical methodology of path analysis. In the article, we did not indicate that this method provided a final or definitive answer. However, the methodology does serve to advance the field in this area and generated reason to believe that olanzapine's negative symptom effects were above and beyond those attributable to superior efficacy in positive symptoms, associated mood symptoms, or extrapyramidal side effects (referred to as indirect).

Dr. Licht is incorrect in suggesting that the original study was designed "for evaluating the effect on positive symptoms." Rather, the primary objective was the evaluation of the comparative effectiveness of olanzapine and haloperidol on symptoms as assessed by the Brief Psychiatric Rating Scale. This scale includes, but is not limited to, positive and negative signs and symptoms. It should have detected several of the clinical features mentioned in Dr. Licht's letter. A secondary prospective objective, as stated in the protocol, was the comparative efficacy of both compounds on negative symptoms. These data were presented in our manuscript. The overall path analysis was conducted on all randomly assigned patients participating in this very large, multinational, controlled clinical trial, not on "a subgroup of patients" as implied by Dr. Licht. The only post hoc stratification was according to predominant baseline negative signs and symptoms. This analysis only served to provide additional confirmation for the prospective treatment differences reported in the article. Determination of the extent that these data can be replicated in patients defined a priori as exhibiting a chronic deficit state is the logical progression of this research program. We trust that such results will be of interest to Dr. Licht and others in further evaluating this important question.

We would conclude that the reported path analysis illustrated the potential advantages of olanzapine in reducing the spectrum of potential neuroleptic side effects highlighted by Dr. Licht. In our study we also presented a comparison of haloperidol and placebo effects on negative symptoms. This illustrated that any other indirect factors, not accounted for in our path analysis, likely exerted a negligible effect. The most important observation, regardless of the debate as to whether the olanzapine treatment advantage on negative symptoms relates to direct and/or indirect mechanisms, is that patients experienced significantly greater negative symptom improvement with olanzapine. In light of the associated morbidity (7), any benefit in negative symptom outcomes is welcomed.

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Language and Definition Changes in DSM-IV

TO THE EDITOR: In the clinical case conference of the May 1997 issue of *The American Journal of Psychiatry* (1), Drs. Panzer and Fullilove usefully remind readers that not all patients may meet formal criteria for mental disorder. The authors describe a patient, Belinda, who was undergoing a crisis due to the pressures of both work and home. The authors concluded that her condition was not a mental disorder but justified a V code—a condition not attributable to a mental disorder that warrants therapeutic attention.

It is important to note, however, that in DSM-IV, the language and definitions for these terms were changed from those in DSM-III-R. Because in some circumstances these conditions are, in fact, attributable or at least related to a mental disorder, a broader conceptualization was applied, and the section was entitled "Other Conditions That May Be a Focus of Clinical Attention." Further, not all of the specific codes included in this section are V-codes—e.g., 316, Psychological Factors Affecting Medical Condition; 313.82, Identity Problem; and 995.5, Physical Abuse of a Child (where the focus of clinical attention is on the victim).

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Sustaining the Effect of Sleep Deprivation

TO THE EDITOR: The June 1997 issue of the *Journal* featured an article (1) concerning the possibility of sustaining the acute effect of total sleep deprivation with a subsequent 1-week sleep phase advance therapy in drug-free and amitriptyline-nonresponder patients. Given the high response rates, the rapidity of action, and the short duration of the proposed treatment, this report raises high clinical interest and several issues.

Do total sleep deprivation and sleep-wake rhythm manipulations trigger remission from the depressive episode, or do they cause only transient positive mood fluctuations? Several nonpharmacologic strategies have been proposed to sustain the effect of total sleep deprivation, and simple serial repetition of total sleep deprivation prevents short-term relapse among drug-free depressed patients (2). In agreement with the literature (3), however, we observed a subsequent relapse among unmedicated patients after a variable delay. Moreover, total sleep deprivation has been shown both to hasten the antidepressant action of fluoxetine in previously unmedicated patients (4) and to trigger a sustained response in fluoxetine nonresponders (5). Similar effects could have occurred with

unmedicated patients and nonresponders to amitriptyline, and differences between groups might have been revealed later in the course of the depressive episode.

Does the unipolar/bipolar dichotomy influence the effect of manipulations of the sleep-wake rhythm? When strictly defined diagnostic criteria are applied, bipolar 1 patients show better responses than unipolar patients to total sleep deprivation (6, 7). The same may be true for the effects of sleep phase advance.

REM sleep deprivation is a powerful antidepressant treatment, and REM pressure follows a circadian rhythm. Could changes in sleep architecture explain the clinical effect of sleep phase advance?

A discussion of these issues will help in evaluating the clinical usefulness of this new technique.

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Drs. Riemann and Berger Reply

TO THE EDITOR: We would like to thank Dr. Smeraldi and his colleagues for commenting on our article. They raise some important questions relating to our data.

They ask whether total sleep deprivation and other sleep-wake manipulations trigger remissions from the depressive episode or cause only transient mood fluctuations. According to our knowledge, our clinical experience, and the literature (1), total sleep deprivation itself only very rarely leads to a full remission from major depression. The main purpose of our study had been to confirm findings from our earlier pilot study (2) that the positive effects of total sleep deprivation were preserved by a succeeding phase advance of the sleep period lasting for 7 days. We have to mention that our previous study did not include further psychopathological measurements beyond that time period. In addition, the unmedicated patients who participated and responded well to our sleep-wake manipulation all were given antidepressant medication after termination of the study, in order to prevent relapses. We considered this necessary for ethical reasons because we were unsure how long-lasting the effects of our therapy might be. In order to properly answer the issue raised by Dr. Smeraldi and his colleagues, it would be necessary to conduct a longitudinal study of unmedicated patients and to monitor their clinical outcomes after the end of the study.

We cannot exclude the possibilities hypothesized by Dr. Smeraldi and his colleagues 1) that our sleep-wake manipulation triggered a sustained response in the amitriptyline nonresponders and 2) that differences between medicated and unmedicated patients might only have been revealed later during the course of the episode. The latter possibility seems rather unlikely, however, since the length of the stay in the hospital after the study did not differ between the two groups of patients.

In our data set, we did not find a superiority of total sleep deprivation combined with phase advance among bipolar I patients as compared to unipolar patients.

In a new study (unpublished data) of 40 depressed patients who responded to total sleep deprivation and were afterward subjected to either phase advance or phase delay of the sleep period, polysomnographic recordings were performed during the whole course of the study. Contrary to our expectations, even among the responders to the procedure, REM latency decreased and REM percentage increased at the end of the study when the clinical effect was most pronounced. This finding raises interesting speculations about the REM sleep hypothesis (3) of depression. Because we are still in the process of analyzing and interpreting these unexpected data, it would be premature to draw definite conclusions concerning relationships between changes in sleep and psychopathological outcome.

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