

Addressing Ethical Issues in the Psychiatric Research Literature

Allegations of ethical problems in psychiatric research have received intense public attention in the past few years. Two of the most widely publicized examples are research involving withdrawing medication from patients with schizophrenia at the University of California, Los Angeles, investigated by the US Office of Protection From Research Risks, and litigation concerning research conducted by the New York State Office of Mental Health.^{1,2} Philip J. Hilts, writing in the science section of *The New York Times*, described a range of psychiatric research considered to be ethically problematic, including “challenge” experiments in which psychiatric patients were administered drugs to study provoked symptoms.³ *The Boston Globe* recently published a 4-part series, entitled “Doing Harm: Research on the Mentally Ill,” detailing alleged abuses of human subjects in psychiatric research.⁴⁻⁷ The use of placebos in research that tests new drugs to treat psychiatric disorders has also been criticized in the professional medical literature.⁸ In December 1998, the National Bioethics Advisory Commission issued a comprehensive report and recommendations on research involving subjects who suffer from psychiatric disorders with the potential to impair decision-making capacity.⁹

Some of the criticisms of psychiatric research expose genuine ethical problems, while others distort the scientific and ethical contexts of studies alleged to be abusive. In view of public and professional attention to the ethics of psychiatric research, we recommend that published reports of psychiatric research address ethical issues in a more comprehensive fashion. It is rare for these journal articles to go beyond stating that the research was approved by an institutional review board (IRB) and that investigators obtained informed consent from the research subjects. This minimal attention to ethical issues is sufficient for studies that are not ethically problematic. However, more detailed discussion of ethical issues is warranted in reports of research involving patients with disorders that may impair decision-making capacity, such as Alzheimer disease and schizophrenia, and in reports of research involving interventions that pose ethical concerns—for example, studies in which patients are withdrawn from standard medications, receive a placebo treatment trial, or are administered a challenge agent that can provoke psychiatric symptoms.¹⁰⁻¹² In published accounts of the results of such research, ethical issues concerning the process of obtaining informed consent and the risks of harm or distress associated with research procedures need to be addressed.

We suggest that there is an analogy between devoting attention in the research literature to scientific methodology and to ethical considerations. Professional journals require that biomedical research reports include a section describing study methods, which designates techniques of data collection and analytical and statistical operations employed in the research. The purpose is to enable critical readers to assess the reliability and validity of the research findings. Likewise, research reports should review pertinent ethical issues to permit readers to assess the ethical adequacy of the research.

It might be objected that more than minimal attention to ethical issues is unnecessary for reports published in the scientific literature, since all research protocols receive prior review and approval by IRBs. The adequacy of IRB review remains open to question.¹³ Yet, even if IRB review is exemplary, public accountability for human subjects research, particularly studies involving vulnerable groups of patient volunteers, warrants careful attention to ethical issues in published reports. The published literature is the public face of biomedical research. Research involving human subjects must not only be ethical; it should be seen as ethical. Of course, attention to ethical issues in published research reports offers no guarantee of ethical adequacy; however, a requirement to address ethical issues as a condition of publication should enhance the ethical quality of planning and execution of human subjects research.

Although the rationale for attention to ethics in research reports is not unique to psychiatric research, recent criticism of the ethics of psychiatric research makes it opportune for psychiatric journals to take a leadership role in setting standards for addressing ethical issues. Journal editors should consider issuing guidelines for discussion of pertinent ethical issues, which should be incorporated into peer review of submitted manuscripts. The ethical issues to be addressed would depend on the scientific design, research interventions or procedures, and characteristics of the human subjects under investigation. Some of the ethical issues that might be discussed in published articles, when relevant, include (1) procedures adopted to assess the capacity of research subjects to give informed consent; (2) the use of surrogate decision makers; (3) the rationale for withholding or withdrawing standard medications as part of the study and the length of the drug-free period; (4) the rationale for and duration of a placebo phase in a clinical trial; (5) the intensity and duration of symptoms exacerbated by drug “washout” or administration of a challenge agent; and (6) safeguards adopted to protect vulnerable research subjects.

Just as scientific standards for publication in leading journals contribute to methodological rigor in the design of studies, so ethical standards for publication should

improve protection of the rights and welfare of research subjects. Investigators often view ethical requirements stipulated in regulations governing human subjects research as legalistic standards external to the scientific enterprise. Ethical standards that must be addressed in published research reports, which are key markers of professional reputation, may hold greater promise for being internalized as guides to good science with human subjects. Moreover, addressing pertinent ethical issues in the scientific literature constitutes a proactive measure that may enhance public trust in biomedical research.

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The Role of Residual Subthreshold Depressive Symptoms in Early Episode Relapse in Unipolar Major Depressive Disorder

There is increasing realization that unipolar major depressive disorder (MDD) is primarily a chronic disease with frequent episode relapses and recurrences across the life cycle and not merely an isolated single acute episode illness. This recent paradigm shift in the concept of unipolar MDD¹ has made delay or prevention of episode relapse a fundamental treatment goal in the clinical management of unipolar MDD. It is surprising, that apart from the earlier series of investigations by the Pittsburgh group,^{2,3} that there is a scarcity of controlled studies, in which delay or prevention

of episode relapse is the main focus of the study. Thus, we read with interest the study of Fava et al.⁴ This is an important study for which we wish to commend the authors. However, we would like to raise an issue that may be important for the interpretation of their data.

Our group has been investigating the clinical significance of residual subthreshold depressive (SD) symptoms. We have reported that residual SD symptoms are as common as the MDD symptoms during the course of illness of unipolar depression, with 17% and 15% follow-up weeks, respectively, being spent in these 2 symptomatic states during 12 years of systematic follow-up.⁵ In addition, in 2 separate samples, residual SD compared with no depressive symptoms, were associated with small, but significant, increases in psychosocial disability ($P < .01$).^{6,7} Moreover, we reported that patients with unipolar MDD recovering from major depressive episodes with residual SD experience very rapid episode relapse and have strikingly more chronic future courses of illness that are characterized by early and more frequent episode relapses and recurrences.⁸ From these studies we have concluded that residual SD represents a prevalent and a clinically integral part of illness activity during the course of unipolar MDD. Hence, our contention that the removal of residual SD by treatment is very important in the delay or prevention of episode relapse.

Although not stated in their manuscript,⁴ we predict based on our data, that the cognitive behavioral treatment (CBT) delay of episode relapse is directly related to the capacity of CBT to remove residual SD symptoms. Our first question to the authors is—what was the number and prevalence of CBT patients who achieved full asymptomatic recovery vs those who continued with residual SD or did all CBT patients achieve asymptomatic recovery? Second, was there a significant difference in survival time between CBT patients divided on this basis? Third, would Fava et al be willing to divide their entire sample on the basis of patients who achieved asymptomatic recovery vs residual SD recovery regardless of whether they were in the CBT or standard clinical management track? Survival analysis of the overall sample divided by recovery status, could be used to test whether the greater effectiveness of CBT in delay or prevention of episode relapse is in fact due to achieving full asymptomatic recovery.

Our data,^{8,9} strongly suggest that full major depressive episode remission or recovery should be defined in terms of patients achieving an asymptomatic status, not merely having depressive symptoms fall below syndromal criteria for the disorder. Although depressive symptom reduction to SD levels is defined by *Research Diagnostic Criteria for a Selected Group of Functional Disorders* and other clinical systems, (eg, Hamilton Depression Rating Scale) as full “recovery,” we contend, it is not full recovery. Rather, it appears that residual SD symptoms are a partial remission representing a subthreshold continuation of a active major depressive episode, which places patients at high risk for early episode relapse.

The Fava et al⁴ study is promising in that it delineates a specific role for CBT in the treatment of residual SD symptoms and describes an effective and sequential treatment strategy for use of antidepressants and CBT in

the treatment of unipolar MDD. If this study can be replicated with larger samples with appropriate controls, it would have important public health implications.

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In reply

In our article,¹ we indicated how CBT induced significant improvement in residual symptoms, unlike CM. We may provide a closer look at what happened by classifying patients according to the presence of at least one residual symptom with a score of 3 or more in the Clinical Interview for Depression,² as was done in previous research.³ At enrollment in the study, no patients in the CBT and 2 of the 20 in the CM group had no residual symptoms. As a result, fully asymptomatic status was achieved by only 5% of the sample. This percentage was found to be only slightly higher in non-recurrent, successfully treated, MDD.^{3,4} After CBT, 12 of the 20 patients became fully asymptomatic. They had a significantly longer survival time (mean = 101.2 weeks; SD = 9.8 weeks) compared with the 8 patients who still had residual symptoms (mean = 72.7 weeks; SD = 28.9 weeks) by survival analysis (log-rank test, $\chi^2_1 = 4.82$; $P < .05$). There were 2 cases of fully asymptomatic status on retest in the CM group.

When the patients were divided according to the presence of residual symptoms regardless of treatment assignment, the differences became striking (log-rank test, $\chi^2_1 = 11.28$; $P < .001$). The 14 patients without residual symptoms had a significantly longer survival time (mean = 98.4 weeks; SD = 14.3 weeks) compared with the 26 with residual symptoms (mean = 65.4 weeks; SD = 27.7 weeks).

These data thus confirm the predictions by Judd et al: abatement of residual symptoms according to the sequential treatment strategy seems to be a key factor. The relationship between residual and prodromal symptomatology—ie, the rollback phenomenon⁵—seems to be important: prodromal symptoms of relapse tend to mirror those of the initial episode and some residual symptoms may progress to become prodromal symptoms of relapse.⁶

It cannot be determined from our study, however, whether enhancement of well-being by a specific therapy^{7,8} might have played a protective role. Indeed, there were individual patients with residual symptoms who did not relapse and patients who were fully asymptomatic who did. The neglected area of psychological well-being warrants further investigation.⁹ The time has come to switching gears in the treatment of mood disorders: too often clinicians have partial therapeutic targets, neglect residual symptoms and equate therapeutic response with full remission.¹⁰

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