Fetal Hypoxia, Genetic Risk, and Schizophrenia

TO THE EDITOR: Theo G.M. van Erp, M.A., and co-workers (1) presented interesting data that link fetal hypoxia to smaller hippocampal volume and subsequent greater risk of schizophrenia. Commenting on their results, the authors asserted that the differences they found between patients' hippocampal measures and those observed in unaffected siblings and unrelated comparison subjects were unlikely to be a consequence of the larger magnitude of the hypoxic event among probands than among healthy comparison subjects. However, analysis of the obstetric histories of schizophrenic patients' mothers has often revealed a significantly higher risk of unfavorable pregnancy outcome (2, 3). Among schizophrenic patients' mothers, pregnancies end with miscarriage or preterm birth more often than among comparison subjects (4). It is therefore reasonable to suppose that the mothers of schizophrenic patients are, in general, at greater risk of suffering from obstetric complications, which might determine the death of the fetus or the birth of brain-damaged offspring.

This enhanced risk of negative pregnancy outcome may be under genetic control: only the children who actually suffered brain damage would develop schizophrenia—if they survived the initial cerebral damage (4). However, even if it is under genetic control, it is unlikely that the factor conditioning fetal hypoxia always exerts its effect with identical magnitude. Where there is equal exposure to risk, as in the case of twins, one twin may still be more at risk: monozygotic twins would show similar reactions to harmful stimuli to a larger extent than dizygotic twins. This may explain the incomplete concordance among twins. What evidence did Dr. van Erp and colleagues find that a larger magnitude of the hypoxic event does not explain all the differences they found?

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Drs. van Erp and Cannon Reply

TO THE EDITOR: In our article, we presented the finding of smaller hippocampal volumes among schizophrenic probands who experienced fetal hypoxia than those who did not, a difference that was not noted in their full siblings and/or in unrelated healthy volunteers. We interpreted this finding as potentially reflecting a genotype-environment interaction. Dr. Preti suggests that the result may actually reflect the significantly higher risk of unfavorable pregnancy outcome among schizophrenic patients' mothers, which in turn may be under genetic control (a genotype-environment covariation), or more generally, a greater degree of hypoxic complications in the patients.

We interpreted our data as consistent with a genotype-environment interaction rather than a genotype-environment covariation because we did not find evidence of a greater number of hypoxia-associated obstetric complications in the probands or their full siblings in relation to the comparison subjects in this study group (1, 2), which would have been predicted in the case of genotype-environment covariation. We did, however, observe more hypoxia-related complications among the patients with an early age at onset.

Measures of fetal hypoxia based on standard records collected at the time of pregnancy and delivery, as used in our study, are likely to be less biased than measures taken from maternal interview or other retrospective scores. Nevertheless, the records-based measure of hypoxia used in this study is dichotomous, coding the presence or absence of hypoxia-associated obstetric complications. Ideally, fetal hypoxia would be assessed with direct quantitative measures, such as fetal blood oxygenation level.

We thus accept the possibility suggested by Dr. Preti that the magnitude of the hypoxic obstetric complications in the patients may have been larger than the magnitude in the siblings and comparison subjects, a possibility that awaits testing in studies with direct quantitative measures of fetal blood oxygenation.

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Comparing Depression Treatments

TO THE EDITOR: The comparison by Nicola Casacalenda, M.D., et al. (1) of pharmacotherapy and psychotherapy for major depression included six studies. Only three had a placebo condition. Without a placebo comparison group, we cannot address the question of superiority of drug or psychotherapy because a finding of no difference may mean that neither treatment had a therapeutic effect. Although many drugs have shown greater antidepressant activity than placebo, that does not occur in all studies. Imipramine, perhaps the antidepressant most often compared to placebo, was shown in 31% of 36 trials as not superior to placebo (2). Indeed, one of the trials referred to by Dr. Casacalenda et al., a study by Elkin et al. (3), had as its main a priori hypothesis that neither imipramine nor psychotherapies would show an advantage over placebo.

If we examine the three studies that used a placebo, we get a different picture from the meta-analysis of the six studies. As

mentioned, the study by Elkin et al. (3) showed no advantage for the drug or two psychotherapies, although a secondary analysis after stratification of the study group by severity indicated that imipramine and one type of psychotherapy showed an advantage over placebo.

Mynors-Wallis et al. (4) compared amitriptyline, problem-solving psychotherapy, and placebo and reported after 6 weeks of treatment—the most relevant duration since giving ineffective antidepressants for longer than 6 weeks is not usual practice—that amitriptyline was not superior to placebo but psychotherapy was. This study does not address the comparison of psychotherapy to drug treatment since the most relevant comparison (at 6 weeks) showed no drug effect for a well-proven drug treatment. It is not helpful to compare psychotherapy to drug treatment if that proven drug happens not to show efficacy in the study group.

A third study, by Jarrett et al. (5), compared phenelzine and cognitive therapy to placebo in subjects with atypical depression. Their main outcome measure was a repeated-measures analysis of covariance with scores on the Hamilton Depression Rating Scale. Although the main effects of time and treatment were significant, the most relevant measure—the interaction between treatment and time—was not. Nevertheless, pairwise comparisons showed significant differences most weeks between each active treatment and placebo and no difference between the active treatments.

Dr. Casacalenda et al. (1)used as their measure of remission a final score of 7 or lower on the Hamilton depression scale. Jarrett et al. (5) used a threshold of 6 or lower on the Hamilton depression scale. The overall chi-square values for remission with the three treatments (phenelzine, psychotherapy, and placebo) were significant; the pairwise comparison of phenelzine and psychotherapy was not. This led the authors to conclude that the treatments were effective and equivalent. Yet, the risk ratio of cognitive psychotherapy and phenelzine was 1.1, with a 95% confidence interval of 0.7 to 1.9. This indicated a wide spread and a substantial lack of precision, leading, I believe, to reasonable doubt about the equivalence of the treatments.

I conclude that none of these studies supports the contention that drug therapy and psychotherapy are equivalent in the treatment of major depression, and a meta-analysis of studies that includes those without a placebo cannot answer the question.

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Dr. Casacalenda and Colleagues Reply

TO THE EDITOR: We thank Dr. Rifkin for his thoughtful comments, in particular for emphasizing the importance of including a meaningful comparison group in any study comparing the efficacy of drugs and psychotherapy for the treatment of major depression. As discussed in our article, this approach "is the only safeguard against…inadequate implementation of pharmacotherapy, and nonspecific treatment effects" (p. 1357).

Dr. Rifkin points out that the study by Elkin et al. (1989) showed no advantage for imipramine or either of two psychotherapies over placebo. However, this conclusion was based on analyses comparing changes in scores on the Hamilton depression scale from pretreatment to posttreatment within each of the treatment conditions. Secondary analyses examining remission, the focus of our review, found that the effects of both imipramine and interpersonal therapy—but not cognitive behavior therapy—were superior to those of placebo.

Dr. Rifkin also concludes—erroneously in our view—that the study by Mynors-Wallis et al. (1995) "does not address the comparison of psychotherapy to drug treatment since the most relevant comparison (at 6 weeks) showed no drug effect for a well-proven drug treatment." First, that study showed amitriptyline to be superior to placebo at 6 weeks on the basis of another analysis comparing mean scores on the Hamilton depression scale before and after 6 weeks of treatment. Second, the remission rates at 6 weeks (29% for subjects taking amitriptyline versus 3% for subjects taking placebo), although not significantly different (the groups were small), were clearly clinically meaningful. Finally, the results at 12 weeks consistently showed that both amitriptyline and problem-solving therapy were superior to placebo but not significantly different from each other.

Finally, Dr. Rifkin expresses concern regarding lack of precision for the measures of efficacy in the study by Jarrett et al. (1999). Again, we believe this was attributable to the small group sizes in this study and in no way casts doubt on their finding of no difference in efficacy between phenelzine and cognitive therapy since they consistently showed, across five different stringent definitions of remission, that the remission percentages for both active treatments were almost identical to each other and approximately double that for the placebo group.

Therefore, despite the limitations of each study reviewed, the remarkably consistent findings across these studies lead us to conclude, as we did in our original review, that "antidepressant medication…and psychotherapy…were more efficacious than control conditions, but there were no differences between active treatments" (p. 1355).

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Childhood Trauma and Depression

TO THE EDITOR: We reviewed with great interest the recent article by Kate L. Harkness, Ph.D., and Scott M. Monroe, Ph.D. (1), demonstrating a strong link between early childhood trauma and endogenous depression, in contrast to prior work linking early adversity with nonendogenous subtypes of depression (2). However, we are skeptical of these new findings in view of critical exclusions in their data collection, including a lack of consideration of atypical depression and overly narrow inclusion criteria.

Atypical depression, by definition, is characterized by mood reactivity, hypersomnia, and increased eating, in contrast to the lack of mood reactivity, insomnia, and loss of appetite seen in endogenous depression. Subjects with atypical depression thus provide a natural comparison group for linking particular vulnerability factors with endogenous depressive subtypes. Using this latter approach in a community-based sample of 653 individuals with major depression, we previously demonstrated a significant association between early childhood physical and/or sexual abuse and atypical but not endogenous symptoms of depression (3). Biological studies also point to a mechanistic link between atypical depression and severe trauma. More specifically, low baseline cortisol levels and hypersensitivity to low doses of dexamethasone have been found in both posttraumatic stress disorder (4) and atypical depression (5, 6), consistent with a hypothalamic-pituitary-adrenal (HPA) axis that is hyperregulated. In contrast, a large body of work has demonstrated hypercortisolemia and resistance to dexamethasone in endogenous depression, consistent with a stress response that is chronically overactivated and hyporegulated (7). This further suggests that severe trauma is more closely linked with atypical than endogenous depressive symptoms.

Given these links between atypicality and early trauma, the sampling procedure of Drs. Harkness and Monroe becomes problematic in that individuals with chronic depression and many with a "comorbid exclusionary diagnosis" were excluded from consideration in their study. Chronicity and comorbidity are hallmarks of atypical depression (8–10) and are themselves associated with early trauma; thus, elimination of subjects with these characteristics establishes a significant sampling bias.

Another issue relates to the cross-sectional nature of their study, in that many patients with recurrent depression have a fluctuation of neurovegetative symptoms over time; i.e., they may appear endogenously depressed at one point in time, while exhibiting atypical symptoms at other times (11). This is not a trivial point in that we have previously reported that depressed individuals with this fluctuating course have particularly high rates of severe childhood abuse (3). We speculate that several individuals labeled endogenous in the current study would have been designated as fluctuating had this been a consideration, further diluting the authors' ability to find a putative link between early trauma and nonendogenous symptoms.

In sum, it may be that in a heterogeneous group of individuals with major depression, particularly high rates of trauma will be found in those with atypical symptoms, while in a more homogeneous group with nonchronic illness without certain comorbidities, a link with endogenous symptoms will emerge. This is an important consideration in designing and interpreting research linking early trauma with particular depressive subtypes.

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Drs. Harkness and Monroe Reply

TO THE EDITOR: We thank Drs. Levitan and Parikh for their thoughtful comments regarding our article and for giving us the opportunity to discuss the association of childhood adversity to depression subtypes. They note that our report of a significant association of childhood adversity to endogenous depression is inconsistent with their relation of early trauma to atypical but not endogenous depression (Levitan et al., 1998).

This confused us because Dr. Levitan and colleagues did not assess endogenous or atypical depression subtypes. Instead, they examined the relation of trauma to three reverse versus typical neurovegetative symptoms: increased appetite, weight gain, and hypersomnia versus decreased appetite, weight loss, and insomnia. We assume they meant to equate reverse neurovegetative symptoms with atypicality and typical neurovegetative symptoms with endogeneity. However, the relation of stress to depression symptoms versus subtypes/syndromes should be distinguished. For example,

these typical symptoms are just as likely to be present in subjects with nonendogenous/nonatypical depression as in endogenous depression. Nevertheless, the comments by Drs. Levitan and Parikh highlight a crucial test that remains to be undertaken comparing endogenous, atypical, and nonendogenous/nonatypical depressive subtypes. This may reveal further specificity.

Another key difference in methods is that Dr. Levitan and colleagues simply coded abuse as present or absent, while we distinguished gradations in trauma severity. While nonsevere childhood adversity was associated with nonendogenous depression, consistent with earlier reports (Levitan et al., 1998, and Parker et al., 1997), severe childhood adversity was strongly associated with endogenous depression. Our fine-grained assessment of childhood adversity thus allowed for greater specificity in describing the relationship between early trauma and depression.

Drs. Levitan and Parikh support their contention by noting the differential association of atypicality and endogeneity to HPA axis dysregulation (Yehuda, 2001; Anisman et al., 1999; Levitan et al., 2002; Gold and Chrousos, 2002). The neural consequences of stress are complex and depend on the nature of the stressor (e.g., acute versus chronic) and the developmental period of exposure. For example, while exposure to acute traumatic stressors leads to a hyperregulated HPA axis, a history of chronic and/or uncontrollable stressors may lead to hypercortisolemia (1). Furthermore, certain forms of stress induce anhedonia in rodent models, as assessed by deficits in reward reactivity (2). These points reinforce the inference that early trauma has important implications for endogenous depression.

Drs. Levitan and Parikh note that we used a cross-sectional study design that excluded participants with chronicity and certain comorbidities. However, most of the subjects (89%) had recurrent illness. In addition, a number of comorbid disorders that are strongly linked to trauma (e.g., anxiety disorders) were not excluded (3). Most important, childhood adversity remained significantly associated with endogenous depression even after control for depression history and comorbidity.

It is unclear how our cross-sectional strategy diluted our ability to find a relation between childhood adversity and nonendogenous depression. Although it is possible that some of our participants with endogenous depression had a fluctuating course and were at one time exhibiting nonendogenous/atypical symptoms, such a course seems just as likely among the nonendogenous participants. Nevertheless, we were limited in our ability to illuminate the relation of childhood adversity to syndrome development across and within episodes. We urge researchers to pursue longitudinal studies examining this question.

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Randomized Controlled Trials

TO THE EDITOR: We read with great interest the article by Murray B. Stein, M.D., and his colleagues (1), which reported on a double-blind randomized study. Randomized controlled trials are always cited as the gold standard for detecting treatment efficacy. However, they often can be flawed in design and are not immune to bias. The relevance of such a study has been criticized on the grounds of small group size, selection bias, and improper random assignment to groups.

The authors failed to provide information about how many subjects were initially assessed, how many subjects were excluded from study, and any reasons for exclusion. We do know the rate of participation, the rate of response, and the implications for generalizability and future research. The selection of patients in randomized controlled trials has been a controversial issue. In this context, the guidelines for the Consolidated Standards of Reporting Trials (CONSORT) state that all patients assessed for trials should be accounted for and that the report should be accompanied by a diagram that explains what happened to all of the patients involved in the trial (2).

Random allocation to intervention groups remains the only method of ensuring that groups being compared are on an equivalent footing at the outset of the study, thus eliminating allocation and confounding biases. In this particular article, information was lacking on both components of randomization, concealment and method. Improper randomization can introduce serious allocation bias. Assessment of the quality of randomization in published trials has consistently found flaws (3, 4). CONSORT guidelines have emphasized that methods of randomization should be clearly reported (2). It has also been reported that trials with adequate or unclear allocation concealment may yield larger estimates of effect than those with inadequate concealment. This exaggerated estimate of treatment effects reveals a meaningful level of bias. In the absence of adequate information on the methods of randomization, the possibility of allocation bias may be raised. Elimination of bias would have been possible if the authors of this article had strictly followed CONSORT guidelines.

Finally, the authors failed to communicate effect size precisely. Since they presented their results almost solely as p values, it is difficult to understand their meaning. It is possible for small effect sizes to become statistically significant, which is evident in this study. However, it is the precision of effect size rather than the level of significance that determines how much faith a critical reader will have in the authors' results. We also do not know the response rate and the remission rate, which determine the clinical importance of the results.

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Dr. Stein and Colleagues Reply

TO THE EDITOR: We thank Drs. Jainer and Chawla for their interest in our work. We agree with the gist of their letter emphasizing the importance of detailed reporting of methods for randomized controlled trials. The CONSORT guidelines provide an excellent framework for publication of the results of randomized controlled trials, and we agree that each of the elements recommended therein should ideally be provided. Earlier drafts of our article did, indeed, include more of these methodological details, but several pieces of information were deleted as we worked to make our manuscript fit the Brief Report format. We support provision of additional space to permit more rigorous adherence to the CONSORT guidelines in all future reports in the *Journal*. It will be up to the *Journal*'s editors, of course, to determine if this is feasible.

We will use this opportunity (and space) to provide some of this additional information. The subjects included in this report were all 19 participants who met the entry criteria and agreed to participate; no other subjects were enrolled. We believe that we discussed the unique characteristics of our subjects (i.e., treatment-resistant male combat veterans) and the resultant probably limited generalizability of our results in sufficient detail in the report. Randomization was conducted by using a random-numbers table prepared by our research pharmacy. The code for randomization was also maintained in the pharmacy, where it could be broken in an emergency—which did not occur. Medications (active drug and identically appearing matching placebo tablets) were provided by the drug's manufacturer and dispensed by the research pharmacy. We have no reason to believe that the double blind was compromised at any point during the study. We did not report effect sizes in the report, but these were easily calculated from the data provided (i.e., mean change/standard deviation). The effect size (≈1.0) was actually large for the drug-placebo difference in change on the Clinician-Administered PTSD Scale, as it would have to be in order to be statistically significant with such a small group. Response rates were clearly indicated in the article.

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Mental Disorders Among Military Personnel

TO THE EDITOR: We greatly enjoyed the article by Charles W. Hoge, M.D., et al. (1). They made excellent points on mental illness and mental health care in the military. Our one concern was a possible underreporting of outpatient substance abuse. Data collection systems for patient encounters in military outpatient settings challenge providers in keeping accurate accounts of client diagnosis or even encounters. As part of a quality-improvement program at military mental health clinics, 1 year's worth of charts (for nearly 900 individual patients) were reviewed for diagnosis, health care use, comorbid substance use disorders, severity of illness, and health care use. We generally agreed with the findings of the authors but note that our rate of substance use disorders, specifically alcohol abuse and dependence, was much higher and closer to 50% for all 900 clients. Other published studies have also reported fairly high rates (2, 3). This did not take into account the local drug and alcohol clinic's population, which the authors presumably included in their analysis. Our mental health clinic and drug and alcohol clinic, in which this quality assurance project was conducted, did not consistently use the collection systems referred to in the article until 1999 or later. It is likely that other clinics did not use the data systems accurately as well. Oftentimes providers code for only for one diagnosis (e.g., depressive or adjustment disorder); hence, substance use disorder is not recorded. We would be interested in the authors' comments on these issues and thoughts for future study.

The views expressed in this manuscript are those of the authors and do not reflect the official policy or position of the Department of the Army, the Department of Defense, or the U.S. government.

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TO THE EDITOR: As a former military psychiatrist and military psychiatric researcher with over 12 years of service, I read with interest the article by Dr. Hoge and colleagues. Their main conclusions 1) that mental disorders are common in military personnel as discharge diagnoses and 2) that far more attrition from military service occurs after mental disorder diagnoses than from physical disorders is far from "striking." What is surprising is the apparent lack of appreciation by the epidemiologist authors of the military medical regulations that specifically discriminate against service members with mental disorders to a far greater degree than those with primarily physical ICD-9 diagnoses. One could argue the merits of this discriminatory approach for some personnel in sensitive positions (a point not made in the article), but the fact remains that such regulations would readily account for this differential attrition rate. The authors cited the widespread use of antidepressants by military personnel as an ex-

ample of why they appeared puzzled by their attrition findings; of greater concern is their false statement that the use of psychotropic medications is "not grounds for separation" (p. 1582). I respectfully beg to differ.

On many occasions I advocated for my patients on active duty who desperately wanted to remain in the military after recovery from an episode of mental illness. Patients taking medications who were in full remission from cyclothymia, bipolar disorder, major depressive disorder, obsessive-compulsive disorder, and other conditions that did not include psychotic symptoms were routinely discharged involuntarily in spite of expert military psychiatric opinion recommending retention. I would not deem this to be attrition; it was involuntary separation and, as such, should not be included in the attrition statistics. If an active duty member with an illness is not deemed "worldwide qualified," he or she is medically discharged, irrespective of his or her wishes and in spite of attaining full remission. This is true even if the service member's job is clerical, secretarial, medical technical, or one of the majority of military careers that do not involve the use of—or access to—firearms, explosives, aircraft, nuclear weapons, or highly classified information. Another clear example of enforced involuntary separation—not attrition—is that any patient treated with lithium is not considered worldwide qualified, irrespective of diagnosis or clinical condition.

Given the serious institutional discrimination against service members with mental disorders, "equal access to 'free' medical care" (p. 1581) should not imply that those with a need or desire for treatment will necessarily receive this care. In fact, it is widely known by service members that reporting for mental health care may be a death sentence for a promising military career. The figures reported by Dr. Hoge et al. for mental disorder diagnoses (11.9% for any diagnostic position) should therefore be viewed as, at best, a minimum rate. Given the protections afforded most civilian employees who develop mental illness compared to the institutionalized discriminatory policies against retention of many of these service members who report or are forced to present for evaluation (commander-directed evaluations: members must report for psychiatric evaluation or face disciplinary action), it should not be surprising that the occupational attrition rate is high. This finding is not generalizable to most nonmilitary populations.

I do not quibble with the authors in their statement that the "U.S. military remains one of the most highly respected and effective military organizations in the world" (p. 1582), but to imply in their last paragraph that their data "do not suggest that the impact of mental disorders is greater among service members than in the general population" (p. 1582) suggests that the authors are unfamiliar not only with military medical regulations regarding the administrative management of personnel with mental disorders extant during their study period but also with the hard-won protections many Americans with psychiatric disorders enjoy in civilian venues. Their final conclusion that "mental disorders may have a greater adverse influence on occupational functioning than any other medical illness category" (p. 1582), is not supported by their data if one takes into account the administrative context outlined.

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Dr. Hoge and Colleagues Reply

TO THE EDITOR: Regarding the letter by Dr. Staudenmeier and Dr. David Brown, we agree that military ambulatory data systems (like other medical data collected for administrative purposes) have limitations, and to the extent that only primary diagnoses are reported, the prevalence rates of alcohol and substance-related comorbidity are underestimated.

Although Dr. George Brown has practiced as a military psychiatrist researcher, his letter unfortunately illustrates commonly held misconceptions regarding the generalizability of findings from studies in military populations. Certainly, caution is warranted, but our research suggests that there are more similarities than differences between military and civilian populations (1). For example, the rates of inpatient and ambulatory mental health care use that we reported are similar when demographically adjusted to civilian data from statistics from the National Center for Health Statistics. Adjusted suicide rates are virtually identical (2). The association of high attrition among service members diagnosed with mental disorders extends the findings in nonmilitary populations that disorders such as major depression are on par with diabetes and other chronic medical conditions in their occupational and social impact (3). Regarding attrition, currently approximately one-third of all soldiers who enlist in the military services fail to complete their first term of service, a rate comparable to the college dropout rate in the United States. Our study begins to define the relationship between mental disorders and the risk of occupational attrition in an important segment of the young adult population.

We do not agree that "discrimination" explains the differences in attrition that we reported, although we acknowledge that there are unique interfaces in the military between mental and behavioral problems, occupational requirements, administrative practices, and the mental health care system. For example, behaviors related to a personality disorder or alcohol abuse that can lead to rapid termination from a civilian job may instead lead to mental heath referral, counseling, and rehabilitation efforts before administrative separation procedures are initiated. Failure to adjust to a new civilian job setting may lead to resignation, but in the military, the process of separation sometimes affords care that may yield an adjustment disorder diagnosis. These examples do not reflect discriminatory practices or differences in protections afforded to civilian Americans with psychiatric disorders compared with military service members. One could even argue that military service members have higher levels of protection.

In today's military, the average service member can expect to be deployed overseas several times in his or her career, and there are no occupations (including clerical, secretarial, or medical technical) that are exempt. It is true that service members taking mood stabilizers such as lithium are usually not considered deployable and may be medically separated (often with disability benefits if the condition started while they were on active duty); however, bipolar disorders account for only 2% of the diagnoses of mental disorders. Regulations regarding medical separations for nonpsychotic mood or anxiety disorders are based on the severity and persistence of symptoms that interfere with duty (4), not on the use of psychotropic medications per se, and many service members with these conditions remain on active duty. Psychotropic

medications, particularly the newer antidepressants, are now routinely used, even in deployed environments, as long as they do not require blood-level monitoring and have wide safety margins.

We agree with Dr. George Brown that service use does not equate with treatment need. The Epidemiologic Catchment Area Survey (5) and the National Comorbidity Survey (6) have shown that in the general population only 25%–30% of people with diagnosable mental disorders receive professional help. This figure is probably lower in the military, given the stigma and the predominantly male population. Additional research is needed to understand the reasons for attrition related to mental disorders in the military and to design prevention and intervention strategies that will reduce the barriers to care for patients, encourage earlier treatment, and reduce the occupational impact of these disorders.

Finally, research on veterans' health issues has been widely published and accepted, even though the population is highly selected and the health care system is unique. Just as we have learned from veterans about trauma, health, and aging, we believe the military offers a rich and largely untapped environment for achieving new insights into the epidemiology of mental disorders and their impact on occupational functioning in younger adults.

The views expressed are those of the authors and do not reflect the official position of the Department of Defense or the Department of the Army.

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Suicide and Major Depression

TO THE EDITOR: I wish to offer some comments on the article by Maria A. Oquendo, M.D., et al. (1). The topic of their study is important—how to reduce the occurrence of suicidal acts in people suffering from major depression. However, the present study contains some flaws in methods and logic that deserve comment.

In this naturalistic, prospective study, the authors wanted to demonstrate an association between antidepressant treatment and reduced acts of suicide. They did not find one and concluded that the reason was inadequate doses of antidepressant medication. However, their article did not support this conclusion. Their Discussion section stated, "We were unable to demonstrate that pharmacotherapy of major depression protected patients against suicide attempts," and then went on to note that "nine (43%) of the 21 follow-up suicide attempts occurred while patients were receiving adequate treatment" (p. 1748). This is indeed the authors' important finding. The problems with this article are in the first sentence of the discussion: "Relapse of recurrence of major depression increased the risk of suicide attempt during the 2 years after discharge from the hospital, *underlining the importance of optimal maintenance antidepressant treatment as a suicide prevention strategy* [italics added]" (p. 1748). But this association is precisely what their article does *not* show.

We know that the authors believe that there is a significant association here, as witnessed by their ample citations of European studies to support it. But their own study does not support it, and the authors think they know why—inadequate antidepressant dosing of the subjects during the study period. But even this case is not made convincingly. In their Method section, they asserted (without apparent reference) minimum adequate daily doses for 25 antidepressants. They did not state their basis for assigning these standards, by which they then measured adequacy of treatment. I do not disagree with the doses themselves (except for the authors' recommendation of 400 mg/day of trazodone) but only with their treating these "guidelines" as if they were universally accepted and clinically meaningful. The act of using something as a premise that is in fact a conclusion to be proven is a form of begging the question, an error in the logic of question framing.

This problem is compounded in the Results section, where the authors attempted to show that over one-half of their study group was underdosed. They cited mean daily doses of fluoxetine (32.9 mg/day), paroxetine (42.5 mg/day), sertraline (120.7 mg/day), and citalopram (38.3 mg/day) as apparent evidence of underdosing. Yet these doses met the authors' own standards! I work in a large group practice and know that these four antidepressants together constitute about 90% of all antidepressants in our setting. So were the patients in this study actually underdosed?

The authors can certainly be excused for following the common belief that antidepressants treat both depression and suicidality. But the inability of their study to support this belief should serve to make us cautious about our assumptions and careful about our questions. If the 43% of the authors' study group receiving adequate antidepressant medication showed significant suicidal behavior after treatment, then something else must be at work. One cannot ascribe this to treatment resistance, as some authors do. Suicidality is not synonymous with depression, and treatment does not equal medication. An article such as this does not suffer so much from poor science as from a (common) failure in psychopharmacology research to "think outside the bottle." At this time in

our field, we still have not proven that selective serotonin reuptake inhibitors are clinically better than placebo (2). We all know that depression and acts of suicide are mentally complex phenomena. Until we begin studying them in sufficient depth, we will only get articles that raise more questions than they answer.

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Drs. Oquendo and Mann Reply

TO THE EDITOR: We found that 43% of the patients who attempted suicide during the follow-up period of our study met minimum standards for adequate pharmacotherapy for depression. Therefore, we do not believe that this finding means that optimal aggressive pharmacotherapy for depression does not reduce the occurrence of suicidal acts in those with major depressive episodes. Rather, we think that it reflects the problem of undertreatment more than treatment-resistant depression contributing to suicidal behavior and, in some cases, the effect of comorbidity with axis II cluster B personality disorder. As Dr. Wright points out, our literature review supported this interpretation of our data.

Dr. Wright objects to the choice of minimum adequate daily doses. He is referred to Sackeim et al. (1) as the basis for the medication standards used in our study. Dr. Wright also objects to our statement that most of our subjects received suboptimal antidepressant treatment. However, adequacy of treatment is related to dose *and* duration of treatment. Therefore, without both pieces of information, a complete judgment about the adequacy of the treatment cannot be made.

We agree with Dr. Wright that suicidality and depression are not synonymous. It is our opinion that in those at risk for suicidal acts, the presence of an episode of depression increases the risk for acting on suicidal thoughts. This view is supported by the increased odds (by sevenfold) of making a suicide attempt when a major depressive episode occurs during a follow-up period.

Of course, psychotropic interventions are not the only tool in the clinician's armamentarium. However, they are a critical element in the continuation treatment of severe major depression in inpatients.

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Sensitivity of the D8/17 Assay

TO THE EDITOR: Mae S. Sokol, M.D., and colleagues (1) recently reported a significantly higher rate of D8/17 positivity among 16 adolescents with anorexia nervosa (81%) than among 17 psychiatric comparison subjects (12%). The mean percentage of D8/17 positivity might "be useful in identifying PANDAS [pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections] anorexia nervosa" (p. 1431). The results of that investigation are similar to findings in two previous studies (2, 3) demonstrating excellent performance of the D8/17 assay in distinguishing patients with obsessive-compulsive disorder (OCD) from healthy comparison subjects—85% to 100% of OCD patients were D8/17 positive in comparison with 5% to 15% of healthy comparison subjects. However, our subsequent experience has been less satisfactory and suggests that the assay is not yet reliable enough to be used as a diagnostic tool.

In our work, a total of 216 samples were gathered over a 4-year period from 26 subjects with Sydenham's chorea, 42 subjects with OCD and/or tic disorders (PANDAS subgroup), and 19 healthy comparison subjects. Samples were obtained at the National Institute for Mental Health (NIMH) by workers blind to patient diagnosis and sent to Rockefeller University, where assays were performed by immunofluorescent microscopy before August 1998 and subsequently by flow cyometry, according to methods previously reported (4). Written informed consent or assent was obtained from all subjects, who were participating in studies of Sydenham's chorea and OCD that were approved by NIMH institutional review boards.

Overall, the sensitivity of the D8/17 assay for the 68 patients with Sydenham's chorea or OCD/tics was 61.8% (42 assays were positive). Of concern, only 12 assays (46.2%) obtained from the 26 Sydenham's chorea patients were positive, which is significantly lower ($z=5.2$, $p<0.001$) than that previously reported for patients with rheumatic fever (89%–100% were D8/17 positive) (5, 6). Thus, the D8/17 assay failed to "diagnose" the majority of the patients with Sydenham's chorea. Furthermore, the reliability of the assay was suboptimal. Longitudinal observations of 54 subjects tested at random intervals over the study period demonstrated test-retest agreement of 61.1% (N=132) for the 216 samples assayed (kappa=0.18). Of particular concern, agreement was observed in only 48 of 61 split samples (78.7%, kappa=0.48).

In conclusion, the sensitivity of the D8/17 assay decreased to unacceptably low levels during the period of observation. The declining sensitivity may have been due to changes in methods or the characteristics of the monoclonal antibody. If so, the performance might be improved by reversion to earlier techniques. Meanwhile, it appears premature to include the D8/17 assay in the diagnostic workup of patients with neuropsychiatric disorders such as OCD, tics, and anorexia nervosa.

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Dr. Sokol Replies

TO THE EDITOR: The inconsistency of the D8/17 test reported by Dr. Hamilton and colleagues (1) indicates that work probably needs to be done to make the test more reliable as a diagnostic tool. This is particularly important because recent research (2) also points to a possible autoimmune process in some cases of eating disorders. Fetissov et al. (2) reported that there might be an autoimmune disorder involving specific brain structures responsible for feeding behavior in some cases of anorexia and bulimia nervosa.

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