Retreatment With Clozapine After Erythromycin-Induced Neutropenia

Agranulocytosis and neutropenia are significant adverse effects of clozapine treatment (1). We report the case of a patient who was retreated with clozapine several years after developing neutropenia under unusual circumstances.

Antonio, a 17-year-old adolescent with childhood-onset schizophrenia, was admitted for clozapine treatment. Despite adequate trials of chlorpromazine, thioridazine, trifluoperazine, molindone, and haloperidol, he had chronic hallucinations and delusions as well as aggressive behavior that necessitated hospitalization for over a year. Over 6 weeks, his dose of clozapine was increased to 600 mg/day with good response and no significant side effects.

Over the following 5 years Antonio continued to improve at this dose. He was able to live with his parents and attended an outpatient day program. At age 21 he developed a fever and sore throat and was treated with erythromycin. Before he began taking the antibiotic, his WBC count was 14,000 cells/μl; it had consistently been above 7,400 cells/μl in the previous month. Within 2 weeks his absolute neutrophil count had dropped to 918 cells/μl. He also had a WBC count of 5,100 cells/μl, so clozapine therapy was discontinued.

In the subsequent 2 years Antonio underwent gross deterioration, again resulting in chronic hospitalization. Despite appropriate trials of haloperidol, risperidone, and olanzapine, he remained profoundly impaired.

At age 24 Antonio was retreated with clozapine, the only antipsychotic that had given him significant benefit; the dose was slowly titrated to 400 mg/day. During this period he developed a fever with no apparent focus of infection. There was an appropriate rise in WBC and absolute neutrophil counts, so conservative management aimed at fever reduction was employed. Within several days both his temperature and WBC count had returned to normal. He was discharged with clozapine therapy, 400 mg/day. Six months later he was doing well clinically and was again living at home.

This report illustrates the case of a patient with refractory schizophrenia who responded well to clozapine treatment. The addition of erythromycin therapy precipitated neutropenia and prevented the continuation of clozapine treatment. However, the patient was retreated 2 years later without difficulty. Because neutropenia almost invariably occurs within 3 months of the initiation of clozapine treatment (1), the development of neutropenia after 5 years is unusual. This suggests that the interaction of clozapine with erythromycin was the precipitating factor for the patient's blood dyscrasia, particularly since erythromycin-induced agranulocytosis has been reported (2). Erythromycin has also been associated with increased clozapine plasma concentrations and a subsequent seizure (3).

In view of clozapine's efficacy in patients with schizophrenia, and because of its adverse effects and drug interactions, the addition of other medications to an established treatment regimen of clozapine should be undertaken carefully. Additionally, in patients who develop neutropenia under unusual circumstances, retreatment with clozapine should be considered if previous response has been good.

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Exacerbation of Psychosis by Phenylpropanolamine

We report the case of a patient initially treated for methamphetamine psychosis whose psychotic symptoms recurred while she was taking phenylpropanolamine.

Ms. A was a 31-year-old woman with a history of methamphamine abuse who was initially admitted to the inpatient psychiatry unit with a depressed mood, command hallucinations, and paranoid delusions. She had been using methamphetamine heavily up until 3 weeks before admission. Her depressive symptoms, including anhedonia, decreased energy, increased sleep, suicidal ideation, and tearfulness, worsened 2 months before admission. In addition, her psychotic symptoms had been present for many weeks but had been getting progressively more severe. In the hospital, treatment with paroxetine was initiated because it had reportedly been effective previously in spite of episodic methamphetamine use. Ms. A was also treated with perphenazine. Her depressive symptoms improved, and her psychotic symptoms disappeared over 3 weeks. At discharge, she was no longer psychotic.

Six months later Ms. A was readmitted to the inpatient psychiatry unit after a 2-week recurrence of command hallucinations and paranoia. The results of a urine drug screening test were negative for methamphetamine; there was no historical evidence of resumed use. Approximately 3 weeks before admission Ms. A was prescribed a combination of phenylpropanolamine, 75 mg, and guaifenesin, 400 mg, for congestion. She had also been taking cimetidine for 1 month for gastritis. In the hospital she continued to received paroxetine, perphenazine, and oral contraceptive pills, which she had been taking as an outpatient. The congestion medication and cimetidine were stopped. Within 3 days the voices and paranoia had disappeared, and she was discharged.

It is commonly accepted that methamphetamine use can cause psychosis. It has also been reported that chronic exposure to methamphetamine may alter the response to stimuli, resulting in a recurrence of psychotic symptoms in abstinent patients (1, 2). For example, there may be an increased sensitivity to psychosis after exposure to stimulant amines (3). To our knowledge, psychosis activated by phenlypropanolamine has not previously been documented. We report that phenylpropanolamine can cause a recurrence of psychotic symptoms that were initially precipitated by previous methamphetamine use. It is unclear whether the concurrent

administration of cimetidine, an inhibitor of hepatic metabolism, elevated the patient's serum phenylpropanolamine level, although she did not demonstrate peripheral signs of toxicity. Once treatment with cimetidine and phenylpropanolamine had been discontinued, her psychosis remitted. Caution must clearly be used in prescribing phenylpropanolamine to former methamphetamine users with histories of psychosis. It is possible that other stimulant decongestants may be hazardous in these patients as well.

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Serotonin Syndrome From Addition of Low-Dose Trazodone to Nefazodone

Serotonin syndrome, a potentially fatal condition of serotonergic hyperstimulation, has been characterized by diagnostic criteria that include at least three of the following: mental status changes (confusion or hypomania), restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, and incoordination (1). Nefazodone has previously been implicated in two cases of serotonin syndrome, one with paroxetine (2) and one with valproic acid (3), whereas trazodone has been implicated in combination with buspirone (4), paroxetine (5), fluoxetine (6), and amitriptyline with lithium (7). To our knowledge, this is the first report of serotonin syndrome associated with the combination of nefazodone and trazodone.

Ms. A was a 60-year-old woman with a long history of depression and hypertension. After a relapse of depression due to noncompliance with her medication, nefazodone therapy was initiated at 200 mg/day and increased to 400 mg/day 6 weeks before she was seen in the emergency room. Four days before admission she was evaluated for an exacerbation of her depression. Her dose of nefazodone was raised to 500 mg/day and trazodone, 25–50 mg/day, was added as a hypnotic. Ms. A used trazodone for three nights. She was seen in the emergency room after her blood pressure increased to 240/120 mm Hg when she measured it at home.

Ms. A reported intermittent numbness of the right side of her lips and nose and the fingers on her right hand, which improved with time. She described an appearance of flushed pruritic skin for a day. She noted nausea and several loose stools. Her son found her to be confused, and she reported concentration difficulties.

On examination, Ms. A was restless, hyperreflexic, and diaphoretic (oral temperature: 36°C, pulse: 92 bpm, blood pressure: 255/130 mm Hg, dilated pupils: equal at 4 mm). Her creatinine kinase level was 180 U/liter (normal range: 30–170 U/liter), and her total cholesterol level was 249.8 mg/dl. All other laboratory values were within the normal range. Nefazodone and trazodone therapy was immediately discontinued. Ms. A was treated with labetalol, clonidine, amlodipine, and an increase in her usual dose of irbesartan for high blood pressure. The confusion, restlessness, hyperreflexia, nausea, diaphoresis, flushed pruritic skin, and intermittent numbness all disappeared within 12 hours, and her blood pressure was stabilized at 160 mm Hg systolic pressure within 48 hours.

This patient clearly had an episode of serotonin syndrome meeting at least five of Sternbach's criteria for diagnosis, including confusion, restlessness, hyperreflexia, diaphoresis, and diarrhea (1). Serotonin hyperstimulation can also account for her hypertension, nausea, and flushing (1). A transient ischemic attack was ruled out since this could account only for the transient intermittent right-side numbness; a computerized tomography scan of her head was normal. Furthermore, nefazodone has been associated with paresthesias (pp. 859–862, Physicians' Desk Reference, 53rd ed.). An allergic reaction to trazodone was considered, but this would account only for her pruritic flushed skin. Although it is common practice, the addition of low-dose trazodone as a hypnotic to another serotonergic agent can lead to potentially fatal serotonin syndrome.

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Acute Onset of Auditory Hallucinations After Initiation of Celecoxib Therapy

Celecoxib is a nonsteroidal anti-inflammatory agent that is selective for cyclooxygenase-2. This selectivity offers the ability to control inflammation and pain without some of the side effects of traditional nonsteroidal anti-inflammatory drug therapy, particularly gastrointestinal bleeding (1). The multiple side effects of traditional nonsteroidal anti-inflammatory drugs are well described; they include psychiatric manifestations such as psychosis, delirium, agitation, and depression (2–5). We report a case in which a patient developed overt auditory hallucinations after treatment with celecoxib.

Ms. A, a 78-year-old woman, reported a progressive onset of auditory hallucinations within 10 days of initiating celecoxib therapy, 200 mg b.i.d., for osteoarthritis pain. She reported initially hearing thumping sounds within the first 2 days of therapy, and they progressively increased to the sound of voices calling her name and repeating words from the television and radio. She underwent evaluation by an internist and consulted an otolaryngologist with negative results. She was seen for psychiatric evaluation because of fears that she was "going crazy." Ms. A's concurrent medications included 20 mg/day of quinapril, 240 mg/day of sustained-release verapamil for hypertension, 20 mg b.i.d. of isosorbide dinitrate for angina, 20 mg/day of tamoxifen due to a history of breast cancer, and 500 mg t.i.d. of calcium carbonate for osteoporosis. There had been no changes in her concurrent medication regimen over the past year until the addition of celecoxib.

Ms. A was alert and mildly anxious, with a clear sensorium and intact cognition. She described vivid hallucinations and stated that voices were calling her name and repeating the words of radio and television announcers. She was advised to discontinue the celecoxib; she then reported gradual improvement over the next 3 days. By the 4th day her symptoms disappeared, but she reported increasing pain and was advised by her internist to resume taking the celecoxib at a lower dose—100 mg b.i.d. daily. After 5 days, Ms. A again began hearing voices calling her name and repeating phrases from the television. She was again advised to discontinue the celecoxib, and her symptoms rapidly improved. Because of multiple gastrointestinal side effects from other nonsteroidal anti-inflammatory agents, she resumed taking celecoxib, 100 mg/day, on an as-needed basis. She reports hearing occasional thumping noises but feels able to tolerate them.

Cyclooxygenase-2 is present in brain tissue (1). The potential exists for psychiatric side effects with drugs selective for this enzyme. This patient developed hallucinations that were clearly associated with the initiation of celecoxib therapy and recurred with retreatment. Despite the significant advantages of celecoxib over traditional nonselective nonsteroidal anti-inflammatory drugs in their lack of effects on the gastric mucosa and platelets (1), practitioners must be aware of potential adverse psychiatric events with the use of celecoxib.

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Parenteral Valproate for Control of Acute Mania

Valproate is a safe and effective antiepileptic and thymoleptic drug. An intravenous form has been available since December 1996; it is approved for the treatment of complex partial and absence seizures but not for bipolar disorder (package insert, Abbott Laboratories). A recent case report discusses using intravenous valproate for controlling agitation in an 8-year-old autistic patient (1). We are not aware of any literature on its use for mania.

Ms. A was an 81-year-old nursing home resident with a long history of bipolar disorder, including approximately 10 hospitalizations for manic episodes; her condition was maintained with divalproex and haloperidol therapy. She had recently developed Alzheimer's dementia.

The dementia manifested in growing apathy, with Ms. A often sitting for long periods fully awake but with her eyes closed. It was thought that she was becoming lethargic, and her haloperidol dose was tapered off. This brought no dramatic change, so her divalproex dose was tapered and discontinued. Within a week, Ms. A was euphoric, loud, argumentative, grandiose ("I'm the greatest lion tamer in the Ringling Brothers Circus!"), paranoid, and hallucinating. Soon she refused to take her medications, and a hasty attempt to restart divalproex therapy failed. Finally, she refused all food and fluids, necessitating hospitalization.

Ms. A was admitted to the psychiatric department. Her manic symptoms continued. Attempts to persuade her to take nutrition, fluids, or medications orally failed, and intravenous fluid replacement was begun. Because of her declining nutritional status and persistent agitation, we decided her condition constituted an emergency. With family consent, we began intravenous haloperidol, 1 mg b.i.d. This lessened her agitation but had no effect on her mania or psychosis.

As Ms. A's nutritional status continued to deteriorate, we decided, again with family consent, to administer valproate intravenously. We began with 125 mg of valproate in 100 cc of 5% dextrose in water, infused over 1 hour every 6 hours, and increased the infusion to 200 mg after the first two doses. After 2 days (nine doses), Ms. A's mania cleared. She began eating, drinking, and taking her medications, including divalproex, orally. In the few days until discharge, Ms. A exhibited her baseline playful and pleasantly disoriented dementia ("Get me a beer!"), with no evident psychosis, grandiosity, or other indication of mania. The nine intravenous doses brought her serum valproate level to 53 μg/ml, which had historically been therapeutic for her. She experienced no untoward effects. Ms. A was discharged back to her nursing home with the manic episode resolved.

When acute mood stabilization is required, but the oral route is unavailable, parenteral valproate appears to be a safe and effective alternative. Oral and intravenous total daily doses are equivalent (package insert, Abbott Laboratories). The rapid response in this case suggests that a loading effect might be achieved expeditiously with intravenous administration (presumably with diminished gastrointestinal side effects), although aggressive intravenous dosing for routine control of mania would merit further study for safety.

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Weight Criteria for Diagnosis of Anorexia Nervosa

The primary weight criterion for a diagnosis of anorexia nervosa is a weight less than 85% of what is considered normal for that person's age and height (DSM-IV and ICD-10). According to DSM-IV, a body mass index less than or equal to 17.5 kg/m^2, which originated from the ICD-10 diagnostic criteria for research, is an alternative and somewhat stricter guideline. However, this alternative criterion is not adjusted for age and sex. Because anorexia nervosa typically begins in late childhood, adolescence, or early adulthood, it is crucial to consider age in making a diagnosis because the relation of weight to height changes substantially during this age span. This is highlighted by the fact that with increasing age, the proportion of individuals with a body mass index less than or equal to 17.5 drops dramatically from 57% at 10 years to below 1% at age 35 in the German female population (similar percentages apply to the U.S. population) (1).

From a clinical perspective, the body mass index of a patient can only be interpreted appropriately when the age- and sex-specific distribution of the body mass index is known. Hence, the use of sex-specific age percentiles for body mass index has been proposed in order to assess the degree of underweight in acute anorexia nervosa, to determine target weight, and to assess weight outcome (1, 2). Independent of age and sex, the main DSM-IV weight criterion (less than 85% of expected body weight) corresponds to a body mass index between the fifth and 10th percentiles of the body mass index in both the U.S. and German populations (1). To address the issue of age- and sex-dependent distributions of the body mass index and to introduce a convenient and epidemiologically based definition of the weight criterion for anorexia nervosa, we suggest the use of the 10th percentile of the body mass index as a cutoff for underweight in industrialized countries.

On the basis of these considerations, we warn against indiscriminate use of the two weight criteria, both in clinical practice and research, because misclassifications with potentially serious sequelae can ensue. Thus, a body mass index of 17.5 in a 14-year-old girl is by no means indicative of anorexia nervosa. It is obvious that epidemiological studies cannot readily be compared if they are based on these different weight criteria. It should be realized that a body mass index of 17.5 is a strict weight cutoff only for individuals over age 20. For children, and to a lesser extent adolescents, the body mass index cutoff is less strict than the primary DSM-IV weight criterion.

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Schizophrenias in the Wernicke-Kleist-Leonhard School

The *Journal* regularly highlights the nosology of the schizophrenias from various perspectives (1, 2). Notably, the extension of the schizophrenic spectrum depends on classification (1). We wish to elaborate on the Wernicke-Kleist-Leonhard school within the traditional and current context.

Originally, Kraepelin's dementia praecox and Bleuler's schizophrenias described heterogeneous psychoses with no *restitutio in integrum*. They were unbiased against deficit symptoms. The Wernicke-Kleist-Leonhard school sustained this heuristic notion of the schizophrenias. It rejected nosological hybridism, empirically separating developmentally more conspicuous systematic schizophrenias of insidious onset or course from genetically higher loaded unsystematic schizophrenias inclined to some bipolarity (i.e., periodic catatonia, affective paraphrenia, and cataphasia). Thus, periodic catatonia is but one of three unsystematic schizophrenias that were previously omitted from mention (2). Some well-described conditions dominated by specific deficits were grouped into hebephrenias, which exist only in systematic forms. In fact, various cases of heboidophrenia (Kahlbaum), dementia simplex (Weygandt and Diem), schizoidia (Bleuler and Kretschmer), schizotypes (Rado), latent schizophrenia (Bleuler), and pseudoneurotic schizophrenia (Hoch and Polatin) corresponded clinically to Kleist and Leonhard's hebephrenias. Moreover, Leonhard passionately differentiated early childhood catatonias from mental retardation. Dementia infantilis (Heller) and early infantile autism (Kanner) overlapped to some extent with Leonhard's systematic childhood catatonias, whereas autistic psychopathy of childhood (Asperger) denoted a nonschizophrenic condition.

Currently, DSM and ICD criteria strive for atheoretical consentaneity but impose several inconsistencies. Productive manifestations are appointed as primary gatekeepers for psychoses and schizophrenias that are subtyped but essentially treated as a single entity. Positive symptoms dominate the "A" criteria for DSM-IV schizophrenia. In anamnestic pervasive developmental disorders, DSM-IV defines comorbid schizophrenia as contingent on delusions or hallucinations. Similarly, the inclusion criteria for ICD-10-schizophrenia are largely neo-Schneiderian. Mere duration segregates schizophrenia from schizophreniform disorder. For both, ICD-10 refers to active duration but DSM-IV to total duration as well. Schizotypes are conceptualized either as personality disorders (DSM-IV) or as tightly related to schizophrenia (ICD-10). However, ICD-10 disfavors schizotypes as hardly demarcated from simple schizophrenia and schizoid and paranoid personality disorders. According to DSM and ICD consensus, the

schizoaffective disorders are essentially hybrids. Schizoaffective (Kasanin) and schizophreniform (Langfeldt) psychoses preferentially describe cases of Leonhard's unsystematic schizophrenias or fast-cycling cycloid psychoses. Representing neither schizophrenic nor affective psychoses, cycloid psychoses recur frequently in phases—unlike brief psychotic disorders (DSM-IV)—and without progressing to residua.

According to the Wernicke-Kleist-Leonhard school, the DSM and ICD criteria exclude some cases of schizophrenic psychoses (namely hebephrenias and catatonias) from research on schizophrenias. In other nonschizophrenic (particularly cycloid) psychoses, "schizophrenia" may be misasserted. Supported by genetic evidence (3), Leonhard's classification has just been retranslated (4). For technological sophistication to eventually alleviate a centurial enigma (1), psychopathological disputes (e.g., of primary negative symptoms and alternative dimensional descriptors) must consider the history of the schizophrenias.

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Medication Treatment Versus Cognitive Behavior Therapy

I was disturbed by the mega-analysis of studies of severely depressed outpatients by Robert J. DeRubeis, Ph.D., and colleagues (1), which concluded that cognitive behavior therapy is a treatment equivalent to medication therapy. First, of the four studies analyzed, three used imipramine and one nortriptyline—the latter in modest doses at best. Nevertheless, the authors generalized these two drugs to represent all antidepressant medications. Second, severity was determined by using summed scores on the Hamilton Rating Scale for Depression or the Beck Depression Inventory, as if those alone can tell us the factors most clinicians consider when characterizing a patient's depression severity. For example, were most patients in these studies dysthymic or melancholic? Most clinicians would consider the latter or even major depression without melancholic features to be more severe, whereas they would consider dysthymia more chronic and resistant to medication. Other severity considerations might include the degree of anxiety or agitation, suicidal feelings, suspiciousness or outright delusions or perceptual disturbances, and a history of bipolarity. If we are to take the conclusions of Dr. DeRubeis et al. literally, then a depressed man over 60 years of age with early-morning insomnia, weight loss, mild cognitive problems, psychomotor retardation, and dysphoria is better off with cognitive behavior therapy than with antidepressants and their potential side effects. Does anyone really believe that?

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Dr. DeRubeis and Ms. Gelfand Reply

Our report was more a reaction to treatment guidelines that have been based on scant data than a definitive statement about how specific patients with depression should be treated. In his letter, Dr. Taylor emphasizes important issues about the generalizability of conclusions that can be drawn from any review of empirical research, including our mega-analysis. Specifically, one should not haphazardly generalize our findings to antidepressant medications or doses that were not used in the studies we reviewed, nor should one blithely generalize our findings to all depressed patients. As clinicians, our job is to combine the most relevant research findings with our clinical experience and knowledge of available resources to make the best decision we can about how to proceed in a given case. Indeed, ongoing studies of cognitive behavior therapy versus medication treatment will inform us in the future regarding some of the more specific circumstances that Dr. Taylor describes (e.g., depression subtypes and patient ages).

Until such time, we hope that clinicians will bear in mind the findings summarized in our report. In our mega-analysis, based on four major studies that compared antidepressant medications and cognitive behavioral therapy in the acute treatment of severely depressed outpatients, we found equivalent performance of these two treatment modalities. As for Dr. Taylor's specific concerns, first, especially with severe or melancholic depression, the evidence suggests that tricyclic antidepressants such as those used in the four studies reviewed are at least as potent as other classes of antidepressants, including selective serotonin reuptake inhibitors (1). Second, we understand that there are many ways to define severe depression. As our aim was to present data germane to existing treatment guidelines, we applied the criteria used in those guidelines. Moreover, despite the original investigators' attempts to find interactions of treatment and subtype in the data sets of the four studies reviewed, there is virtually no empirical evidence for the presumed superiority of medication treatment over cognitive behavioral therapy in patients with melancholic depression or in any subgroup of depressed patients for that matter. As for the 60-plus-year-old man with classic melancholic symptoms, we have observed that many such patients benefit greatly from well-delivered cognitive behavioral therapy, just as they do from well-managed antidepressant medication regimes.

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Short Screening Scale for Posttraumatic Stress Disorder

I offer these comments about the short screening scale for posttraumatic stress disorder (PTSD) described by Naomi Breslau, Ph.D., and colleagues (1), both to help those who will use this instrument and to promote better understanding of the roles of sensitivity, specificity, and prevalence in test interpretation (2).

From the authors' Table 3, one sees that when four or more items on the seven-symptom scale are endorsed, sensitivity equals 0.803 and specificity equals 0.973. In the population evaluated, the proportion of individuals with PTSD, or disorder prevalence, was 142/1,830=0.078. Using this prevalence, Dr. Breslau and colleagues correctly calculated the positive predictive value as (sensitivity × prevalence) / (sensitivity × prevalence + [1 – prevalence] × [1 – specificity]) = 0.713 and the negative predictive value as (specificity × [1 – prevalence]) / (specificity × [1 – prevalence] + prevalence × [1 – sensitivity]) = 0.983. The authors should have pointed out, however, that these values are correct only for the prevalence in their group. The prevalence of PTSD has been reported to range from 1% in community-based samples to 75% among rape victims (3). If the cutoff of four or more symptoms is used in a population where the prevalence is 2%, the positive predictive value is 0.378 and the negative predictive value is 0.996; if the same cutoff is used in a population in which the prevalence is 50%, the positive predictive value is 0.967 and the negative predictive value is 0.832.

The authors say that with the cutoff of four or more symptoms, "less than 2% of 'true' cases of PTSD were missed, whereas 29% of subjects without PTSD were falsely identified as having PTSD" (p. 910). This is incorrect. A positive predictive value of 0.713 means that about 29% of the subjects identified as having PTSD do not actually have it, and a negative predictive value of 0.983 means that about 2% of the subjects identified as not having PTSD actually have the disorder. The scale's sensitivity is the probability that it will detect PTSD if a subject has the disorder; the scale's specificity is the probability that a subject without PTSD will be deemed not to have the disorder. So if sensitivity is 0.803, the fraction of "true" cases missed is (1 – sensitivity) = (1 – 0.803) = 0.197, or about 20% of the subjects. If specificity is 0.973, the chance of falsely identifying someone without PTSD as having the disorder is (1 – specificity) = (1 – 0.973) = 0.027, or about 3%.

Dr. Breslau and colleagues say that the cutoff of four or more symptoms is well suited "to maximize the number of true cases of PTSD" detected initially when a subsequent evaluation will be used "to reclassify those who were wrongly classified as having the disorder" (p. 911). However, better cutoffs for such a purpose might be two or more symptoms (sensitivity=0.993) or three or more symptoms (sensitivity= 0.951); these cutoffs would miss only 1% or 5% of the actual cases of PTSD, respectively.

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Dr. Breslau and Colleagues Reply

Dr. Mossman correctly interprets the positive and negative predictive values in Table 3 of our article—namely, the values of those who scored four or more on our scale (defined as cases). A total of 29% did not have PTSD according to the clinical assessment, whereas of those who scored four or more (defined as noncases), 2% did have PTSD according to the clinical assessment. Despite our awareness of the common tendency to confuse positive and negative predictive values with sensitivity and specificity, we regret that we did not avoid this pitfall and that we misstated the positive and negative predictive values as if they were sensitivity and specificity (i.e., using as denominators the number of cases and noncases defined by the clinical assessment instead of by a score of four or more on the screening scale).

However, we disagree with Dr. Mossman in his emphasis on sensitivity and specificity instead of on positive and negative predictive values. The latter constructs are of considerable utility for potential users, who wish to know what proportion of persons identified as cases by the scale would be confirmed by clinical examination.

We wish to emphasize that the prevalence of PTSD in our study is typical of that in recent general population studies, such as the National Comorbidity Survey. Therefore, estimates of the performance of the scale based on this prevalence estimate are useful.

Our recommended cutoff of four or more symptoms was based on the data for both positive and negative predictive values in Table 3. We considered the fact that positive predictive value diminishes rapidly with lower cutoffs (i.e., two or three), whereas the accompanying improvement in negative predictive value is slight. If we were to use a cutoff of two or three instead of four, the number of identified cases that would not be confirmed would double or triple.

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