Alendronic Acid for Antipsychotic-Related Osteopenia

TO THE EDITOR: Hyperprolactinemia is associated with osteopenia and osteoporosis (1). Antipsychotics can cause persistent hyperprolactinemia and menstrual disturbance (2). We report an association of antipsychotic treatment, hyperprolactinemia, and osteopenia and describe the patient's response to bisphosphonate treatment.

Ms. A was a 58-year-old woman with paranoid schizophrenia. She had received trifluoperazine, 10 mg/day, for 2 years, followed by a depot injection of haloperidol decanoate, 125 mg every 2 weeks, for the past 12 years. After starting the haloperidol depot, she was amenorrheic for 18 months. Her periods were then regular until menopause, which occurred 7 years before she was seen. She was taking procyclidine, 5 mg/day, for mild extrapyramidal symptoms and had been stable since her only hospital admission 12 years ago.

Our medication review service gave Ms. A a systematic evaluation of symptoms, side effects, and physical health. The assessment showed a mildly elevated prolactin level (505 mIU/ml, upper limit of normal=450 mIU/liter). Her gonadal hormone levels were consistent with her postmenopausal status (estradiol, 44 pmol/liter; follicle-stimulating hormone, 54 IU/liter; luteinizing hormone, 30.9 IU/liter; progesterone, 1.08 nmol/liter).

In view of her hyperprolactinemia, Ms. A's bone mineral density was evaluated with a dual X-ray absorptiometry scan of her lumbar spine and hip. Her spine and hip t scores were –2.02 and –1.74, respectively, both indicating osteopenia and an increased risk of fracture (3). Her age-corrected scores were low, at –0.67 (spine) and –0.84 (hip), compared to normal values of 0. She was uniparous and had never smoked or breast-fed. Her diet typically included 500 mg/day of calcium. She performed 140 minutes of weight-bearing exercise per week. There was no personal or maternal history of bone fracture or medical conditions.

Ms. A did not wish to change antipsychotic treatment, citing its convenience. She began taking alendronic acid, 5 mg/day, to treat her osteopenia. A dual X-ray absorptiometry scan at 1 year showed that her spine and hip t scores had improved by 7% and 9% to –1.87 and –1.58, respectively. Her prolactin level remained mildly elevated.

Hyperprolactinemia, hypogonadism, and amenorrhea are major risk factors for low bone mineral density (3). Our patient experienced antipsychotic-induced amenorrhea and hyperprolactinemia. The hormonal side effects of antipsychotics may have contributed to the osteopenia in this case, although other factors cannot be excluded. This case highlights several issues. Stable patients may experience undetected side effects with significant health consequences. Medication review programs may ameliorate this risk. High rates of hyperprolactinemia (75% of women, 35% of men), hypogonadism (65% of women, 6% of men), and menstrual disturbance (65% of women) are reported in patients taking antipsychotics (2, 4). Some antipsychotics, such as clozapine, olanzapine, and quetiapine, show less prolactin elevation and may be a treatment option (5). Alternatively, the dose of the antipsychotic could be lowered. For antipsychotic-treated patients with osteopenia for whom changes in medication are unadvised, the addition of a bisphosphonate offers a successful treatment option.

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Extrapyramidal Syndrome and Long-Acting Injectable Risperidone

TO THE EDITOR: The following are reports of three male inpatients who developed extrapyramidal symptoms within 24 hours of an injection of depot risperidone. All three men met DSM-IV criteria for schizophrenia.

Mr. A, a 32-year-old man, had been taking 15 mg/day of olanzapine for the last 4 months. Because of a long history of poor adherence to treatment in the community, we prescribed a depot antipsychotic. Injectable risperidone, 25 mg, was given while Mr. A was taking 15 mg/day of olanzapine. Twenty-four hours after the injection, he developed oculogyric crisis, dysarthria, torticollis, dysphagia, tremor, and rigidity. These symptoms responded to procyclidine.

Mr. B, a 36-year-old man, was taking depot zuclopenthixol decanoate, 400 mg every 2 weeks, for 12 months. Because of extrapyramidal side effects, we decided to change the zuclopenthixol decanoate to injectable risperidone. Instead of his regular depot treatment, Mr. B received 25 mg of injectable risperidone. Twenty-four hours later, his extrapyramidal symptoms worsened. These symptoms remitted in 1 week without specific treatment.

Mr. C, a 28-year-old man, was taking olanzapine, 20 mg/day, for 4 weeks. Because of a long history of poor adherence to treatment in the community, we decided to offer depot medication. Olanzapine was reduced and finally stopped within 1 week. After that, we began treatment with oral risperidone and reached 4 mg/day in 3 days. The next day, a few hours after the injection of 25 mg of risperidone, Mr. C developed akathisia, which responded to lorazepam.

The development of extrapyramidal symptoms within 24 hours of administering the depot was not expected. Despite adherence to current guidelines on switching to long-acting injectable risperidone (1), extrapyramidal symptoms still developed in our patients within 24 hours of the depot injections. These symptoms maybe attributed to the initial release of risperidone in the bloodstream.

After a single intramuscular injection of risperidone, there is a small initial release of drug (<1% of the dose), followed by a lag time of 3 weeks when risperidone is not released. After the intramuscular injection, the main release of the drug starts at week 3 and is maintained from 4 to 6 weeks. The release of the drug begins to decrease at week 7 (2).

To limit the risk of developing extrapyramidal symptoms around the time of the injection, it may occasionally be necessary to reduce or omit the dose of the oral antipsychotic in the days after the injection. Attention should be paid to the half-life of any other depot drug given in the period before the initiation of injectable risperidone.

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Seizures and Prolonged QTc With Atomoxetine Overdose

To the Editor: Atomoxetine is a new norepinephrine reuptake inhibitor indicated for attention deficit hyperactivity disorder (ADHD). We present a case of atomoxetine overdose with consequent seizures and prolongation of the QTc interval.

Adam was a 15-year-old Caucasian adolescent who weighed 54 kg and had a history of major depression and ADHD. He was brought to the emergency department after an intentional overdose of atomoxetine. There was no past history of seizures, head injury, medical illness, or substance abuse. His medications included 150 mg b.i.d. of sustained-release buproprion, 0.25 mg b.i.d. of risperidone, 0.25 mg of alprazolam as needed, and 80 mg/day of atomoxetine. He had been taking bupropion for the past 1½ years and risperidone for the past 7 months. Two months before we saw him, he was switched from amphetamine to atomoxetine, 60 mg/day. Two weeks before we saw him, his atomoxetine dose was increased to 80 mg/day, and his bupropion dose was decreased to 150 mg b.i.d. because of continued ADHD symptoms. Soon after this change, however, he relapsed into severe depression.

Adam ingested 1200 mg (22 mg/kg) of atomoxetine about 1½ hours before coming to the emergency department. Pill counts confirmed that this was the only drug involved. He was treated with intravenous fluids and charcoal. About 3 hours after ingestion, he had a witnessed generalized seizure with postictal confusion that spontaneously resolved. He had a second generalized seizure 2 hours later that was treated with two doses of intravenous diazepam, 5 mg, and a loading dose of phenytoin. He was transferred to the medical intensive care unit for observation. The Poison Control Center had no specific recommendations.

Adam complained of anxiety, tremulousness, and dry mouth during the first few hours. A physical examination showed an alert, oriented, anxious, and afebrile patient with a pulse in the 110s and a stable systolic blood pressure in the low 100s, with equal and reactive pupils and fine motor tremors. A neurological examination produced nonfocal results. Routine blood tests produced normal results. The results of a urine toxicology screen and tests for alcohol, acetaminophen, and salicylate were negative. His QTc interval was 607 msec at 3 hours and 435 msec at 6 hours after ingestion. Adam was discharged 2 days later to an inpatient psychiatric facility.

We believe this to be the first published case of atomoxetine overdose. The drug has a half-life of 5 hours and is metabolized by the P450 2D6 enzyme (1). Coadministration with 2D6 inhibitors, such as paroxetine and fluoxetine, can increase serum atomoxetine levels three- to fourfold (2). Animal studies have found convulsive activity at doses of 12 mg/kg and higher (data on file, Eli Lilly, 2002). The higher serum level of atomoxetine, or its main metabolite, hydroxyatomoxetine, may have caused our patient's seizures and cardiac conduction delay. Bupropion may have contributed to the seizures (3). Since atomoxetine is not a controlled drug, there is likely increased accessibility for abuse and overdose. Further research is needed to explore the risks of seizure and arrhythmia with atomoxetine and to develop guidelines for the management of overdose and toxicity. Until more data are available, we advise caution when using atomoxetine in individuals at risk for seizure or receiving 2D6 inhibitors.

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Tardive Dyskinesia in an Autistic Patient Treated With Risperidone

To the Editor: Several open-label trials and case reports have suggested the usefulness of risperidone in treating maladaptive behaviors associated with autism (1–3). More recently, a double-blind, placebo-controlled study (4) has shown that risperidone reduces symptoms such as irritability, stereotypy, hyperactivity, aggression, and self-injurious behavior in children with autism. However, these reports also acknowledged that the relatively brief periods of treatment have precluded conclusions about the safety of risperidone with respect to tardive dyskinesia in children with autism. The following is a case report of an adolescent boy with autism who developed tardive dyskinesia while being treated with risperidone.

Alex was a 14-year-old boy who was brought to the Stanford University Pervasive Developmental Disorders Clinic for increasingly aggressive and disruptive behavior. He had been diagnosed with autism at an early age. The diagnosis was confirmed with DSM-IV criteria. Although the aggres-

sion began earlier in childhood, he was becoming progressively more dangerous in his community because of his increasing size and the increasingly frequent and indiscriminate nature of his assaultive behavior. Previously, numerous medications were prescribed for Alex, including stimulants, selective serotonin reuptake inhibitors, tricyclic antidepressants, buspirone, and secretin. Of note, Alex had never received any antipsychotic medications.

Risperidone was begun at 0.5 mg/day in our clinic and was increased gradually because of ongoing episodes of aggression and impulsivity. Alex's dose eventually reached 3 mg/day after 16 months of treatment. Shortly thereafter, Alex's behavior improved dramatically, with decreased aggression, less hyperactivity, improved language functioning, and increased sociability.

By the 23rd month of treatment, Alex began to develop a "jerking" of his trunk and abdomen. He and his mother reported that he was moving and writhing his shoulders and trunk throughout the day. Upon examination, Alex had periodic choreic movements of his shoulders and trunk. No oral, lingual, or buccal movements were seen or reported. A neurological examination revealed no other abnormalities. Trials of anticholinergic agents and vitamin E proved to be of little to no benefit. When risperidone was reduced to 2 mg/day, Alex's behavior deteriorated dramatically, so his dose was returned to 3 mg/day. Subsequently, Alex also experienced dyskinetic movements in the oculomotor muscles.

After numerous discussions with Alex and his parents about the risks and benefits of risperidone, Alex continues to take risperidone at 3 mg/day, along with benztropine, 2 mg b.i.d., and a vitamin E supplement. He continues to benefit behaviorally from the drug regimen.

This report presents the emergence of tardive dyskinesia secondary to risperidone in an individual with autism who had previously been naive to antipsychotics. This case demonstrates the effectiveness of risperidone in treating the disruptive behaviors of autism. The use of atypical antipsychotics to ameliorate the maladaptive behaviors associated with autism is likely to increase, given the absence of treatments that robustly address its core symptoms. The case points to the need for a careful discussion of the potential risks and benefits of risperidone, the identification of specific target symptoms, and education regarding the time course of treatment. The risk of tardive dyskinesia should be discussed explicitly. There should also be thorough discussions about pharmacological and nonpharmacological interventions that may need to be exhausted before considering the use of antipsychotic medications.

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Can Interpersonal Loss Precipitate Panic Disorder?

TO THE EDITOR: A central aspect of the DSM-IV diagnosis of panic disorder is that the symptoms appear to come "out of the blue." Nonetheless, there is a substantial literature documenting psychosocial stressors precipitating panic disorder (for example, references 1 and 2) and, specifically, anxiety disorders in bereavement (3). No investigator to date, to our knowledge, has examined the frequency of events involving interpersonal loss (through death or relationship disruption) that immediately preceded the onset of panic disorder.

We examined the frequency of interpersonal loss events immediately preceding the onset of panic disorder (within 6 weeks) in two groups of patients with panic disorder, both of whom participated in the evaluation of efficacy of panic-focused psychodynamic psychotherapy at Weill Medical College of Cornell University (4).

We examined the onset of panic in 51 patients, 21 of whom had participated in an open trial of panic-focused psychodynamic psychotherapy (5) and 30 of whom had been treated in an ongoing randomized, controlled clinical trial, as rated on the Anxiety Disorders Interview Schedule for DSM-IV: Lifetime Version (6). All patients met DSM-IV criteria for panic disorder with or without agoraphobia.

Twenty-four (47%) of our patients experienced an onset of panic disorder within 6 weeks after a significant interpersonal loss. Without a control group, it is not clear whether a similar rate of interpersonal loss would be found for patients in other diagnostic groups.

Panic disorder has heretofore not been conceptualized in the psychiatric literature as an outcome of loss or a form of complicated bereavement. It will be important to determine whether other groups of panic patients experience panic onset after loss with the same high frequency. It remains to be determined whether the history of interpersonal loss in panic onset may function to moderate the outcome of specific treatment interventions (7).

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Sertraline and the Cheshire Cat in Geriatric Depression

TO THE EDITOR: The study by Lon S. Schneider, M.D., and associates (1) on the treatment of geriatric depression with sertraline does not rank among the glories of clinical research. It does raise questions about corporate influence and Orwellian "newspeak" in reporting clinical trials.

The study is remarkable first for its size, determined a priori by a power analysis. The aim was to achieve power sufficient to detect a mean difference of 2 points in change scores on the 17-item Hamilton Depression Rating Scale. With a projected pooled standard deviation of 8 points, this difference would represent an effect size of only 0.25. Based on past trials, a group of 700 patients was deemed necessary. The group finally enrolled numbered 747, a stunning instance of excess to answer the straightforward question of whether sertraline is superior to placebo, especially considering the low bar that the drug was asked to clear. The study has all the hallmarks of an "experimercial," a cost-is-no-object exercise driven by a corporate sponsor to create positive publicity for its product in a market niche.

The authors concluded that sertraline is superior to placebo. The difference in mean Hamilton depression scale change score in the key intent-to-treat group was 0.8 points, less than half the stated goal. This clinically trivial difference achieved statistical significance by virtue of the gargantuan group size and because the pooled variance was less than the authors had assumed in the preliminary power analysis. "Statistically significant" differences on other dimensional primary outcome measures were likewise clinically trivial. Somewhat more encouraging data were obtained for the "completer" group, but with 131 fewer patients, that group was not representative of the drug's performance in clinical settings. Completer data are no longer accepted as evidence of efficacy.

In the intent-to-treat group, the authors further reported a "statistically significant" advantage for sertraline in a categorical measure of response, defined as a 50% reduction of Hamilton depression scale score (35% response rate for sertraline and 26% for placebo). This difference is also clinically trivial. It translates to a number needed to treat of 11. This means that clinicians would have to use sertraline 11 times to obtain one response that would not have occurred anyway with placebo (2). In an earlier time, when antidepressant drugs first were developed, the drug-placebo difference in response rates averaged 30%–35% (3, 4), based on a number needed to treat of about three. Clearly, as reflected in this trial and elsewhere, there has been much "dumbing down" of expectations for antidepressant efficacy in recent years.

And where, by the way, are the data on remission? There is currently wide agreement that remission is the optimal indicator of antidepressant efficacy (5). The authors withheld remission data. When challenged, they will doubtless use the procedural rationalization that remission was not specified a priori as an outcome measure. The question must be, why not? By this fig leaf they conceal clinically relevant data that would probably reflect poorly on the putative efficacy of sertraline. This technique allows the authors to present their results with the best "spin." Thus does the corporate mandate to put lipstick on the pig prevail over the academic duty to communicate independent analyses of the data (6–8). The *Journal* is complicit in this scientific failure.

The authors also failed to emphasize in the abstract (where most readers would notice it) that none of the functional or quality-of-life outcome measures favored sertraline over placebo. Something has changed in our conceptual paradigm when a drug can be described as "effective" for depression, but the patients do not confirm that their lives are any better with respect to vitality, social functioning, emotional role functioning, or mental health. Like the Cheshire cat's smile, the only evidence that sertraline was there is the disembodied p value, grinning in statistical space, with no connection to clinical reality. That is not quite what Percy Bridgman had in mind when he introduced operationalism in science. Lewis Carroll, on the other hand, would have appreciated the irony.

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Dr. Schneider and Colleagues Reply

TO THE EDITOR: Dr. Carroll's essential complaint seems to be that there was no reason to perform this trial but to "create positive publicity" for "niche" marketing. He elaborates with sarcasm and hyperbole that 1) statistical significance was achieved as a product of an excessively large group size; 2) the

effects of sertraline were "trivial," not clinically significant; 3) we used—he says—"newspeak" and p values "disembodied" from the underlying statistics in order to confuse readers; and 4) we acted unethically in concealing data and in reporting results. These assertions are ill-informed and without foundation, and we reject them.

This trial makes important contributions to clinical pharmacological research in late-life depression, it provides relevant information about the likely effects of selective serotonin reuptake inhibitors (SSRIs) that clinicians can evaluate, and there are no particular controversies to it.

The trial was not "oversized" and not planned to reveal "trivial" differences. As we described, the determination of group size was based on the results of a previous large placebo-controlled SSRI trial in late-life depression (1), the expectation that outcomes in clinically heterogeneous elderly depressed populations with extensive medical comorbidity would be themselves heterogeneous and modest on average, and the ability to assess potential moderators such as melancholia or anxiety. With that exception, other placebo-controlled trials in late-life depression have been underpowered and undersized. The consequences of underpowered trials are that they tend to yield noninformative results and type II errors. Conversely, when results are statistically significant, it is because the effect sizes are implausibly large. In some instances, results from smaller trials have not been published simply because they are negative. Most experts would consider an adequately powered trial of typical clinical patients and outcomes generalizable enough to inform clinical practice as a distinct strength and not a "scientific failure."

Contrary to his assertions, the statistics and outcomes in this report are clearly described and understandable. No "disembodied p values" were reported; every p value was explicitly connected to an outcome parameter and a statistical test. Any reader could assess the baseline characteristics of the population and the magnitudes of differences and calculate effect sizes of outcomes—just as Dr. Carroll did himself. Moreover, if the trial had been underpowered and undersized, he would not have been able to calculate an interpretable number-needed-to-treat statistic because the confidence interval (CI) would have been so broad as to be uninformative.

It is inappropriate and misleading for Dr. Carroll to compare this geriatric depression outpatient trial to the earliest imipramine trials performed around 1960 in younger adults (Klerman and Cole, 1965) in order to support his assertion that sertraline has a "trivial" effect. These trials, landmarks as they were half a century ago, were seriously deficient in nearly all areas. They used inexplicit diagnostic and inclusion criteria (e.g., mixing inpatients and outpatients, psychotic and neurotic depression, schizophrenia and mania) and methods for dosing and maintaining the blind or placebo control (e.g., many used atropine and thiopental as "placebos"). Outcomes assessments were idiosyncratic, and dropouts were not accounted for; most were so small, averaging about 60 to 70 patients, that they were not statistically significant individually.

Subsequent antidepressant trials, those from the 1980s and 1990s that used modern diagnostic criteria, rigorous methods, and specified outcomes, and modern evidence-based reviews based on these trials (2) demonstrated a relative benefit of antidepressant response over placebo of 1.6 (95% CI=1.5–1.7) in primarily young and middle-age adults. By comparison, we found a relative benefit for sertraline of 1.4 (95% CI=1.1–1.7). This effect is hardly trivial. Similarly, although number-needed-to-treat statistics from these studies are larger than what Dr. Carroll calculated, they are not statistically significantly so. The relative benefit (or relative risk) is an effect size measure that accounts for placebo response, something that a number-needed-to-treat statistic cannot (Laupacis et al., 1988).

The relevant comparison to make, however, is to the few other placebo-controlled antidepressant trials in late-life depression. Here, the relative benefit is 1.4 (95% CI=1.2–1.6) (2), nearly identical to our finding. We discussed that the effects of sertraline were modest, nearly identical to a similarly sized trial of fluoxetine (1) and suggested that the two trials probably represent best estimates of the treatment effects of SSRIs in outpatients with late-life depression. We submit that this trial is informative of what likely treatment effects are in elderly outpatients over the short term and, unlike some research, will be more enduring and of practical clinical consequence.

Dr. Carroll goes on to fault us for not providing—or worse—"withholding" or "concealing" what he calls "remission" data, presumably based on cutoff scores on outcome instruments, in order to best "spin" the results. The use of such cutoff scores on continuous or ordinal data is clearly unsatisfactory, especially in elderly groups, where there are substantial somatic and residual depression-like symptoms among both depressed and nondepressed individuals (3, 4). In fact, we used standard definitions of a clinically meaningful response, a 50% reduction in baseline Hamilton depression scale scores and, separately, a Clinical Global Impression Scale (CGI) improvement score of 1 or 2 (i.e., markedly or moderately improved). Moreover, we reported that the CGI response of 1 or 2 had to be sustained throughout the remainder of the trial.

Nevertheless, at his request, we calculated "remission" rates, defined as an endpoint Hamilton depression rating scale score ≤10 and a CGI severity score of 1 or 2 (borderline ill or not ill at all). Remission rates on the Hamilton depression rating scale were 34.6% versus 26.6% (Cochran-Mantel-Haenszel χ^2=5.61, df=1, p<0.02), and remission rates on the CGI severity scale were 32.8% versus 22.8% (Cochran-Mantel-Haenszel χ^2=9.43, df=1, p=0.002), respectively, for sertraline versus placebo. The risk difference, or number-needed-to-treat statistic, and the relative benefit of 1.44 are virtually identical, and the absolute rates are similar to the categorical responses we reported for the Hamilton depression rating scale score (35% versus 26%) and the CGI scale score improvement (45% versus 35%).

Abstracts do not substitute for complete reports and do not contain all results. Dr. Carroll would have put quality-of-life scores in the abstract, arguing that most readers would read only the abstract, and says that we should highlight here that patients could not appreciate any effect. He does not similarly fault us for omitting from the abstract the patients' self-assessed global impression of improvement, which strongly favored sertraline. Contrary to his assertion, the patients, in fact, endorsed their own improvements and with an effect size that was larger than the clinicians' assessments.

In sum, we reject Dr. Carroll's assertion that we put aside scientific and public health considerations to write an article under corporate influence to gain a marketing niche. Con-

trary to his assertion, we presented the whole Cheshire cat: face, ears, and tail. We regret that Dr. Carroll cannot offer his points more collegially or professionally.

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Polypharmacy in Psychiatric Inpatient Treatment

TO THE EDITOR: Franca Centorrino, M.D., and associates (1) compared the use of antipsychotics in psychiatric inpatients using data from 1989, 1993, and 1998. They found that the proportion of days the patients had received more than one antipsychotic during inpatient treatment had increased from 1.7% in 1989 to 20% in 1998. The most common combinations were typical antipsychotics added to atypical primary agents, and the authors suggested that this might reflect incomplete confidence in the effectiveness of monotherapy with atypical agents. Unfortunately, the authors did not report on other medications besides antipsychotics, and I wonder if a substantial increase had also occurred for these.

As the authors stated, polypharmacotherapy is a growing international phenomenon, and incomplete trust in the effectiveness of atypical antipsychotics obviously is just one of many reasons fostering polypharmacy. I recently reviewed the available literature on the number of psychotropic drugs administered during inpatient treatment (2) and found that the proportion of patients (including all diagnoses) being treated with monotherapy has declined significantly during the last few decades. Studies originating in 1980 or before reported monotherapy in 48%, studies between 1981 and 1990 in 31%, and studies between 1991 and 2000 in 20%. Despite all caveats concerning the small database of available studies, there is little doubt that a powerful trend toward polypharmacy is operating. The reasons for this are certainly quite complex, as follows:

1. A more sophisticated diagnostic process leading to diagnoses of multiple comorbid conditions makes more treatments necessary.

2. There are far more drugs available, both new and old, in new indications, and all are intensely promoted by the pharmaceutical industry.

3. Inpatient treatment has to deal with the most severe and often therapy-resistant cases, for which an increasing number of combination and augmentation therapies have been recommended and are widely used in spite of little empirical evidence.

4. A decreasing number of psychiatric beds and decreasing lengths of stay of inpatient treatment add even more pressure to strive for the most effective treatment.

Psychiatrists have to be aware that their clinical practice is far from evidence based. Two conclusions are important. First, clinicians should monitor the trend toward polypharmacy in their treatment regimens extremely critically. Second, we need studies investigating at least those combinations of drugs that are most widely used, e.g., the combination of atypical and typical antipsychotics.

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Dr. Centorrino Replies

TO THE EDITOR: We agree that polypharmacy, including treatment with multiple psychotropic medications not limited to antipsychotics, is a major concern in the field of psychiatry today and one that warrants both consideration and further study. While our focus in our article was primarily on the use of antipsychotic medication, we are writing a second report using the same subject group that examines combination therapy in particular and includes information on combination psychotropic medication in general. The results presented in this report will highlight the increasing prevalence of combination therapy and compare the possible effects of combination versus monotherapy in factors such as length of inpatient stay, clinical status, and side effects. We maintain, however, that further study into the use and outcome of polypharmacy is necessary.

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Fertility and Schizophrenia

TO THE EDITOR: Schizophrenia, a disease with a strong genetic component, has not disappeared, despite the fact that affected patients have lower fertility than the general population. Jari Haukka, Ph.D., et al. (1) tried to explain this apparent paradox by testing the hypothesis that the relatives of schizophrenia patients have higher fertility than the general population. Not surprisingly, the study did not confirm this hypothesis.

The transmission of the schizophrenia phenotype does not conform to a simple Mendelian pattern, even when we allow for incomplete penetrance. There are two models of transmission that fit the data available in the literature: a polygenic model and a multifactorial model (2). In a polygenic model, liability to develop a disease is continuously distributed in the population because of the additive effects of multiple genes at different loci. Only the individuals whose liability exceeds a certain threshold will manifest the disorder. The relatives of affected individuals have an increased mean liability compared with the population as a whole, resulting in more relatives manifesting the disorder. Multifactorial models allow extension of this concept, such that liability can be contributed by genetic and environmental factors in an additive fashion. Most of the discussion regarding the polygenic model applies to the latter.

Given the high prevalence of schizophrenia, these models suggest that the genes that give liability to the illness are not confined to schizophrenia patients and their relatives but are present in variable quantities in all humans, with a Gaussian distribution. Looking at the relatives of schizophrenia patients for a fertility advantage to explain the persistence of these genes is therefore not the right approach. These genes are an intricate part of the nature of *Homo sapiens*. They are not just an advantage to some but indispensable to all of us. The price paid is that 1% of the population develops schizophrenia.

When we look at diabetes as an analogy, it exists because evolution has developed a system dependent on insulin for the metabolism of glucose. The advantages offered by such a mechanism outweigh the disadvantages of having a proportion of the population affected by diabetes. The reason that the genes that give liability to diabetes do not disappear from the human genetic endowment, despite lower-than-average fertility in the individuals affected (3), is therefore clear when we look at the human population in its totality but would defy us if we analyzed only the fertility of siblings of diabetic patients. The same is true for schizophrenia.

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Dr. Haukka and Colleagues Reply

TO THE EDITOR: The idea in our article was to test whether mutations that increase the risk of schizophrenia would also bring some advantage that would appear as increased fertility among the siblings of patients with schizophrenia. The classic example of heterozygous advantage is hemoglobin S, which is protective against severe malaria in heterozygotes but causes often fatal sickle cell disease in homozygotes (1). If we understand correctly, Dr. Procopio feels that our approach was wrong because the genetic background of schizophrenia is polygenic. However, according to a recent review on human genetic evolution (2), "The rate of trait evolution tells us nothing about the number of genes involved. The intensity of selection and heritability are more important determinants of evolutionary rate than is the genetic complexity of the traits under selection." Given the strong selective disadvantage and high heritability of schizophrenia, our interest in whether the mutations predisposing to schizophrenia could also carry some advantage seems justified. We use the word "mutation" instead of "gene" to point out that we also believe that it is quite probable that the genes associated with liability for developing schizophrenia are quite useful but that the mutations within the genes that increase the risk of schizophrenia may not be useful and could be under selective pressure.

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Childhood Abuse and Suicidality in Women

TO THE EDITOR: Angela E. McHolm, Ph.D., et al. (1) reported recently on the relation between childhood physical abuse and suicidality among depressed women. They indicated they were unaware that prior "community-based studies have specifically examined suicidality among adults with a history of childhood physical abuse" (p. 934). In fact, a number of community-based studies have examined the specific relation between childhood physical abuse and suicidality (2). They have appeared in a number of peer-reviewed publications, including premier general medical (3) and child maltreatment (4) journals.

Dr. McHolm et al. depicted their specific focus on physical abuse as a strength. However, children are rarely subject to one form of abuse. There is considerable value in examining the ways in which combinations of child maltreatment are associated with psychiatric outcomes in adulthood (5). Other criticisms of the report by Dr. McHolm et al. can be generalized to other studies of child maltreatment and suicidality. First, they ignored the relations between the duration, intensity, and frequency of abuse and the kinds and degrees of psychiatric outcomes. Second, the kinds and degrees of psychiatric outcomes may vary with the developmental stage (cognitive and socioemotional) at which child maltreatment occurs. Third, popular awareness of physical abuse emerged in 1962 with the reports by Kempe and colleagues of battered child syndrome (6). Variations in awareness and attitudes about child maltreatment over time (7) may be associated with age cohort effects in adult psychiatric outcomes. Dependency and vulnerability in later adulthood may arouse memories of similar feelings in childhood. Older adults who reached adolescence before reports of battered child syndrome became well known, when child maltreatment was not discussed openly or publicly, may be less inclined to report el-

der abuse than their younger peers. Fourth, recall bias is an intrinsic problem of retrospective, cross-sectional research.

Further research with independent corroborators is needed to ascertain the ways in which the confounding nature of retrospectively recalled memories affects adults' self-reported childhood maltreatment (8). As an alternative method, one might begin with records of determined cases of child maltreatment in state or county child protective services files and compare victims' adult psychological functioning by means of a case-control cohort design. Finally, we need to know more about the "ordinary magic" of resilience (9) relative to psychiatric outcomes of child maltreatment. The majority of victims do not succumb to suicidality or psychopathology, suggesting there may be mediating and moderating factors related to resilience vis-à-vis risks.

Dr. McHolm et al. told us little about the policy or applied practice implications of their research. For many readers of the *Journal,* these aspects are certain to be more important than the specific source of the researchers' sample. Replicating the consistent findings of prior research with community-based samples contributes little to our knowledge base. Research in this area could be enhanced significantly by controlling for the developmental stages at which the victims' maltreatment occurred as well as the historical contexts that shaped attitudes toward abuse and neglect. More sophisticated research is needed, and ultimately, clinical science and our clients benefit with higher standards of research and reporting.

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Dr. McHolm and Colleagues Reply

TO THE EDITOR: We thank Ms. Mathy for her interest in our work. We agree that high standards of research and reporting benefit both clinical science and clients; however, we disagree with a number of her comments.

Ms. Mathy cites two articles to challenge our statement that no studies have examined suicidality among a community-based sample of adults with a childhood history of physical abuse. The article by Silverman et al. (1996) regarding the long-term sequelae of child and adolescent abuse followed individuals only to age 21; our work extended this line of investigation to the entire lifespan. The article by McCauley et al. (1997) examined a clinical group of patients from primary care internal medicine practices. This fact was noted by Santa Mina and Gallop in their review (1998), another of Ms. Mathy's citations. Further, Santa Mina and Gallop reported that there were "no studies specific to childhood physical abuse" and underscored the need for "additional studies of…specifically physical abuse from…community subgroups." Although we agree with Ms. Mathy that it is important to consider the overlap between forms of maltreatment, the majority of existing research examines a combination of maltreatment types or focuses on childhood sexual abuse. Far less is known about the association between childhood physical abuse specifically and psychiatric impairment.

In terms of the methodological concerns expressed, her comments reflected general issues that researchers in this field have grappled with for some time. Ms. Mathy suggests that our research "ignores" the relationships between duration, intensity, and frequency of abuse. As noted in the article, data were derived from a comprehensive mental health survey. Although it would have been interesting to include more parameters of maltreatment, practical issues of response burden prevented us from doing so. Ms. Mathy also identifies recall bias and aspects of the timing of maltreatment (e.g., the developmental stage) as limitations of the retrospective research design. We acknowledged potential limitations, such as recall bias, in our Discussion section. Alternative methods that would address such limitations are not easily applied to community samples. Ms. Mathy suggests the use of child protection cases of maltreatment and matched comparison subjects as a preferred research design. In fact, Widom (1) has published widely since 1989 on the results of such a cohort study. However, this case-finding approach precludes the opportunity to study a community sample, as was our focus.

Finally, we must disagree with Ms. Mathy's characterization of our research as a "replication study." We do not claim to have produced the definitive study of the complex interrelationships between suicidality and its correlates. We do, however, suggest that the article contributes to our understanding of suicidality in depressed women through its 1) examination of correlates from multiple domains, 2) focus on childhood physical abuse, 3) investigation of the cumulative impact of psychiatric comorbidity, and 4) separate exploration of suicidal ideation versus attempts within a community sample. Given the potential clinical significance of research in this area, we encourage Ms. Mathy and others to join us in the challenge of furthering our understanding of the relationships between suicidality and correlates such as childhood physical abuse and depression.

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The Nosology of Juvenile Mania

TO THE EDITOR: Ellen Leibenluft, M.D., et al. (1) presented an informative and useful realignment of the nosology for juvenile mania. The authors considered an array of important "methodological and conceptual issues" in their analysis, but they did not clearly distinguish between the methodological and the conceptual. That is, to what extent do the authors put forth the new categorization on the basis of the difficulties in assessment of DSM criteria in the context of the juvenile population? Or do they believe that there is a fundamental distinction among the categories they propose? If the latter, to what extent is the conceptual distinction limited to the juvenile population, or should it be applied or adapted for adults as well?

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Dr. Leibenluft and Colleagues Reply

TO THE EDITOR: We appreciate Dr. Pincus's comments on our article. We suggested these clinical phenotypes for juvenile mania because of the difficulties that arise when clinicians and researchers try to apply the DSM-IV criteria to children. The question of whether there is a fundamental distinction between these categories is an empirical one, and in the article, we suggested research strategies for addressing it (see our Table 1). For example, it is important to ascertain whether there are consistent differences between the phenotypes in neuropsychological and physiological function, longitudinal course, familial variables, etc. Should such differences exist, subsequent studies in adults would be warranted.

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Delusional Thoughts in Alzheimer's Disease

TO THE EDITOR: The article by David Sultzer, M.D., et al. (1) provides strong additional support, by way of correlation analyses of the observer-rated severity of delusions, for the contribution of right frontal brain dysfunction to the appearance of abnormal beliefs in Alzheimer's disease. This form of analysis has the merit of accounting for the contribution of other variables, such as age, age at onset, and severity of dementia, as well as the behavioral factor of agitation, to variations in regional brain metabolism. There are, however, some comments to be made about the interpretation of the results and, perhaps more important, about the method of study adopted by the authors.

The findings were seen as evidence for a linear relationship between delusional "severity" and the degree of impairment of metabolism in areas of the right frontal cortex. There are challenges to this interpretation. It is equally possible that the content and personal significance of the delusions described (about half of those outlined could reasonably be considered elements of a misidentification syndrome) might have had some variable influence on the behavioral assessment of delusion severity on the Neurobehavioral Rating Scale. In other words, an association of the nature, as much as neuropsychiatric severity, of abnormal beliefs with quantitative variation in regional brain metabolism has not been fully examined. Equally, there is evidence from case studies that delusions that have a substantial impact on behavior (and would have been highly rated on the Neurobehavioral Rating Scale) may appear at the minimal stage of Alzheimer's disease in association with subtle and confined cortical dysfunction and that they impair a specific set of cognitive abilities (2, 3).

The results of the study extend previous evidence from cross-sectional studies of similar populations. Reliance on a dimensional approach in a group showing diverse delusional phenomena, however, may continue to divert attention from methods more likely to foster an analytic understanding of delusional states. These methods will rely on the study of multiple single cases, as has been so fruitful in the analysis of Capgras syndrome (4), and will likely combine detailed clinical phenomenology, functional imaging, and cognitive neuropsychology (5). The discrimination of delusions with a factual content satisfying traditional clinical criteria from affectively laden persecutory beliefs may well be of heuristic value but will not sufficiently inform etiological studies in both organic and functional delusional disorders. Firmly held factual delusional beliefs can arise from specific memory failures and be affectively laden when the disorders of memory or other aspects of cognition involve issues of autobiographical knowledge and personal identity.

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ANNALENA VENNERI, PH.D.
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Drs. Sultzer and Mendez Reply

TO THE EDITOR: We appreciate the comments by Drs. Shanks and Venneri that address the interpretation of results from

our study. Cerebral mechanisms involved in the development and expression of delusions in Alzheimer's disease are complex and multifactorial. In their letter, two important concepts are highlighted: 1) specific brain regions and neural processes involved in the expression of delusions are variable and depend on the content of the delusional thought, and 2) deficits in particular cognitive abilities may play an important role in the development of delusional thoughts, perhaps more important than the extent of isolated cortical dysfunction. We agree. Regional cortical hypometabolism and specific cognitive deficits are probably interdependent contributors to delusions.

In our Discussion, we noted several factors that may influence the relationship between regional brain function and delusional thoughts in Alzheimer's disease. We also presented a hypothesis linking dysfunction in specific cortical areas to delusions with particular content or emotional valence. This hypothesis has some empiric support but needs to be rigorously tested. The models of cognitive and physiological contributions to the development of delusions that are cited by Drs. Shanks and Venneri (Ellis and Lewis, 2001, and Frith, 1999) provide a coherent view of possible intermediary processes. Studying patient groups with uniform delusional thoughts and including cognitive neuropsychological evaluations along with measures of regional brain function, as proposed by Drs. Shanks and Venneri, can help test these hypotheses and further refine etiological models.

There are some practical challenges in this approach. Groups of patients with uniform delusions tend to be small, patients often have more than one delusion, and the content can change within certain bounds over time. Moreover, a delusion's interpersonal meaning, emotional valence, or cognitive link to personal identity can be difficult to measure but may be critical in its cognitive or physiological development. There also may be a conceptual advantage to studying patients with a variety of delusional thoughts. Regardless of thought content, memory deficits, or perceptual influences, patients with delusions are unusually willing to accept an implausible conclusion. This cognitive process that extends beyond specific thought content may itself have discrete neurobiological underpinnings.

A complementary approach may be the optimal research strategy for the near term. Studying larger groups of patients with well-characterized thought content and cognitive abilities can help clarify etiological mechanisms. We are currently studying a larger group of patients with Alzheimer's disease with targeted neuropsychological assessments, hoping to shed more light on the factors that influence the development of delusional thoughts.

An additional critical goal is to examine the effects of neural systems rather than individual cortical loci. Discrete nodes in cortical circuits probably each contribute certain aspects to delusional thought content or its genesis, but broad systems are involved in the overall expression. Studies that examine activity in multiple cortical sites and their interactions, along with an assessment of specific content and cognition, as suggested by Drs. Shanks and Venneri, may contribute to an etiological model that elaborates brain mechanisms and can be applied to clinical care.

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Suicide and Psychotic Depression

TO THE EDITOR: I was intrigued by the findings of Meena Vythilingam, M.D., et al. (1) who reported that patients with psychotic major depression have a greater risk of death than patients with nonpsychotic major depression. This finding was based on a study that used survival analysis to assess the outcomes of 61 psychotic and 59 nonpsychotic depressed patients who were followed up for 15 years after hospital admission. The authors also reported that a positive dexamethasone suppression test (DST) result was associated with psychotic depression.

My colleagues and I reported relevant data some time ago that contrasts with these findings (2). We examined suicide rates in a group of 1,593 patients who had been hospitalized for unipolar and bipolar mood disorders. Subjects were followed up for 14 years. We concluded that psychotic and nonpsychotic subjects had similar risks for suicide and that among patients with a mood disorder, psychosis did not predispose to suicide. Dr. Vythilingam and co-workers did not specifically address the issue of suicide. We also reported that for a subset of 423 subjects given the DST, a positive result was significantly associated with the presence of delusions (3). A positive DST at baseline was not associated with subsequent suicide.

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Drs. Vythilingam and Nelson Reply

TO THE EDITOR: We are pleased that Dr. Black was interested in our article on psychotic depression and mortality. He states that he and his colleagues reported relevant data some time ago that contrast with our findings. Namely, they found no increase in suicide in psychotic depression. Dr. Black then notes that we did not address the issue of suicide.

The contrasting findings that Dr. Black refers to in his letter are unclear. We will reiterate our findings. First, we reported that psychotic depression was associated with all causes of mortality—not suicide. Thirty of the 37 deaths were from medical causes, and the increase in mortality in psychotic depression appeared to be from medical causes. In fact, Dr. Black's findings are similar to ours in that the suicide rate in psychotic depression was not significantly different from the rate in nonpsychotic depression. Further similarities are

highlighted by the absence of a significant relationship between DST results and suicide.

Second, Dr. Black overlooked our discussion of suicide in the Results and Discussion sections. In our group, there were three definite suicides and one death that was suspicious for suicide. These four cases were evenly split between the psychotic and nonpsychotic groups.

We do acknowledge, however, that the findings from our study are in contrast to those from another study that demonstrated an association between DST nonsuppression and suicide risk in patients with affective disorders (1). Prospective studies in larger numbers of subjects with psychotic and nonpsychotic depression could help tease out the complex relationships between neurobiology, clinical symptoms, and mortality.

Reference

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Suicide Among Police Officers

TO THE EDITOR: I have several comments regarding the methods employed in the study of suicide among New York City police officers by Peter M. Marzuk, M.D., et al. (1), as well as the interpretation of the police occupational context.

This study compared police officers with the general population of New York City. While age, gender, race, and region were statistically adjusted for, an inaccurate comparison of suicide rates may have resulted. The comparison involved a healthy and psychologically tested working group (the police) with the New York general population, which included the unemployed, institutionalized, incarcerated, and mentally ill. These population groups generally experience higher suicide rates. Thus, the study compared a New York population containing segments that have high suicide rates with the police, who *should have relatively low suicide rates.* Even if this study were accurate, the fact that police officers have suicide rates equal to those of the New York population demonstrates that suicide is a problem.

The work exposures involved in policing are confounders that add considerable weight to an analysis of suicide. Incidents such as witnessing death, encountering abused children, and street combat weigh heavily as precipitants to depression, alcohol use, and suicide. The study may have better compared the police with an occupation similar in confounder weight distributions, in addition to including such confounders in the analysis to assess their impact.

While psychological testing is an important screening tool for bringing in officers suitable for police work, it does not tell the whole story. Exposure and job socialization in policing have profound impacts on officers. It was interesting that the mean age of suicide for police officers in this study was 33.5 years, an age much younger than the national norm for suicide. It was also interesting that police suicide rates were noticeably unstable, while population rates remained stable over the 20-year period. The high police suicide rate in 1994, for example, occurred during a time of citywide internal investigations into a police drug scandal.

Some researchers have stated that occupation is not on the list of suicide risk factors. While we cannot yet be certain that police work by itself is a suicide risk factor, we can state that it serves as a fertile arena for suicide precipitants, including relationship problems, culturally approved alcohol use, firearms availability, and exposure to psychologically adverse incidents. This job is part of the causal chain of suicide.

In sum, this study reflects statistics that tell us that we need to look deeper into police suicides and their root causes. While statistics such as rates per 100,000 tell us about numbers, they do not tell us about suicide risk. We may be better informed if we know the inherent risk of police suicide in both a quantitative and a contextual sense. Policing is a psychologically dangerous occupation. We still have a way to go with police suicide research, but I remain with the premise that police are at a significantly higher risk for suicide.

Reference

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TO THE EDITOR: In their article, Dr. Marzuk and colleagues reviewed the rate of suicide among New York City police officers and compared it with the rate of suicide among New York City residents. After adjusting for demographic differences, they found that the rate of suicide was lower among the police officers (14.9 per 100,000 person-years) than among the general population (18.3 per 100,000 person-years).

It is estimated that over 90% of the individuals who commit suicide suffer from diagnosable psychopathology, including substance abuse and dependence, mood disorders, and psychotic disorders (1, 2). New York City police officers are screened for the presence of psychiatric disorders at the time that they are hired. No doubt, some preemployment psychopathology is missed, and some officers develop addiction problems and other psychiatric disorders while working in the department. It would be interesting to know the incidence and prevalence of such disorders among police officers during the period studied.

If we assume that few of the officers who committed suicide had diagnosable preemployment psychopathology, it may not be a fair comparison to look at their rates of suicide compared with the residents of New York City generally unless the prevalence of serious psychopathology among the comparison population is accounted for. The fact that the rate of suicide among police officers is about 80% of that of the general population may speak to the enormous stresses associated with police work, and the more proper conclusion may be that being a police officer greatly increases the risk of suicide in individuals suffering from no significant preemployment psychopathology.

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TO THE EDITOR: On the basis of the limited data available, Dr. Marzuk et al. concluded that the suicide rate of police officers may be lower than the suicide rate of the New York City population. However, there are several concerns about the study. Since death certificates were used, it is likely that the number of police suicides was underreported. Although the authors adjusted for accidental deaths and undetermined deaths (potential suicides), the graph does not include this information. In addition, some reported police homicides may actually be suicides. A suicidal officer may expose himself or herself to a life-threatening situation that also allows an opportunity to spare peers and family the aftermath of a suicide. The entire New York City population, which includes some who are jobless, have significant legal histories, or who have severe mental illness or personality disorders, is not an appropriate comparison group. These factors all increase the risk of suicide. In addition, most officers live outside the city, which decreases their risk of suicide.

Violanti and colleagues (1) compared police officers to other municipal workers and reported that the officers had a higher suicide rate and lower homicide and accidental death rates. An analysis of reported deaths in municipal workers demonstrated that police suicides (including likely suicides such as gunshot wounds to the head or drowning) were more likely to be reported than nonsuicides (2). In a department of about 40,000 officers with about five to six reported suicides per year, reclassifying just two missed suicides per year would raise the reported rate from 15 in 100,000 to 20 in 100,000, higher than the rate in the New York City population.

A New York City Police Department employment screening includes administration of a psychological interview, an MMPI, a California Personality Inventory, and a Cornell Index and the gathering of prior legal history, work history, and relationship history. Many high-risk candidates (e.g., with psychotic symptoms, severe mood disorder, poor work history, severe personality disorder, or extensive legal history, each of which is a risk factor for suicide) are not hired. If similar people were excluded from the New York City comparison group, the city's suicide rate would be much lower than reported. If the city population was "adjusted" to be more comparable to police officers, we are confident that the police department's suicide rate would be significantly higher than the appropriate comparison group.

We are concerned that the results presented may negatively affect police officers. Fears of stigmatization, job loss, or perceptions of personal weakness already are barriers that officers must overcome. If they are led to believe that suicide is not a problem for law enforcement personnel, they may see their own suicidal ideation as a personal weakness or failure and become less likely to seek assistance.

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TO THE EDITOR: Suicide among the police has been described as an epidemic (1). It is claimed that the suicide rate of law enforcement personnel is between two and three times that of the general population (2). Repetitive citations may have given the impression that the suicide rate among the police is appreciably greater than that for other occupational groups. However, research on police suicide has yielded widely varying rates, ranging from 5.8 suicides per 100,000 police officers per year in London to 203.7 per 100,000 per year in Wyoming (3). Perhaps the greatest challenge is the lack of empirical, reliable evidence on police suicides (1). Hence, the study by Dr. Marzuk et al. of the New York City police was most welcome. They stated that "with one exception…studies have shown police suicide rates to be lower than those of the general population" (p. 2070). This is not correct. We published what we believe to be the first systematic review of suicide among police in which strict methodological inclusion criteria were applied to the original studies (3). We identified 41 original studies, 20 of which fulfilled the inclusion criteria. All studies were from North America (13 studies), Europe (six studies), and Australia (one study). The results showed that some studies found elevated suicide rates among police officers; others showed an average or low rate of suicide. However, the rates varied widely and were inconsistent and inconclusive, especially because of methodological shortcomings. Most studies have been conducted in limited specific police populations, particularly in the United States. Local and regional variations in suicide can affect the rates of police suicide. Moreover, the reason for studying police suicide in a specific region may be due to a local "epidemic" of suicide in a subgroup. This may lead to publication bias. However, our review identified three nationwide studies of suicide in police from France (4), Germany (5), and England and Wales (6). These studies do not suggest an increased suicide rate in police (4–6), which is in accord with the results of Dr. Marzuk et al. However, we agree with the authors that these findings do not imply that suicide is not a problem among police officers.

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Dr. Marzuk and Colleagues Reply

TO THE EDITOR: We appreciate the many thoughtful comments raised by the correspondents regarding our study about police suicide in New York City. Dr. Violanti, Dr. Roth, Dr. Dowling and Mr. Moynihan, and Dr. Hem and colleagues raise the same concern: that comparing police officers who are screened out for mental disorders with a general population that presumably has higher rates of serious mental illness makes it appear that police are at lower risk for suicide. We acknowledged this in our discussion, where we stated, "Since recruits undergo psychological screening, it could be argued that a police suicide rate that is not substantially lower than that of the general population is effectively high" (p. 2070). Our main finding was not so much that police rates were low per se but rather that they were not *inordinately* high. It must be added, however, that screening for mental illness among job applicants is always difficult since candidates are likely to minimize the reporting of their own psychopathology. In addition, many police recruits are screened at an age that may be younger than the maximum period of the risk for the onset of some mental disorders.

Regarding misclassification bias, as raised by Dr. Dowling and Mr. Moynihan, we accounted for accidents and undetermined deaths that involved methods that are typically used in suicide cases. Even if one assumes that such deaths were misclassified and really were true suicides, the police suicide rate was not different from the general population rate. The proposition that some homicides of police officers were actually suicides is difficult to prove and places us all on slippery ground. Moreover, this argument could also be made for some homicides and accidents in the general population.

We agree with Dr. Hem and colleagues that studies in different communities with different methods and different time frames have yielded inconsistent results. Because of the low base rates for suicide and the instability of rates, we do think it is important for future studies of police suicides to examine long time periods rather than focus only on several years.

We would also agree with the correspondents that our study should not be interpreted to mean that suicide is not a problem, a statement that we, ourselves, made in our discussion. Clearly, the loss of a single life to suicide is tragic. Police work is, no doubt, stressful for the officers and their families. Police officers deserve as much support as possible in coping with the stresses of their occupation. We hope additional studies can help clarify the elements that contribute to suicide risk among officers.

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Acknowledgments of Anatomical Advances

TO THE EDITOR: After reflecting on my article that was published last year (1), I want to recognize the scientific advances of Janice Stevens, who presented an anatomical framework for schizophrenia more than 30 years ago (2). In the context of anatomical studies, I also want to acknowledge Walle Nauta's pioneering work in the field of silver techniques and regarding the anatomical organization of the forebrain, which has served as an impetus for much of our work in the basal forebrain.

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