Risperidone-Induced Hyperprolactinemia in an Elderly Woman

TO THE EDITOR: Risperidone, an atypical antipsychotic, has been reported to cause hyperprolactinemia, which may induce gynecomastia, galactorrhea, amenorrhea, and loss of libido and increase the long-term risk of osteoporosis. However, to our knowledge, all previous reports have focused on premenopausal patients (1, 2), and no geriatric cases have been reported. We present the case of an elderly patient who developed mastitis with risperidone-induced hyperprolactinemia. The lack of menstrual dysfunction and galactorrhea impeded the detection of the hyperprolactinemia side effect, which needs more attention in geriatric patients.

Ms. A, a 72-year-old schizophrenia patient who was married and had three children, had suffered from schizophrenia from age 32. Poor insight and poor drug compliance made her psychiatric condition unstable. She was admitted for auditory hallucinations and religious, persecutory, and somatic delusions. Treatment trials with many conventional antipsychotics had failed to produce any significant improvement. Risperidone was initially administered, at 4 mg/day; 3 months later, the dose was increased to 5 mg/day because Ms. A had not achieved remission.

Two months later, a tender 3×2-cm mass with an erythematous skin change over the left breast was noted, with purulent discharge from the nipple. Two left auxiliary lymph node enlargements (0.9×1.2 cm and 1.5×0.8 cm) were also detected. A medical evaluation revealed an elevated serum prolactin level (104.68 ng/ml). A sonogram-guided biopsy showed edema and diffuse infiltration by leukocytes within lobules, but no abnormal cells were noted. Results of tests for two tumor markers (CEA and CA 153) were both negative. Because of the appearance of mastitis, the oral antibiotic cefadroxil monohydrate was administered, and risperidone was switched to quetiapine, 600 mg/day. Ten days later, the breast mass and lymph node enlargement subsided completely, and Ms. A's prolactin level fell to 20.55 ng/ml.

To our knowledge, this is the first reported geriatric case of risperidone-induced hyperprolactinemia with mastitis. Kearns et al. (3) reported that the prolactin level is inversely related to the age of risperidone-treated patients, and Kleinberg et al. (4) reported no association between prolactin level and the occurrence of side effects. In this case, the prolactin level was not very high but had led to severe side effects. It is possible that the changing endocrine system of geriatric patients may have different representations of hyperprolactinemia side effects. Although the results of human studies remain inconclusive, animal studies have shown that elevated prolactin levels increase the incidence of spontaneously occurring mammary tumors (5). Since geriatric patients are at higher risk for cancer, greater vigilance for hyperprolactinemia-related side effects is advised, and further research is required.

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Topiramate and Anorexia Nervosa

TO THE EDITOR: Topiramate is an anticonvulsant that can induce weight loss (1). It has also been used as a mood stabilizer (2) and as a treatment for binge eating disorder (3) and clozapine-induced weight gain (4, 5). Clinical testing of topiramate as an obesity drug was recently discontinued because of unfavorable side effects (http://www.obesity-news.com/inuse.htm). Here we report on a woman with a previous history of anorexia nervosa who relapsed upon treatment with topiramate.

Ms. A, a 30-year-old woman, had suffered from idiopathic generalized epilepsy since childhood; at her initial visit to our outpatient epilepsy unit she was switched to topiramate because of unsatisfactory seizure control with both valproic acid and lamotrigine. She was overweight (72 kg, 162 cm, body mass index=27.5 kg/m^2). Topiramate (25 mg/day) therapy was started and the dose increased biweekly to 200 mg/day. Four months later Ms. A was free of generalized myoclonic-tonic-clonic seizures, but absences and myoclonic jerks persisted. She had lost 7 kg. Shortly thereafter, another generalized myoclonic-tonic-clonic seizure occurred, so her topiramate dose was gradually increased to 400 mg/day. Subsequently, no further generalized myoclonic-tonic-clonic seizures were reported.

However, Ms. A was admitted to our inpatient unit 6 months later for nausea and severe weight loss over the last 12 weeks. On admission she weighed 43 kg (body mass index=16.4 kg/m^2) and had eczema from compulsive washing. Topiramate was replaced by levetiracetam, 2500 mg/day. During the next 6 weeks Ms. A's weight increased to 51 kg (body mass index=18.3 kg/m^2) but subsequently dropped to 40 kg (body mass index=15.3 kg/m^2). At her last visit, she refused to be weighed and reported her weight as unchanged. Ms. A, who had been severely sexually abused as a child and has a longstanding psychiatric record, had discontinued a recently initiated inpatient treatment program for anorexia nervosa of the binge eating/purging type and anxiety attacks. With her weight at 40 kg, she did not eat at all some days; on other days she would experience binge eating episodes followed by a sensation of fullness leading her to induce vomiting (four times per week). She viewed her anorexia nervosa in the context of the previous episode at age 19 and intermittently considered that topiramate might have triggered her current episode.

On the basis of this case report, we suggest that in susceptible individuals topiramate might indeed trigger anorexia ner-

vosa, which in our patient persisted after discontinuation of topiramate treatment. We advise that before initiation of treatment with this drug patients be screened for a history of anorexia nervosa.

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Paroxetine-Associated Psoriasis

TO THE EDITOR: Psoriasis is a chronic remitting inflammatory skin disease of unknown etiology. Various medications have been reported to induce or exacerbate psoriasis (1), but to date we believe that fluoxetine is the only selective serotonin reuptake inhibitor (SSRI) to have been reported to do so (2). We report two cases of paroxetine-associated psoriasis.

Mr. A, a 37-year-old man with no history of psoriasis, was diagnosed with hepatitis C and began treatment with thrice-weekly subcutaneous interferon injections and oral ribavirin. Psoriatic plaques developed around the injection areas over his bilateral anterior upper thighs. These were controlled adequately with topical hydrocortisone ointment. He began taking paroxetine, 20 mg/day, for clinical depression.

His preexisting mild psoriasis flared up and spread to his arms, legs, back, chest, hands, and scalp. He required 0.1% mometasone scalp lotion and cream to control the psoriasis. Later he stopped taking paroxetine because of sexual side effects. Within a week, he noted an improvement in the psoriasis that continued to resolve over the ensuing months, with treatment with a variety of topical agents. His depression was subsequently treated with mirtazapine with no recrudescence of the psoriasis.

Ms. B, a 51-year-old woman, was referred for treatment of persistent depression with comorbid kleptomania that was only partially responsive to moclobemide, 600 mg/day. She was taking no other medications. Her medical history included psoriasis, which had pursued a relapsing pattern since she was 3 years old. Her last attack had been several years earlier, and no lesions had been present since.

After a washout period, Ms. B began taking paroxetine, 10 mg/day, for 1 week. The dose was then increased to 20 mg/day. After the first week of paroxetine therapy, she noted a return of psoriatic lesions, which proceeded to worsen over the next 2 weeks to involve the scalp, extensor regions, and chest. The psoriasis required treatment with two courses of psoralen and ultraviolet A light, plus topical therapy. It gradually receded after 2 months.

Ms. B was treated with paroxetine for 5 weeks; her symptoms of depression and kleptomania resolved. Given the potential role of paroxetine in exacerbating her psoriasis, fluvoxamine, 100 mg/day, was substituted; at Ms. B's 6-month follow-up, there was no recurrence of depression, kleptomania, or psoriasis.

Despite extensive use of SSRIs in clinical practice, there have been very few reports of SSRI-related psoriasis. This is possibly because of underreporting, nonrecognition of the association, or nonassociation of the event. The time scale of these two case studies suggests that paroxetine played a causative role in the exacerbation of these patients' psoriasis. Given the putative role of paroxetine in exacerbating the psoriatic symptoms, rechallenge with paroxetine was not considered.

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New-Onset PTSD After Thalamic Infarct

TO THE EDITOR: The onset of symptoms of posttraumatic stress disorder (PTSD) and the reawakening of old traumatic memories after brain injury have been cited (1); there are anecdotal reports relating thalamic dysfunction to PTSD on neuroimaging (1–3). However, as there are no reports, to our knowledge, of PTSD as a sequel of a thalamic lesion, a similar case is described.

Mr. A, a 70-year-old Korean War veteran with a history of hypertension, was treated for a pure sensory stroke after a lacunar infarct in the left posterior thalamus. Although his sensory symptoms gradually improved, a year after the stroke he started losing interest in his hobbies and became aloof. However, he reported no other depressive symptoms. Four months later, Mr. A suddenly started experiencing repetitive thoughts about a colleague's suicide, which he had witnessed in 1953. This colleague, although not Mr. A's buddy or close friend, had the same rank as Mr. A and shared the same dormitory.

Mr. A began feeling anxious and jittery and had difficulty falling asleep. He was startled by the ring of the telephone and began avoiding television programs displaying war scenes. No depressive cognitions, obsessions, flashbacks, delusions, or hallucinations were elicited. His family history was unremarkable, and so was his past psychiatric history, including that for PTSD symptoms, such as reexperiencing, avoidance, or hyperarousal. There was no history of recent trauma or stressors, and he had never thought about this incident before. A repeat cranial computerized tomography scan showed no new findings. Mr. A was diagnosed with PTSD with delayed onset.

This case provides an opportunity to study the role of thalamic amygdalar and thalamic cortical pathways in PTSD. Af-

ter a brain infarct, there is a surge in glutamate (4), which in turn increases glutamatergic transmission in the thalamic amygdalar pathway (5). Of interest, this pathway is involved in long-term potentiation, which induces plastic changes in the amygdala; the amygdala is involved in fear conditioning and in the processing of traumatic memories (5). Moreover, with the infarction of the left thalamus, there could be a partial disconnection in the thalamic cortical connection, which would parallel the functional dissociation between the thalamus and cortex during sleep. Hippocampal cells have been shown to have a higher rate of synchronous discharge during this phase, which contributes to memory consolidation (6). Thus, integrating these observations, one can hypothesize that the possible thalamic cortical disconnection, with its resultant greater availability of hippocampal information, compounded by an enhanced thalamic amygdalar transmission, may contribute to a greater conscious awareness of old, unwanted traumatic memories.

This notion is supported by the role of thalamic-cortical connections in modulating the content of consciousness (7). Moreover, thalamic hypofunction in PTSD has been shown in a recent functional neuroimaging study (3), while two individual case reports have indicated greater thalamic activity in PTSD (1, 2). Thus, future studies are needed to clarify the role of the thalamus in PTSD. Finally, the role of glutamate in PTSD, as highlighted previously (4), deserves further exploration.

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Death Associated With Quetiapine Overdose

TO THE EDITOR: Several reports in the literature have noted the favorable risk-benefit profile of quetiapine, an atypical antipsychotic used in the treatment of schizophrenia. The main clinical findings in quetiapine overdose—resulting from α-adrenergic and histamine receptor blockade—are hypotension, tachycardia, and somnolence. Potentially life-threatening consequences from overdose include QT prolongation and respiratory depression. To our knowledge, overdoses ranging from 1,200 mg to 20,000 mg have not yet been noted to result in fatalities. We report here what we believe is the first fatality associated with an overdose of quetiapine.

Mr. A was a 52-year-old white man with chronic paranoid schizophrenia and a history significant for multiple psychiatric hospitalizations, poor response to neuroleptic therapy, and irregular medication compliance. His history was also significant for overdosing, usually during attempts at self-adjustment of medications. After an overdose of risperidone in the past, he was noted to have a QT interval of 496 msec. Mr. A's medical history was significant for cardiac dysrhythmia and hypertension, which were managed with felodipine, 10 mg/day. His psychiatric medications were 600 mg/day of quetiapine, 100 mg/day of sertraline, 20 mg of buspirone t.i.d., and 50 mg of haloperidol decanoate by intramuscular injection every 2 weeks.

On the day of the overdose, Mr. A was discovered to be comatose, presumably a few hours after ingestion of the quetiapine, and in acute respiratory distress. Resuscitation efforts by paramedics were unsuccessful. An autopsy revealed cardiomegaly, with left ventricular hypertrophy and bilateral pulmonary congestion. Further testing revealed quetiapine and nicotine in his urine and a negative immunoassay screening test for his other medications. Mr. A's serum quetiapine level was 18,300 ng/ml (steady-state expected range: 100–1,000 ng/ml). Quetiapine was also detected in his gastric contents. Calculation of pill ingestion from pharmacy records of his last refill, based on an assumption of regular medication compliance, estimated his overdose at approximately 10,800 mg of quetiapine.

To the best of our knowledge, this is the first report of a death associated with an overdose of quetiapine. Quetiapine overdose, alone or in combination with other medications, has resulted in QT prolongation (1), loss of consciousness (2), sinus tachycardia (3), and hypokalemia with first-degree heart block (4). All of the patients in these reports recovered with symptomatic and supportive treatment, including one patient with an overdose as high as 20,000 mg, which resulted in serum levels of 12,700 ng/ml (3). Factors possibly contributing to the death of our patient were a history of cardiac dysrhythmia and hypertensive heart disease. There was no evidence to suggest overdosing with medications other than quetiapine. Drug interactions did not appear to play a significant role in toxicity. Hence, despite quetiapine's safety record in overdose, medical comorbidity in extreme overdoses may contribute to a fatal outcome.

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Training in Psychodynamic Psychotherapy

TO THE EDITOR: We read with great interest the Clinical Case Conference by Kristin Kassaw, M.D., and Glen O. Gabbard, M.D. (1), and appreciate their emphasis on creating a psychodynamic formulation within the doctor-patient relationship. We strongly believe that the consideration of such a formulation should be paramount during residency training in psychiatry. From a literature review (2) it emerged that this kind of formulation can be used to better organize clinical data, induce empathy, design a treatment, and generate a hypothesis in the field of research. We believe that the 10 major reasons for creating a psychodynamic formulation that were underlined by the task forces of the Association for Academic Psychiatry and the American Association of Directors of Psychiatry Residency training (3) should always be reviewed during residency training in psychiatry.

We owe Drs. Gabbard and Kassaw a great deal for their efforts in teaching how to improve the doctor-patient relationship in the fields of psychiatry and psychotherapy. It should not be forgotten that beginning therapists can improve their psychotherapeutic skills; this process is actually facilitated in the psychodynamic psychotherapy practice (4). Psychodynamic psychotherapy, no doubt, allows the development of the particular skills involved in the doctor-patient relationship; thus, psychiatrists may be able to understand inner conflicts, fears, and anxiety (5). During psychiatric training, it is crucial to develop empathic skills and a deep emotional awareness, as facing psychic sorrow moves one toward experiencing specific projective and identification anxieties. The acquisition of these professional skills must be also considered a valid and fundamental therapeutic element. Nevertheless, the psychodynamic psychotherapy model has still to deal with empirical validation, its legitimacy in the academic environment, and more widespread use in clinical practice.

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Drs. Gabbard and Kassaw Reply

TO THE EDITOR: We thank Drs. Pompili and colleagues for their kind words about our contribution. We share their view that the teaching of psychodynamic psychotherapy to psychiatric residents is fundamental and essential for all psychiatric practice. Psychiatric illness occurs in the context of a person. Addressing that person requires the listening skills and complex understanding gained from psychodynamic psychotherapy training. If we lose the psychodynamic component to psychiatric education, we do so at our own peril.

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Mania or Anxiety Disorders Linked to Panic Disorder

TO THE EDITOR: A simpler explanation of the data in the articles by Alessandro Rotondo, M.D., et al. (1) and Dean F. MacKinnon et al. (2) was not disqualified. It is that panic disorder is part of a larger anxiety picture that includes generalized anxiety disorder or posttraumatic stress disorder (PTSD). The symptoms of these disorders can mimic bipolar disorder and thereby produce the appearance of an association between bipolar disorder and panic disorder. These reports did not exclude influences from these disorders.

DSM-III-R and DSM-IV criteria for a manic episode overlap with those of generalized anxiety disorder. Criterion A, a 1-week period of irritable mood, is met by the irritability of anxiety. Criterion B can be met by any four of these common anxiety symptoms: expressions of entitlement, habitual insomnia, pressure to ventilate, subjective thought racing, distractibility from anxiety, agitation, and indulgences to compensate for feelings of deprivation. The remaining criteria concern exclusions and severity. Meeting the criteria for a manic episode in this way is a technicality rather than evidence of bona fide mania. There is similar overlap in the criteria for anxiety disorders and a hypomanic episode. The risk of false positive identification of mania would be lower if relatively specific signs were required, e.g., observable euphoria or derailment; however, the analyses were not restricted to patients with such signs. One of us (C.M.S.) has seen dozens of patients who had been diagnosed as having bipolar disorder but whose symptoms were explained by PTSD or generalized anxiety disorder.

By this reasoning, the comorbidity of panic disorder with generalized anxiety disorder (3, 4) should explain at least some of the apparent association between panic disorder and bipolar disorder. A link from panic disorder to other anxiety disorders is simpler and more ordinary than a link to bipolar disorder; by Occam's razor, it takes precedence unless disproved.

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Dr. MacKinnon Replies

TO THE EDITOR: The purportedly "simpler" explanation of our findings offered in the letter by Drs. Parvin and Swartz actually rests on an unsupported assumption. We found that the co-occurrence of panic disorder with bipolar disorder in families ascertained for a high prevalence of bipolar disorder was predicted to a significant degree by one's membership in a family in which the bipolar proband had comorbid panic disorder. This, we concluded, implies the existence of an inherited risk factor for panic in a subset of families. Drs. Parvin and Swartz argue that the relationship between panic and what we called "bipolar disorder" was really between panic and anxiety disorder symptoms that overlap with manic symptoms. To accept this argument, one has to assume that our diagnosticians systematically overdiagnosed bipolar disorder. This is unlikely since we based our diagnoses on the work of trained interviewers and research psychiatrists using a reliable diagnostic instrument (1) and state-of-the-art diagnostic methods (2). Therefore, it would seem to be "simpler and more ordinary" to assume that we did not confuse anxiety with mania. It is also surprising that Drs. Parvin and Swartz prefer the explanation that panic disorder is associated with generalized anxiety disorder rather than bipolar disorder, since the validity of generalized anxiety disorder syndrome remains open to debate (3) and, at any rate, is apparently a syndrome distinct from panic disorder (4).

On the other hand, I agree with Drs. Parvin and Swartz that the boundaries between anxiety and mood disorders may not be as clear as the current diagnostic nomenclature makes them seem. This is the problem we hope further investigation can address.

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Integrated Treatment Approaches

TO THE EDITOR: The clinical case of Angela's illness, presented by Eva M. Szigethy, M.D., Ph.D., and colleagues (1), contrary to what the authors wrote, did not illustrate "the critical importance of how an accurate diagnosis of major depressive disorder…resulted in a reduction of both psychiatric and physical morbidities" (p. 375). Recovery was, as they noted, due to an appropriate multimodal treatment applied over time.

Would the outcome have been different had the accurate diagnosis of major depression not been made? What if the therapeutic team had "erroneously" diagnosed anxiety disorder with a subthreshold depressive syndrome (rather than depression with anxiety, as they did)? What if the DSM-IV authors had allowed for a diagnosis other than depressive disorder in the presence of irritable mood (in adolescents) and accompanying symptoms? What if either conversion or somatization disorder (contemplated by the authors) had been diagnosed in Angela or a combination of any of these and other diagnoses? Would any of these "inaccurate" diagnoses have resulted in a different approach to management and treatment? I hope not; they should not have.

A longitudinal integrated biopsychosocial psychiatric treatment consisting of "a blend of supportive, psychodynamic, cognitive behavior, and family therapy," an antidepressant/antianxiety medication and a benzodiazepine prescribed temporarily together with "relaxation and distraction techniques," "continuing head halter traction and frequent but gentle physical therapy" with "passive manipulation of [Angela's] head" and "neck brace adjustments" (p. 374)—all this, as described by the authors, would have been an optimal approach to Angela's condition, regardless of the diagnosis of major depression.

Diagnoses are not to be dismissed, but they should not be worshipped either. They are social conventions. It is not a diagnosis that we treat. Not even a disorder. It is a patient. The "accurate" psychiatric diagnosis, a description based on the phenomenology, a description that attempts to approximate our perception of the patient's particular situation, rarely matches the reality experienced by that patient.

The authors, I am sure, have had many opportunities to use exactly the same management as they described, with equally positive results, regardless of diagnoses. And I hope they would agree with anybody's claim that the description of Angela's case would allow for many other diagnoses. Perhaps simply having decided that Angela's condition was not primarily physical, did not require surgery, and was not likely a psychosis was as accurate a diagnosis as one could have hoped for and quite sufficient.

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TO THE EDITOR: Drs. Szigethy et al. presented an interesting clinical case conference of an adolescent girl who, after a neck injury, developed neck dystonia (torticollis), pain, and depression. She was treated for 6 weeks as an orthopedic inpa-

tient with an integrated longitudinal medical-surgical and psychiatric approach. After discharge, she had psychiatric follow-up. Treatment was successful. The authors presented this case as an example of what psychiatry consultation services can offer, indicating that current managed care systems often carve out psychiatric services, not allowing the type of psychiatric approach used in this case.

I would like to present another pole of the managed care issue using this case. It is clear from this case report, although not presented as such, that this patient had chronic neck pain and was a chronic pain patient. Multidisciplinary pain facilities have been shown in a number of meta-analyses to be effective in treatment for a number of outcome variables, such as less pain, greater function, and return to work (1–3). These meta-analyses have even been critically reviewed and found to be of good quality (4). It is interesting that referral to a multidisciplinary pain facility, however, was not considered, in spite of the fact that nonintegrated treatment of this patient had previously failed. The kind of treatments (physical therapy, counseling, psychiatry, rehabilitation, etc.) provided to this patient are usually available to patients at multidisciplinary facilities in an integrated fashion. One could then argue that a referral should have been considered.

There are two possible reasons why pain facility treatment was not considered. First, the orthopedic attending physician either did not know or did not believe that treatment in a multidisciplinary pain facility could have been of value. In this case, consultation-liaison psychiatry should have made such a recommendation. Second, the patient's insurance may not have covered such treatment. Such a situation would have then forced the orthopedic attending physician to proceed with alternative treatment. This second scenario again would speak to the issue of managed care and the consequences of such a system.

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Dr. Szigethy and Colleagues Reply

TO THE EDITOR: We thank Dr. Wystanski and Dr. Fishbain for their thoughtful comments on our recent case report of an adolescent with complicated emotional and physical illness complaints. We wholeheartedly agree with Dr. Wystanski that it is not diagnoses we treat but the patient. He raises two additional important issues: 1) Was the diagnosis of depression accurate? 2) Would diagnosing Angela with either an anxiety or conversion disorder have changed the treatment algorithm used? Clearly, in all patients we identify target symptoms to guide our treatment approach. Angela had a symptom cluster most consistent with a depressive disorder. She did have additional symptoms in the realm of anxiety and even somatoform disorder. However, she only met full DSM-IV diagnostic criteria for depression, which provided us a framework around which to organize treatment. Having such a framework was important from two perspectives: 1) it allowed us to integrate empirically driven interventions for depression, such as paroxetine, cognitive behavior therapy, and family psychoeducation; and 2) it allowed us to organize the complex information for her family to help them develop a more cohesive illness narrative. Certainly, had Angela not shown progress in both physical and emotional symptom remission, we would have reformulated the case to consider other diagnostic possibilities and other treatment approaches. Using depression as the illness model allowed Angela's family to recognize the early signs of a more clear-cut depressive episode 1 year after her hospital discharge and to reseek the appropriate treatment after they had self-terminated treatment. Although on the surface, similar medications and therapeutic approaches could be used to treat anxiety or somatoform symptoms, we argue that there would have been subtle differences in the interventions, such as the specific manual-based cognitive behavior therapy modality used, the psychoeducational approaches used with the family, and the target symptoms tracked to determine the medication algorithm used.

We agree with Dr. Fishbain that Angela's chronic neck pain in the context of neck torticollis was essential to address as part of a comprehensive treatment, and we did. We are fortunate to have a first-rate inpatient pain service at our children's hospital, and as stated in the case report, pain treatment staff were consulted and involved in treatment decisions. The pain management physician also helped medicate the patient with intravenous methohexital for neck brace adjustments so the patient could practice relaxation techniques without distraction from pain. The integration of the pain treatment with the psychiatric and medical care Angela received led to a full remission of her symptoms, and thus it was not necessary to refer her to an outside pain treatment facility, a reasonable option had her pain not remitted.

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Religion, Spirituality, and Spiritualism

TO THE EDITOR: In her review of *Handbook of Psychotherapy and Religious Diversity*, Leslie M. Lothstein, Ph.D., A.B.P.P. (1), illustrated how complex and controversial the subject of religion and spirituality can be when combined with the art and science of psychotherapy. Personal preferences abound and feelings can be intense, contributing to potential for misunderstandings among professionals and across disciplines. In order to combat any unnecessary confusion, I feel compelled to clarify the definitions of three terms Dr. Lothstein used in her review: religion, spirituality, and spiritualism.

The definition of "religion" has been actively debated by theologians since the early 1800s, when awareness of reli-

gions from more remote cultures grew, and the assumption of the centrality of dominant religions, such as Christianity, came into question. Religion is generally regarded as any system of belief regarding humankind's relation to the divine, which includes practices of worship, sacred texts, and usually administrative and physical structures to promote the ongoing practice of the religion and member cohesion.

"Spirituality" is a term that has been used for centuries, and its meaning has evolved over the years. The term has been associated with the charisms of certain religious orders, such as the Carmelites or Franciscans of the Catholic Church or the Cabala of Jewish mysticism, and has represented the belief that an individual can be affected directly by a transcendent, divine spirit within the context of an established religious system. The experience of this spirit by the individual is facilitated by a disciplined life of prayer and, often, a spiritual guide. This leads to greater discernment about what path the individual should take to achieve enlightenment and union with God. There has been increased interest in spirituality over the past two decades, and the definition of this term has expanded to include experiences outside traditional religious settings. Nature-based spiritualities, such as Native American spirituality and eco-spirituality, are currently explored by individuals who feel alienated by the hierarchies of organized religion and feel reverence for the earth. The common thread in definitions of spirituality is the belief in a personal communion with what is holy through prayerful meditation and conscious living.

"Spiritualism" describes the belief that spirits of the dead can communicate with the living. Evidence of this belief system can be found in biblical times as well as in the Middle Ages, although modern spiritualism surfaced in the mid-1800s with the belief that mediums could connect individuals with deceased relatives. Spiritualism prospered during the 19th century as mediums conducted seances for individuals hoping to communicate with dead loved ones or hoping to find evidence of immortality. These longings were sometimes exploited, and cases of fraud were reported before the practice of spiritualism waned.

As we discuss the issues that religion and spirituality bring to the practice of psychotherapy, it is important to have some common understanding of the terms we use in this dialogue.

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Comparable Dopamine 2 Receptor Occupancy

TO THE EDITOR: Robert M. Bilder, Ph.D., and colleagues (1) concluded in their article that "patients with a history of suboptimal response to conventional treatments may show cognitive benefits from newer antipsychotic drugs" (p. 1018). Although their study was well conducted, we feel it is important to point out a limitation that, in our opinion, has been inadequately addressed.

In the Discussion section, the authors mentioned that in their study, "relatively high doses of all medications, particularly risperidone" (p. 1026), were used. The mean dose levels (milligrams per day) achieved during the first 8 weeks of the study were 20.2 (SD=1.0) of olanzapine, 8.3 (SD=2.2) of risperidone, and 19.6 (SD=2.0) of haloperidol. In our opinion, these dose levels do not reflect similar levels of dopamine D_2 receptor occupancy in each treatment group: about 77% for olanzapine (2), 83% for risperidone (3), and about 94% for haloperidol (2). We were not informed about the mean dose levels during the last weeks of the study; however, the ranges in which doses were allowed to vary also do not reflect comparable levels of D_2 receptor occupancy in each treatment group. Although the mean dose of risperidone may have been higher than considered optimal, the mean dose of haloperidol *was* much higher than optimal.

Because of these high doses, all patients taking haloperidol also received anticholinergic drugs that are known to lead to cognitive impairments. Given the relationship between dopaminergic neurotransmission and aspects of cognitive functioning (4), differences in D_2 receptor occupancy could partially explain the results achieved by Dr. Bilder et al. (1). The question of whether atypical antipsychotic drugs have cognitive benefits compared to typical antipsychotic drugs should be studied in treatment conditions with comparable D_2 receptor occupancy.

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Dr. Bilder and Colleagues Reply

TO THE EDITOR: We appreciate the comments of Drs. de Haan and van Amelsvoort regarding our recent article and are happy to expand on speculation regarding putative mechanisms underlying the observed treatment effects. First, we should highlight that our comments regarding the doses used in our study referred to clinical practice in the management of patients with suboptimal treatment response—not to putative levels of receptor occupancy—and readers should recognize the unique challenges inherent in treating this patient population.

Second, we believe that the contention of Drs. de Haan and van Amelsvoort that higher D_2 receptor occupancy limited cognitive improvement is not supported by our data. Several facts argue against this interpretation. The mean dose levels (milligrams per day) achieved in the second period of the study (last observation carried forward) were 526.6 (SD=140.3) for clozapine, 30.4 (SD=6.6) for olanzapine, 11.6 (SD=3.2) for risperidone, and 25.7 (SD=5.7) for haloperidol, as described elsewhere (1). We thus believe that at follow-up all patients in the olanzapine, risperidone, and haloperidol groups likely had levels of D_2 receptor occupancy well in excess of 80% and within the range at which D_2 occupancy asymptotes (2). Therefore, the possible discrepancies between groups in D_2 occupancy were probably subtler than suggested by Drs. de Haan and van Amelsvoort.

It is still conceivable that even subtle differences in overall D_2 occupancy or other differences, such as rates of D_2 receptor dissociation (2, 3), may help explain the differences in neurocognitive function observed in our study. If the differences between treatments were mediated primarily by differences in D_2 receptor occupancy, changes in motor function (the strongest correlates of D_2 receptor availability in the striatum [Volkow et al., 1998]) should have differed between groups, but this was not the case. Moreover, if neurocognitive improvement had been limited by high D_2 occupancy, the clozapine-treated patients might have been predicted to show the greatest improvement, but they did not (despite good clinical efficacy).

We examined the effects of all antipsychotic doses and anticholinergic treatment effects (using benztropine doses and extrapyramidal symptom ratings) and found that these variables did not substantially influence our findings. In summary, we believe that our data do not support a simple explanation of neurocognitive improvement in terms of lower D_2 receptor occupancy, and thus we highlighted in our Discussion not only the possible D_2 receptor effects but also a broad range of other possible mechanisms that might be responsible, including serotonergic, adrenergic, cholinergic, histaminergic, and non-D_2 dopaminergic receptor effects, that may have differed among treatments.

We believe further that our findings agree well with a larger literature, suggesting that attempts to explain complex clinical effects in terms of receptor binding profiles have been challenging at best (4). We agree that it would be valuable to conduct research comparing the neurocognitive effects of antipsychotic treatments, specifically targeting levels of D_2 receptor occupancy, as an experimental manipulation. It is important to recognize, however, that any strategy of reducing D_2 receptor occupancy for cognitive augmentation might best target patients with a history of treatment response more favorable than our patients showed to minimize the possible clinical risks of relapse.

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