Stress Regulation and Self-Mutilation

TO THE EDITOR: We studied the relationship between acts of self-mutilation and fluctuations in levels of nocturnal urinary cortisol excretion in a female inpatient who developed borderline personality disorder after traumatization during childhood.

Ms. A, a 36-year-old woman, had pronounced repetitive self-mutilating behavior in addition to borderline personality disorder diagnosed according to an interview with the German version of the Dissociative Disorders Interview Schedule (1) (DSM-IV diagnoses 296.32, 300.6, 300.12, 300.15, 300.81, 301.83, and 307.1). She collected her entire nocturnal (8:00 p.m. to 8:00 a.m.) urine output on 86 consecutive nights (2) Her nocturnal urinary volumes were almost identical (mean=983 ml, SD=128), but the fluctuations in her nocturnal cortisol excretion were extreme, varying from 2 to 30 μg a night. Compared to normative data (cortisol excretion during 24 hours: 20–90 μg/day), her nocturnal cortisol secretion appears low on average; this is in accordance with data from other studies (3). However, our longitudinal study revealed that periods of low cortisol excretion were followed by periods of continuous increases in excretion over several nights. Above 20 μg a night, she performed one or several acts of self-mutilation. Subsequently, an instantaneous decrease to low initial baseline values of cortisol was observed. Thereafter, her nocturnal cortisol excretion remained at this low level for several days. The next period of increasing cortisol secretion was again terminated by an episode of self-mutilation.

It has long been speculated that self-mutilating behavior serves a coping function that is activated by an increase in emotional arousal (4, 5). Between 1 and 3 days before an episode of self-mutilating behavior, our patient reported increasing feelings of dissociation and depersonalization, flashbacks, and depressive states that were difficult to control either by herself or by therapeutic interventions. It seems that above a critical excitation threshold, Ms. A coped with escalating arousal with self-mutilating behavior.

We believe that our results provide the first empirical demonstration that episodes of self-mutilating behavior occur in response to hyperactivity of the central stress-sensitive neuroendocrine systems and increased cortisol secretion. Further longitudinal studies are needed to confirm this finding. Observations in nonhuman mammals have shown that self-mutilating behaviors may emerge as a consequence of deprived rearing conditions (6, 7). Thus, self-mutilating behavior may be regarded as an unusual but effective coping strategy for the self-regulation of hyperarousal and/or dissociative states and for regaining control over an otherwise uncontrollable stress response (8).

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Serotonin Syndrome and Atypical Antipsychotics

TO THE EDITOR: Serotonin syndrome is characterized by a symptom triad of altered mental status, neuromuscular abnormalities, and autonomic dysfunction; it occurs mostly when two serotonergic agents are given in combination (1). There are rare reports of its occurring in association with atypical antipsychotic treatment (1, 2). A case of serotonin syndrome precipitated by the addition of olanzapine to a mirtazapine and tramadol combination is described.

Mr. A, a 53-year-old man with a family history of chronic schizophrenia, was under treatment for major depressive disorder with schizotypal personality disorder. He was taking 45 mg/day of mirtazapine and 150 mg/day of tramadol, the latter for chronic back pain. Recently, he had been admitted to the hospital for a micropsychotic episode, for which treatment with olanzapine, 10 mg/day, had been initiated; he was discharged after a week. After 8 days of olanzapine treatment, Mr. A was found by the police wandering the streets in inappropriate dress and in a confused state, and he was readmitted to the hospital. He reported that he had not taken any substances of abuse or overdosed on any of his medications.

Results of a physical examination revealed tachycardia (120 bpm), flushing and twitching of his face, tremors, myoclonus, hyperreflexia, and an ataxic gait. In an examination of mental status, Mr. A was found to be disoriented and agitated. He spoke with a stutter, had marked derailment, appeared perplexed, and had prominent perceptual abnormalities in the form of alterations in the color of objects and auditory hallucinations. The results of a comprehensive biochemical and hematological profile were unremarkable, as were a toxicology screen and a cranial computerized tomography scan. After Mr. A's second admission, all medications were discontinued; there was a dramatic improvement in his clinical picture within 12 hours.

Although neuroleptic malignant syndrome was a possibility in this case, since the patient's symptoms appeared after the addition of olanzapine, the absence of hyperthermia and

rigidity and the presence of a normal creatine phosphokinase level favored a diagnosis of serotonin syndrome. Moreover, the patient had features corresponding to the classic symptom triad associated with serotonin syndrome, and his rapid recovery upon discontinuation of the medications was more in line with serotonin syndrome (1). Both tramadol and mirtazapine have been found to be associated with serotonin syndrome, especially when given in combination with other serotonergic drugs (3, 4). However, there are only anecdotal reports of atypical antipsychotics being associated with this syndrome (1, 2).

The most widely accepted pathophysiological mechanism for serotonin syndrome is the excess stimulation of serotonin receptor subtype 1A (5-HT_{1A}) (1). One of the mechanisms of action of mirtazapine is disinhibition of serotonin neurotransmission by means of mediated antagonism of α_2-adrenergic receptors, with subsequent selective activation of 5-HT_{1A} receptors in view of its antagonistic properties for 5-HT_2 and 5-HT_3 receptors (5). Tramadol, in its own right, increases serotonergic transmission by inhibiting the reuptake of serotonin (3). Thus, this patient had already been at risk of developing serotonin syndrome. Olanzapine, an antagonist at 5-HT_2 and 5-HT_3 receptors, could have potentiated the mirtazapine-induced biased activation of serotonin in favor of the 5-HT_{1A} receptors, which could have precipitated serotonin syndrome.

There is evidence that antagonists of serotonin receptors other than 5-$HT1_A$—especially 5-HT_2 and 5-HT_3—such as risperidone and ondansetron, can precipitate serotonin syndrome when given in combination with serotonergic drugs, including mirtazapine (2, 4). This is supported by animal studies showing enhanced behavioral response to 5-HT_{1A} agonists in animals given 5-HT_2 antagonists, such as ritanserin (6). Hence, a clinician needs to bear in mind the possibility of serotonin syndrome when a patient taking a serotonergic agent plus an atypical antipsychotic develops altered mental status and other typical features of serotonin syndrome that—such as in our case—may superficially resemble a worsening of psychosis or even neuroleptic malignant syndrome.

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Ziprasidone Induction of Hypomania in Depression?

TO THE EDITOR: Atypical antipsychotics are being increasingly used in the acute and maintenance treatment of bipolar illness. Although more evidence is needed, they are often reported to be "thymoleptic," having therapeutic benefits for both mania and depression, in bipolar patients. However, a review by McElroy and Keck (1) indicates that risperidone and olanzapine occasionally precipitate mania or hypomania in bipolar depressed patients. We report on three patients for whom we believe ziprasidone precipitated a hypomanic syndrome while it was being used to treat depressive symptoms.

Mr. A was a 43-year-old man with recurrent major depressive disorder that had been treated with partial success with sequential trials of fluoxetine, venlafaxine, buproprion, and lamotrigine. All were discontinued because of side effects and/or lack of efficacy. Mr. A began taking ziprasidone, 20 mg b.i.d., for 1 week, then his dose was increased to 40 mg b.i.d. He began to experience insomnia, waking up at 3:00 a.m. He also reported feeling "really good" and "wide open" and said, "I haven't had energy like this for 15 years" and that he was "washing dishes and cleaning continuously." His dose was reduced to 40 mg at bedtime; his insomnia and subsequent euthymia remitted. Mr. A has remained fully recovered.

Mr. B was a 31-year-old man with a long history of generalized anxiety disorder, attention deficit hyperactivity disorder, and recurrent depression. He had previously taken nefazadone, sertraline, and buproprion without an improvement in symptoms. He began taking ziprasidone, 20 mg b.i.d., and within 4 days he described feeling "wonderful" and "euphoric." He had racing thoughts, "great powers of concentration," and was impatient and irritable with others. After Mr. B had been in this state for 2 weeks, we decreased his ziprasidone dose to 20 mg/day, but he then experienced "profound depression," which persisted despite ziprasidone discontinuation.

Ms. C was a 33-year-old woman with a history of treatment-resistant major depression with panic attacks. She was hospitalized, and her condition was maintained with buproprion therapy, from which she sustained some but not sufficient antidepressant benefit. Ms. C was given ziprasidone, 20 mg b.i.d., and within 10 hours she experienced a marked increase in energy, reported feeling "wonderful," and was able to be discharged. At home she continued to experience a marked increase in energy and an elevated mood. However, 3 days after starting to take ziprasidone, she experienced severe insomnia followed by a relapse into her previous depressive symptoms and a recurrence of panic attacks. Ziprasidone was discontinued, and risperidone treatment was begun. The dose was titrated to 3 mg/day, which produced mood stabilization (euthymia) and a resolution of panic attacks and insomnia.

These three cases and anecdotal reports from colleagues suggest that ziprasidone, like other atypical antipsychotics, may precipitate a "hypomanic syndrome" in unipolar patients or possibly "unmask" latent bipolar illness. The appropriate management of such patients, whether by lowering doses, raising doses, discontinuing ziprasidone, or adding mood stabilizers awaits further clinical investigations.

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Quetiapine and Pregnancy

TO THE EDITOR: In comparison with the literature on classical antipsychotics, less is known about the risks associated with prenatal exposure to atypical antipsychotics (1).While experiences with clozapine (2) and olanzapine (3) and pregnancy are found in the literature, to our knowledge, data concerning the use of quetiapine during human pregnancy has not yet been reported. We report on a patient who was treated with quetiapine during her entire pregnancy without complications.

Ms. A, a 38-year-old woman, had been treated for a diagnosis of schizophrenia (paranoid type) since 1998. After a period of outpatient treatment with zuclopenthixol, which resulted in insufficient response, her medication had been changed to quetiapine, 300 mg/day. She was not taking any other medications. After the change in medication, her symptom profile showed considerable improvement. Ms. A's pregnancy was discovered at week 17, when she reported amenorrhea. A consultation with a gynecologist resulted in a diagnosis of an intact pregnancy, with no complications at that stage. She had been taking quetiapine when her child was conceived.

At the 20th week of pregnancy, Ms. A's dose of quetiapine was reduced to 200 mg b.i.d.; from week 22, she was taking only 150 mg b.i.d. because her symptoms had improved significantly. She had no side effects from quetiapine during treatment. Ms. A was in remission during her pregnancy, and at week 38, she gave birth to a healthy boy. The newborn's weight was 3120 g, his height was 48 cm, his Apgar score in the first minute was 9, and at 5 minutes it was 10. Because Ms. A continued taking her medication, breast-feeding was not introduced. Five days after delivery, Ms. A and her newborn were discharged from the hospital. Since that time both Ms. A and her son have been without any neuropsychiatric or perinatal complications. The son's development was intact during the first 6 months of his life.

An instance of human pregnancy with quetiapine use is interesting, since the only data we discovered on the use of quetiapine during pregnancy are from an animal experiment in which the effects of maternal deprivation on prepulse inhibition could be reversed with the use of this novel atypical antipsychotic (4). It is important to note that our patient took quetiapine during her entire pregnancy. The lack of perinatal extrapyramidal side effects and the growing number of experiences of safe use of atypical antipsychotics during pregnancy can encourage clinicians to promote such treatments. However, nothing is known about the potential for long-term behavioral abnormalities in children exposed to antipsychotic drugs, especially atypical antipsychotics, in utero. A cautious clinical approach is needed, with consideration of every risk and benefit.

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Nerve Growth Factor and Smoking Cessation

TO THE EDITOR: Nerve growth factor is the best characterized neurotrophin essential for neuron survival, differentiation, and function in the peripheral and central nervous systems (1). In addition, it is hypothesized that nerve growth factor plays a modulatory role in the immune system, is involved in the regulation of specific neuroendocrine functions, and is elevated in psychologically stressful situations (1). Because acute nicotine withdrawal is associated with psychological stress, and an elevation of nerve growth factor has been shown to also accompany alcohol withdrawal (2), we hypothesized that the level of nerve growth factor is elevated during withdrawal from smoking.

We studied eight female and seven male smokers (mean age=35.0 years, SD=10.7) and 10 matched pairs of nonsmokers. All of the subjects gave their written informed consent. The smokers had consumed more than 10 cigarettes a day for 5 or more years and had been medication free within the past year. Having any psychiatric or medical disorder led to exclusion from the study. Their grade of nicotine dependence was measured with the Fagerstrom Tolerance Questionnaire (3). Serum concentrations of nerve growth factor were measured in smokers on 3 consecutive days at the same time of day (within 15 minutes) and once in nonsmokers. On days 1 and 3, the smokers consumed at least eight cigarettes before blood was drawn; on day 2 they were abstinent for 16 hours or more. Measurement on day 3 was performed to detect delayed changes in nerve growth factor level.

No significant difference was detected in baseline levels of nerve growth factor between the smokers (mean=63.4 pg/ml, SD=117.8) and the nonsmokers (mean=57.3 pg/ml, SD=96.6) (Mann-Whitney-Wilcoxon S=137.0, df=14, exact p=0.71). Our main finding was a significant overall change in nerve growth factor levels in the smokers over the 3 days observed (Friedman S=7.56, df=2, exact p=0.02). Post hoc analysis revealed a significant increase in nerve growth factor levels between day 2 (mean=76.3 pg/ml, SD=176.3) and day 3 (mean=104.5 pg/ml, SD=266.4) (Wilcoxon S=39.50, df=14, exact p=0.03, with Bonferroni correction). Fagerstrom score was positively correlated with nerve growth factor level at baseline (Spearman's r=0.53, df=13, p=0.04) but not with change in nerve growth factor level.

In line with this observation, a release of nerve growth factor into the bloodstream was found in adult male mice in social isolation as well as in parachutists experiencing their first

jump, suggesting that psychological stress is associated with an increase in serum level of nerve growth factor (1). Moreover, high levels of serum nerve growth factor in patients during acute withdrawal from alcohol or heroine addiction (2) indicate involvement of nerve growth factor in addictive behavior and withdrawal distress. The positive correlation found between Fagerstrom score and nerve growth factor concentration strengthens the possibility of a connection with addictive behavior. This study represents, to our knowledge, the first observation that the serum concentration of nerve growth factor is altered during acute withdrawal from nicotine, although this finding must be considered as preliminary and needs replication.

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Topiramate for Refractory Schizophrenia

TO THE EDITOR: Lamotrigine has been used successfully as an adjunctive treatment to antipsychotic medication in refractory schizophrenia (1). Topiramate is a newer antiepileptic agent with a wider spectrum of action than lamotrigine. Unlike lamotrigine, topiramate also blocks AMPA/kainate receptors, thus decreasing glutamate-mediated excitation (2). We report our experience using topiramate to treat extremely refractory schizophrenia.

We treated three men and two women (mean age=40.2 years, SD=6.1) who met DSM-IV criteria for chronic schizophrenia. We obtained oral consent from the subjects or their caregivers for their participation in the study. The mean time since their initial hospitalization for schizophrenia was 19.8 years (SD=5.8). The mean length of their current hospitalization was 8.2 years (SD=5.4). Four patients were taking clozapine. The fifth was taking quetiapine and risperidone, since he had developed agranulocytosis while taking clozapine. No patient had epilepsy. We started the patients with topiramate, 50 mg/day, and titrated their dose upward at the rate of 50 mg/day per week. Their mean maximum dose was 250 mg/day (range=200–300). We held their main medication dose constant while they were receiving topiramate. We administered the Positive and Negative Syndrome Scale for schizophrenia (3) before the patients started taking topiramate and after they had been taking the maximum dose for 1 month.

The condition of the man not taking clozapine and one woman deteriorated to the point that we could not obtain reliable posttreatment scores on the Positive and Negative Syndrome Scale. For the remaining three patients, the mean initial score on the Positive and Negative Syndrome Scale was 95 (SD=1). Their mean posttreatment score was 118 (SD=5). This represented a significant negative reaction to the addition of topiramate (paired $t=8.55$, $df=2$, $p<0.007$, one-tailed). Of note, both positive and negative scores on the Positive and Negative Syndrome Scale increased during posttreatment for all three of these patients.

In retrospect, there were reasons for concern about a negative response. Topiramate has a higher rate of psychotic episodes in epileptic patients than other newer antiepileptics (4). According to the glutamate model of schizophrenia, inhibition of glutamate receptors in the nucleus accumbens and prefrontal cortex should increase positive and negative symptoms, respectively (5, 6). We know of no current clinical evidence that the countertherapeutic effects we observed are mediated by this mechanism.

Topiramate has been suggested as adjunctive therapy to reduce clozapine-induced weight gain and seizures (7, 8). Our observations suggest caution when considering use of topiramate in patients with refractory schizophrenia.

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Creativity and Affective Illness

TO THE EDITOR: We were intrigued by the study by John F. McDermott, M.D. (1). Several systematic studies (2, 3) have demonstrated a connection between affective disorders and the creativity of writers and poets, with a high incidence of these traits in first-degree relatives (4). However, exploiting literary heritage as a tool for postmortem psychiatric diagnosis is rather complicated. Such a study poses both phenomenological argumentation and ethical debate, especially when no reliable psychiatric documentation exists. We encountered similar difficulties in our study of the enigmatic medical biography of the famous 19th-century Russian writer Nikolai

Gogol (5). We found it most useful to adopt methods suggested by Jamison (6) and implemented by Weisberg (7) in a study of the composer Robert Schumann. The quantity and quality of Schumann's compositions per year were compared with the composer's changes of mood on the basis of his diaries and letters and the recollections of his contemporaries.

We applied that method to an examination of the creative productivity of Nikolai Gogol, whose eccentric behavior was enigmatic for both his contemporaries and later generations. The results were astonishing. We identified five phases during Gogol's adult life, strikingly matching the writer's productivity and his mental condition: prodromal, predominant elation, prominent mood swings, overpowering depressions, and decline. Both the quantity and the quality of Gogol's literary work matched the stages of his chronic illness. In August 1841, Gogol completed the first part of his famous work *Dead Souls*. Then his creativity declined, both in quality and quantity. Between 1842 and 1848 he wrote 1,105 pages, mostly letters. The amount further declined to only 278 pages, until his death in 1852. In addition, Gogol burned the manuscript of the second part of *Dead Souls* twice during his depressive episodes.

We also found it most valuable to cross-examine our assumptions with descriptions given in Gogol's personal letters and the reminiscences of his contemporaries, reflecting his mental status at various periods of his work. In our opinion, Gogol was suffering from bipolar II disorder and had a narcissistic personality disorder. We agree with Dr. McDermott's statement that diagnostic impression without examination is conjecture at best. Still, it is a price worth paying for deeper insight into the interface between affective illness and creative genius.

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TO THE EDITOR: My heartfelt gratitude to you for accepting articles related to culture and not only dull statistical assessments of recently approved pharmaceutical agents. The study about Emily Dickinson is, of course, on my mind. I read Dr. McDermott's article with delight.

Without the slightest intention to alter or correct anything in that interesting article, I wish to present additional information regarding the mystery of the emotional "crisis" in Dickinson's poetry and life. The secret of her "emotional disaster" has been subjected to various and even contradictory interpretations. My source is a book written by Rebecca Patterson (1), published in 1951 and thus perhaps forgotten. It is a thoroughly researched work, reporting that Dickinson's "crisis" happened during the breakup of a loving relationship with another woman; this woman was Kate Scott Anthon, a worldly, intelligent, bisexual woman who was herself a poet.

The two ladies met the first time in March 1859 in Amherst, and the mutual attraction was immediate. About a year later, when Anthon visited Amherst for the third time, Dickinson's sister Lavinia was away in Boston. Anthon stayed overnight in Dickinson's room, and they shared a bed. Never was Dickinson happier than during the summer of 1860. They walked together, holding hands, and Dickinson's poetry sparkled with love: "Her sweet weight on my heart at night."

But in that prejudiced, puritan, Calvinistic atmosphere, such a friendship was threatened with danger of large magnitude. Thus Dickinson enveloped the relationship with symbolic substitutions, so much so that analytical expertise is needed to decipher the meaning of words such as "diamond," "pearl," "dusk gem," "soldier," "pilgrim," and a dozen other characters, all representing Anthon. After these happy days, what precipitated an emotional crisis? Anthon realized the socially precarious nature of their entanglement and broke up the relationship in a letter in April 1861. Dickinson was destroyed; she felt more hurt than at any other time in her life. She called Anthon a traitor and contemplated suicide. For the sensitive, naive, and inexperienced girl, this wound remained unhealed for the rest of her life. She changed her name from "Emelie" to "Emily," a little-known fact. Family members, finding her poems and letters after her death, changed her grammar and falsified much of her manuscripts. Lavinia even destroyed Dickinson's letters from Anthon. Her poems were carefully edited, and only a small number were allowed to be published. Dickinson published only seven poems in her lifetime. Her manuscripts were auctioned in 1950, but it is not known how many were actually sold. Several variations exist because of the alterations and exchanges of ownership. Some important poems, however, escaped censorship. Dickinson, her heart wounded, wanted to share her secret and did not mind if the truth emerged after her death. Perhaps the most moving lines that escaped editorial alteration include a frank disclosure and show remorse:

I shall not murmur if at last
The one I loved below
Permission have to understand
For what I shunned so—
Divulging it would rest my heart
But it would ravage theirs
Why, Katie, treason has a voice
But mine dispels in tears.

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TO THE EDITOR: Dr. McDermott provided a provocative analysis to suggest that Dickinson had bipolar, seasonal affective disorder, using the educated judgment of a leading Dickinson analyst of the months or seasons when specific poems were written. The author properly indicated the limitations of both that analysis and the conclusions that may be drawn from those data. There is one point of certain error, however. When in 1883 and 1884 Dickinson's physician O.F. Bigelow diagnosed "nervous prostration," he was not referring to an affective disorder, as Dr. McDermott suggested, but to an episode of severe headache with vomiting and, in 1884, spells of unconsciousness. This illness was quite likely due to acute, severe hypertension, which led to her demise in 1886 (1).

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Dr. McDermott Replies

TO THE EDITOR: I agree with Dr. Kalian et al. that postmortem psychiatric diagnosis is speculation at best, but diagnosis was not the goal. The goal was a better understanding of what comprises creative genius. Their efforts to add quantitative data to the existing biographical store should be encouraged.

Dr. Varga's hypothesis that the mysterious crisis in Dickinson's life, coinciding with the period of her greatest creative productivity, was triggered by a failed love relationship with another woman is shared by feminist scholars. However, most of Dr. Varga's comments appear to be based on information from Dickinson's poems. To consider the metaphor of poetry as autobiography is highly questionable. There has long been speculation about Anthon as her love and/or lover, but little or no correspondence between them survives. The other principal candidate is her sister-in-law Susan Gilbert Dickinson, to whom Emily Dickinson wrote passionate love letters over a period of years.

Dr. Hirschhorn's certainty about what Dickinson's physician meant when he diagnosed her with nervous prostration is puzzling considering that no medical records survive. The headache to which he refers was reported by a neighbor, not by Dickinson or her doctor, and occurred during the time surrounding the illness and death of her beloved nephew the month before. The diagnosis of nervous prostration is consistent with grief superimposed on a long history of self-described anxiety and depressive symptoms, independent of the illness from which Dickinson died several years later.

Nervous prostration, or "neurasthenia," as it was also called by then, was the diagnosis used for affective disorder. It was based on the medical belief that individuals were born with a certain amount of energy stored in the nervous system, and when they were exhausted by stress, it simply ran down, like a battery losing its charge. Nerve tonics were the treatment, and prescriptions for them were listed for the Dickinson household by the local pharmacy around the time of the diagnosis.

In his own referenced article, Dr. Hirschhorn applauds the Dickinson family doctor, O.F. Bigelow, as a progressive and diligent physician who reasoned well and kept up-to-date. However, he also disputes Dr. Bigelow's diagnosis of Bright's disease as the cause of death several years later. To second-guess the physician in attendance more than a century later is a tricky matter. To me, it seems more reasonable to stay closer to the data available than to adopt a new theory that cannot be tested.

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Buproprion and Sexual Dysfunction

TO THE EDITOR: As a clinician, I was disappointed by the negative results reported by Prakash S. Masand, M.D., et al. (1) about sustained-released bupropion for the treatment of sexual dysfunction induced by selective serotonin reuptake inhibitors (SSRIs). However, while awaiting the results of larger studies using the higher doses of bupropion that these authors called for, we can take some consolation in the fact that this study was "supported in part by a grant from GlaxoSmithKline" (p. 807), the makers of sustained-released bupropion. At a time when there are concerns about the influence of the pharmaceutical industry on pharmacologic research and practice (2), it is nice to see that a study in which the company's product did not fare well was published rather than having it end up in the proverbial file drawer.

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Dr. Ashton and Colleagues Reply

TO THE EDITOR: We appreciate the opportunity to respond to comments submitted by Dr. Hierholzer. We, too, found it disappointing to be unable to show the statistical superiority of 3 weeks of sustained-release bupropion, 150 mg/day at 6 p.m., over placebo for the treatment of SSRI-induced sexual dysfunction. We are glad to report that since our letter was submitted, two other studies have given us optimism that sustained-release bupropion may be a useful antidote when managing SSRI-related sexual dysfunction. DeBattista et al. (1) presented new research at the 2001 annual meeting of the American Psychiatric Association showing statistically significant improvement in sexual arousal in 42 patients with SSRI-induced sexual dysfunction who were taking sustained-release bupropion, 150 mg/day, for 6 weeks. In addition, Clayton et al. (2) presented new research at the same meeting showing the statistical superiority of 4 weeks of treatment with sustained-release bupropion, 150 mg b.i.d., over placebo

in enhancing sexual desire and increasing the frequency of sex, which was used as a measure of greater sexual satisfaction. A total of 42 patients, mostly women, were enrolled in this study.

Finally, we were pleased as researchers and clinicians not to have felt limited by GlaxoSmithKline when trying to publish our data. In fact, to its credit, GlaxoSmithKline welcomed dissemination of this information to allow clinicians to get a sense of dosing parameters for sustained-released bupropion and, subsequently, to maximize response. Now that further studies are coming out, we can infer that our dose and duration may have been insufficient to reverse the sexual side effects in some patients and that longer treatment durations or higher doses may be helpful. Our study let physicians understand that underdosing or using too brief a trial may not lead to an optimal response in some patients. This information would not have been widely disseminated had GlaxoSmithKline pressured us not to publish this negative study. We encourage other pharmaceutical companies and journals to allow publication of negative studies for precisely these reasons.

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Early-Stage Vision and Schizophrenia

TO THE EDITOR: We read with interest the excellent contribution of Pamela D. Butler, Ph.D., et al. (1) on the dysfunction of magnocellular visual channels in schizophrenia. We would like to raise some points that merit further clarification and may increase the impact of their contribution. First, the effect of medication on their results should be investigated and discussed in more detail. Although the authors cite a single study in which there was found no acute effects of haloperidol, there is evidence that dopamine receptor antagonists alter both early and late components of visual event-related potentials and that a hypodopaminergic state may predominantly disrupt magnocellular functions (2). More directly, we found that schizophrenia patients receiving higher doses of conventional antipsychotics and exhibiting more severe drug-induced parkinsonism showed poorer magnocellular function (3). This issue is related to the problem of symptom variation. It has been demonstrated with both psychophysics and electrophysiological methods that the presence of different symptoms of schizophrenia is related to distinct patterns of visual information-processing abnormalities (4, 5). These questions should be addressed with correlation/covariance analyses or with the consideration of clinical subtypes, which may help resolve the apparent controversy of the literature correctly outlined, but not targeted, by the authors.

Dr. Butler et al. (1) suggested that magnocellular dysfunction is not related to attentional impairment. However, the sharp separation of early-stage vision and attention is somewhat artificial. The dorsal system, which receives its major input from magnocellular pathways, plays an important role in the attentional regulation of very early perceptual processes and is believed to participate in the integration of domain-specific information mediated by the ventral system (6). Therefore, the magnocellular deficit they measured can be a crucial aspect of attentional problems rather than an independent phenomenon.

This possibility may conceptually lead to the authors' final question for further research: What is the relationship between early visual dysfunctions and higher-level visuocognitive anomalies? We recently demonstrated that nonmedicated schizophrenia patients with spared magnocellular function exhibited dysfunction in a visual backward-masking task in which the spatial location of letters must be detected (a function of the dorsal stream) (7). Therefore, it seems that higher-level visual anomalies cannot be fully explained by a pure magnocellular deficit, which is likely to show a great degree of heterogeneity among patients with schizophrenia.

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Dr. Butler and Colleagues Reply

TO THE EDITOR: We thank Dr. Kéri et al. for their kind comments regarding our article. While the issue of the effects of antipsychotic medication is important, it is unlikely to account for our finding of magnocellular dysfunction in schizophrenia. As cited by Dr. Kéri et al. (Masson et al., 1993), evidence suggests that dopamine may play a role in processing low-spatial, high-temporal frequency stimuli, which are thought to elicit predominantly magnocellular responses. However, the role of dopamine may be to decrease response under these spatiotemporal conditions (1). Thus, blockade of dopamine receptors may in fact increase response under these conditions (1).

In addition, in previous visual backward-masking studies (2, 3), we did not find a difference in performance in patients who were tested while they were and were not taking medication. This finding is in agreement with the results of other studies, showing that antipsychotic medications do not appear to cause this deficit (e.g., reference 4).

In the data set from our article, no significant correlations were found between chlorpromazine-equivalent doses and performance on any of the magnocellular- or parvocellular-biased conditions. Further, there were two patients who received no antipsychotic medication; their performance was either similar to, or more impaired than, that of the patients receiving antipsychotic medication.

Patients with schizophrenia who are more ill frequently receive higher doses of medication. Dr. Kéri et al. cited one of their own studies (Kéri et al., in press) that indicates that patients taking higher doses of medication exhibit greater magnocellular deficits. It is possible that this relationship may not be due to medication; rather, it might be associated with greater negative symptoms in these patients. We have now tested low- and high-functioning patients and found that, even though chlorpromazine-equivalent doses were similar in the two patient groups, low-, but not high-, functioning patients showed a magnocellular deficit in relation to comparison subjects.

We agree that patients with chronic, low-functioning schizophrenia have greater visual-processing deficits than other schizophrenia patients. Also, we agree that magnocellular function may be critically involved in higher perceptual/cognitive processes, such as spatial localization and attention. In our article, however, we suggested that because the patients showed a selective magnocellular deficit (since responses to parvocellular-biased stimuli remained intact), our findings are not the result of general inattentiveness to the task. In fact, we observed that fixation ability is typically excellent in patients. Attentional processes, however, were not investigated directly.

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Neuropsychiatric Testing and the Menstrual Cycle

TO THE EDITOR: The *Journal* should be congratulated for publishing the preliminary work of Anne L. Hoff, Ph.D., et al. (1). However, I suggest that there are methodological flaws in the study design as well as erroneous conclusions drawn from inaccurate data in the report. It is well known that the temporal association of neuropsychiatric testing with documentation of the phases of the menstrual cycle phase is vital if valid conclusions are to be drawn concerning the hormonal milieu and its association with cognitive abilities (2–5). Unfortunately, the authors failed to do so.

It is also well known that the adult brain has tremendous neural plasticity, and manipulation of hormones results in significant improvements in various cognitive domains (6). In the study by Dr. Hoff et al., estrogen and progesterone levels were measured on a weekly basis for 4 weeks. The resulting data were then averaged. One can wonder whether these results were statistically significant, given the large variations during women's menstrual cycles; the range of estradiol has been reported as 50–600 pmol (Canada) or 40–260 pg/ml (U.S.) (7). More important, however, is the fact that not all estrogens are equal. Comparing endogenous estrogen with conjugated equine estrogen is not scientifically valid, since the human radioimmunoassay for 17β-estradiol does not measure levels of estrone sulfate, equilin sulfate, 17α-dihydroequilin sulfate, equilin, equilenin, 17β-dihydroequilin, or 17β-dihydroequilenin, which are all metabolic products of conjugated equine estrogen (7).

The same holds true for ethinyl estradiol, which is the synthetic estrogen found in most oral contraceptives. Taking oral contraceptives usually results in ovarian suppression; thus, there is no production of 17β-estradiol, the most prevalent endogenously produced estrogen. Thus, one has to question the measurement of 17β-estradiol in the women who were taking oral contraceptives. None of your readers would measure an imipramine level in a patient taking fluoxetine; however, measuring 17β-estradiol in patients taking oral contraceptives is its psychiatric equivalent and is therefore inaccurate.

Another methodological flaw in the study by Dr. Hoff et al. is apparent in the authors' progesterone measurement. This arises because endogenous (ovarian-produced) progesterone has a chemical structure different from that of the synthetic progestins used in hormone-replacement therapy (medroxyprogesterone) and oral contraceptives (norethindrone). Consequently, a measurement for endogenously occurring progesterone will not give meaningful values in women who are taking synthetic progestins, which are of a different chemical structure and would not be measured in an assay for endogenous progesterone (8).

In conclusion, because of the methodological problems and questionable significance of the serum assays, the conclusions of Dr. Hoff et al. cannot be justified. There is also the element of the duration of illness affecting cognition, which the authors do acknowledge. The examination of hormone levels performed by radioimmunoassay in the psychiatric population is long overdue. Although this work is needed, it requires rigorous protocols with temporally associated neuropsychiatric testing in populations experiencing similar endogenous hormonal milieus.

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Dr. Hoff and Colleagues Reply

TO THE EDITOR: Dr. Shuer raises some interesting and important issues with regard to our article. She contends that documentation of the phase of the menstrual cycle is critical in understanding the relationship of gonadal hormones to cognitive abilities because of the variation in hormones throughout a normal menstrual cycle. We agree with this point and know that documentation of the menstrual phase is most readily performed in the healthy, nonpsychiatrically impaired individuals Dr. Shuer has vigorously studied. In contrast, our study was an investigation into treatment-resistant female patients with schizophrenia. As we stated in the article, we found patients and staff to be unreliable in providing exact information regarding menstrual cycles. As is true of many schizophrenia patients, a number of our patients were amenorrheic, which complicates the picture even further. Additionally, because testing could not always correspond to the exact day of blood draws because of patient cooperation or ward logistics, we could not guarantee the exact correspondence of serum levels to day of testing. We dealt with these difficulties by sampling weekly over a 4-week period as an estimate of one menstrual cycle. The mean of a group of observations is the best single representation of those observations. We performed correlations of average serum level, variability, and highest level with level of cognitive functioning; all produced significant results. Despite the impreciseness in our measurement, we detected strong relationships, which would speak more to the robustness of these findings than to their lack of validity.

The second point Dr. Shuer makes is that it is unacceptable to measure estrogen levels in patients who are receiving hormone-replacement therapy or oral contraceptives because one must measure all of the metabolic products of these compounds. Because each of these compounds has a complicated pattern of release over time, it was not feasible in this study to measure all of their metabolic products because of the large number of necessary blood draws and associated laboratory costs. Additionally, since we were measuring levels in relatively young patients, some of whom were still ovulating, there was an ethical issue regarding discontinuing contraceptive therapy for these patients. Because of the relatively small numbers of female patients who were available for study (1), a similar study without the use of exogenous estrogen might take an inordinately long time, might leave us with a biased study group, or might not be undertaken at all.

Moreover, when we separated patients into those receiving oral contraceptives or hormone-replacement therapy (N=10) and those receiving neither (N=12), the pattern and strength of correlations of average estrogen with our summary global scale (and other scales) were exactly the same as were found in the total group. Correlations were $r=0.84$, $p<0.002$, and $r=0.83$, $p<0.001$, respectively. For the entire group, the correlation was $r=0.86$, $p<0.0000001$. These findings further support the meaningfulness of the average estrogen level as a global average measure of estrogen exposure.

In summary, we believe our findings are valid and justifiable. As we acknowledged in the article, there is room for refinement of our techniques. We believe, however, that our preliminary study is a good first step at studying this important issue.

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Suicide Risk in Placebo-Controlled Studies

TO THE EDITOR: The article by Jitschak G. Storosum, M.D., et al. (1) is potentially important for its argument for the ethical acceptability of using placebo-controlled trials in studies of major depression. However, the conclusions in the abstract do not reflect the substance of the text.

In the abstract it is stated without any caveats that the "Fear of increased risk of attempted suicide in the placebo groups should not be an argument against performing short-term and long-term, placebo-controlled trials in major depression" (p. 1271). This is in contrast to the text, in which, in regard to short-term studies, it is stated clearly that that is so only when "patients with 'suicide risk' [are] indeed excluded" (p. 1274) at entry into a study.

With regard to long-term studies, the authors noted that for the Netherlands data, suicidal subjects were excluded from one of the seven withdrawal studies for sustained responders, but there was no comment on whether those who were suicidal had been excluded before initial treatment in the other studies. There was only one extension study; again, no comment was made about possible prior exclusion, which the authors had already noted had been the case for 64 of 67 short-

term studies in the Netherlands for which this criterion could be determined. For the 14 long-term studies located with MEDLINE, it was noted of the three extension studies that suicidal subjects had been "excluded from the group of responders in the short-term phase" (p. 1272), whereas for the 11 withdrawal studies, "The exclusion of suicidal patients was not mentioned explicitly" (p. 1272). However, the absence of evidence of such specific exclusion does not constitute evidence by its absence.

These points are not consistent with an unqualified endorsement of placebo-controlled trials of antidepressants for those with major depression and suicide risk.

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Dr. Storosum and Colleagues Reply

TO THE EDITOR: We agree with Dr. Goldney that it might be possible to read a difference between the conclusion in the abstract and the text concerning the exclusion of patients at risk for suicide. However, almost all short-term placebo-controlled studies of major depression are conducted by excluding patients with "suicide risk." Therefore, in practice, placebo-controlled short-term studies are conducted in a patient population in which patients with "suicide risk" are excluded.

With regard to long-term studies, in the placebo-controlled phase of withdrawal studies and the extension phase of extension studies, only responders or remitters are included (1). Therefore, the patients included in the placebo-controlled phase of withdrawal studies and the extension phase of extension studies are probably not at risk for suicide.

On the basis of our study results, including trials conducted in the United States and in the European Union, we are convinced that the conclusion in the abstract reflects the substance of the text and that fear of increased risk of (attempted) suicide in placebo groups should not be an argument against performing short-term and long-term placebo-controlled trials in studies of major depression.

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Panic and Depression

TO THE EDITOR: Renée Goodwin, Ph.D., and Mark Olfson, M.D., suggested that detection and treatment of panic may reduce the risk of developing major depression in the community (1). A significantly smaller proportion (19%) of individuals who received treatment for panic than those who did not receive it (45%) developed major depression. Unfortunately, the authors' broad definition of treatment (consultation with any professional, including priests and counselors) hinders a clinical translation of their findings.

There is now, however, evidence that supports the conclusions of Drs. Goodwin and Olfson. We refer to our 2- to 14-year (median=8) follow-up study of 132 patients who satisfied the DSM-IV criteria for panic disorder with agoraphobia, who became panic-free after 12 sessions of behavior therapy based on exposure homework (2). Only 8 patients (6%) developed a major depressive disorder during the follow-up period.

Even though a control group was not available for study participation, the finding was remarkable because of the liability of patients with panic disorder to develop depression (1). Vollrath and Angst (3) found that the occurrence of depression was the most likely outcome after 7 years for patients initially diagnosed as suffering from "pure panic." Since cognitive behavior treatment of residual anxiety has been found to improve the outcome of depression (4, 5), it is conceivable that psychotherapy may decrease the vulnerability to depression of patients with panic disorder.

This is not necessarily true of the drug treatment of panic disorder. In our investigation (2), concurrent use of benzodiazepines and antidepressant drugs connoted a worse prognosis in terms of relapse into panic, confirming previous reports. In view of the potential sensitizing effects of antidepressant drugs (6), including emergence of depression during treatment of panic disorder, patients treated with these drugs may have a higher likelihood of developing depression than those treated with psychotherapy or placebo. Follow-up studies on this subject are of utmost importance.

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Drs. Goodwin and Olfson Reply

TO THE EDITOR: We were interested to learn from Drs. Ruini and Fava that a low prevalence of major depression has been found in a clinical study group of patients with panic disorder who were treated with cognitive behavior therapy. This obser-

vation is consistent with the association we reported of a lower incidence of major depression among individuals in an epidemiologic sample who received some form of treatment for panic. We are less impressed, however, with evidence linking the treatment of patients with panic disorder with antidepressants to a poorer outcome, specifically in terms of a greater risk of major depression. After a close reading of the literature, we have failed to find strong empirical support for the sensitizing effects of antidepressant medications. At least in the short term, there appears to be evidence that antidepressant medications are associated with a greater, rather than lower, incidence of depression among patients with panic disorder (1).

The work by Fava et al. (2001), suggesting that the combined use of antidepressants and benzodiazepines is associated with a worse prognosis among those with panic disorder, is based on a clinical study group and is open to selection bias. Specifically, patients with more severe or complex psychopathology may be at greater risk of developing comorbid depression and may also be more likely to be prescribed antidepressant medications.

We are in complete agreement with the sentiments expressed by Drs. Ruini and Fava that this is a topic of clinical and public health significance. Research is needed to evaluate the long-term outcome associated with the pharmacological and psychological treatment of broadly representative patient groups with panic disorder.

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Take the Time to Listen

TO THE EDITOR: Observing the metamorphosis of my chosen medical specialty from the 20th-century standpoint, I read with interest and pleasure Dr. Andreasen's editorial (1) and the almost-supplemental introspection by Richard G. Druss, M.D. (2). Dr. Andreasen's appeal is to all members of the association; Dr. Druss's recollections will attract more attention from educators and administrators. Both spread the message: Take more time to listen.

The act of listening for psychiatrists is more than recording the sound of another's voice. It is the most effective action one may take to initiate a bond with another. To me, it constitutes the essential element in opening the human communicative system. Perhaps predisposed but consciously influenced by my psychoanalytic experiences and impressed by interpersonal theory, I was guided in my professional life by the listening command. From its usage have come many rewards and gratifications from relations developed with my patients, students, and colleagues; they were my mentors.

Dr. Andreasen's messages come at a time in psychiatric experience quite different from that of my generation when we coped with the socially distressing issues of the latter half of the last century. Trying as those times were, I perceive the American medical environment of today as more demanding and less personally satisfying than that of the last century. The physician-psychiatrist then was largely in control of his or her professional environment and was able to take the time to listen to patients. Listening time involves much more than turning on the priorities of the auditory system. Then is when one observes as well the nonverbal, reflects, and interprets.

Dr. Druss illustrated by his recollections the long-time influence of a mentor giving unexpected personal time to a student. I doubt that all aspirant writers would take easily to receipt of their editorial gift splashed with red ink. My father also gave me a "red-ink special" shortly after I requested his editorial assistance with an early paper I was preparing. To my chagrin, it was returned to me covered with innumerable brilliant red scratch-outs, inserts, and suggestions. But it also left me angry and with bruised self-esteem. On the positive side, it alerted me to give more personal time to editing my writing efforts before submitting any document for publication.

Later a well-known colleague told me of his response to a "red-ink" editorial exposure requested by him—he never wrote again. Today if I am requested to edit a paper by a family member, student, or fellow worker, I do so in a much more informal manner. Fortunately, Dr. Druss is made of sterner stuff than my inhibited colleague. He has a droll sense of humor and laughs or smiles at the peccadilloes of himself and others. He is a delight to his faculty colleagues, including myself. His writing has never ceased.

Seldom do teachers in this country receive public expressions of appreciation, as was given to me in this Introspection. Badly needed in this country is a vastly improved reward system for teachers. I am grateful to Drs. Andreasen and Druss for their writings. They have aroused in me many gratifying memories of my days of teaching.

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