

## Severe Extrapyramidal Reaction Due to Risperidone in a Case of Neurofibromatosis

**Sir:** McKeith et al.<sup>1</sup> reported severe extrapyramidal side effects (EPS) during treatment with low doses of risperidone in three cases of Lewy body dementia. Subsequently, Mahmood et al.<sup>2</sup> discussed the case of a 30-year-old male schizophrenic who experienced EPS on a daily dose of 4 mg of risperidone. Risperidone has been found to have low propensity to induce EPS, but in some patients these symptoms can be particularly troublesome.

**Case report.** A 55-year-old man had prior history of suboccipital craniotomy for resection of left acoustic neurinoma, which was a manifestation of neurofibromatosis. The course of his illness was remarkable for gradual deterioration over a period of 10 years, due to central nervous system neurofibromas. No evidence of underlying parkinsonism had been present before. He had hypertensive hydrocephalus requiring shunting on three different occasions and exhibited behavioral changes characterized by episodes of violence and paranoid ideation. Risperidone was tried at a dose of 2 mg daily, and his behavioral symptoms gradually improved. Fifteen days later, he experienced a constellation of symptoms—rigidity, cogwheeling, slowness, anorexia, abulia, inability to ambulate, and bacterial conjunctivitis secondary to reduced blinking—requiring hospitalization. EEG showed bifrontal slow-wave abnormality, and brain SPECT markedly decreased activity in both frontal lobes as well as posteroparietal lobes. Neuropsychological testing obtained before this illness episode was relevant for impulsive and clumsy execution of copying tasks. Nonverbal concept formation was characterized by perseverative errors and difficulties changing cognitive set. The patient's executive functions were impaired: he revealed inefficiency in planning, organizing, and executing motor programs as well as emotional dyscontrol. Recurrence of hypertensive hydrocephalus and shunt malfunctioning were ruled out. Risperidone was stopped, and the patient gradually returned to his baseline state in 10 days. The patient was not rechallenged with an antipsychotic agent.

Even though our patient had never presented evidence of parkinsonism, the possibility of subtle Parkinson's disease cannot be completely ruled out. There was clinical, neuropsychological, and imaging evidence of frontal lobe dysfunction. This condition was more likely the sequelae of hydrocephalus rather than causally related to the neurofibromatosis.

Nyberg et al.<sup>3</sup> have postulated that the high 5-HT<sub>2</sub> blocking potency of risperidone is the crucial factor preventing the development of significant EPS. Schotte et al.<sup>4</sup> have demonstrated that risperidone occupies D<sub>2</sub> receptors more slowly than does haloperidol and argue that therapeutic dosages of risperidone are likely to remain below the threshold D<sub>2</sub> receptor occupancy that causes EPS. In the same vein, Kapur et al.<sup>5</sup> argue that if D<sub>2</sub> occupancy exceeds a certain threshold, this 5-HT<sub>2</sub>-mediated protection may be lost. The major excitatory synaptic influence on dopaminergic neurons in the ventral tegmental area comes from the prefrontal cortex via excitatory amino acid fiber pro-

jections that induce NMDA receptor-mediated burst firing of ventral tegmental area dopaminergic cells that project to the nucleus accumbens.<sup>6</sup> It is possible in frontal lobe damage that this circuit has diminished influence, lowering the occupancy threshold of the D<sub>2</sub> receptors for EPS. Even though the mechanisms responsible for EPS remain controversial, patients with frontal lobe damage may be at a higher risk for complete occupancy of D<sub>2</sub> receptors, which in turn would negate the 5-HT<sub>2</sub>-mediated protection against extrapyramidal symptoms. Clinicians are advised to be cautious in the use of risperidone, as well as other antipsychotics, in those patients who have neurofibromatosis.

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### Behavior Therapy and Serotonin Dysregulation

**Sir:** In light of the current popularity of the serotonin hypothesis of obsessive-compulsive disorder (OCD),<sup>1</sup> along with the fact that behavior therapy effectively reduces obsessions and compulsions<sup>2</sup> and normalizes cerebral glucose metabolism in OCD,<sup>3,4</sup> Dr. Baer recently suggested that behavior therapy is a form of endogenous serotonin therapy.<sup>5</sup> This is an interesting conjecture. However, I would like to offer two caveats.

First, the serotonin hypothesis (or hypotheses) does not have a strong empirical basis and has been subject to cogent criticisms (e.g., see the comments by Salkovskis<sup>6</sup>). The possibility of serotonin dysregulation was first suggested by the finding that people with OCD respond to serotonin reuptake inhibitors (SRIs) such as clomipramine. The strongest support for this hypothesis comes from studies showing that OCD can be treated with other SRIs, such as fluoxetine.<sup>1</sup> Pharmacologic challenge studies and studies of peripheral neurotransmitters and metabolite concentrations have failed to consistently support the role of

serotonin dysregulation in OCD.<sup>1</sup> Thus, it seems premature to suggest that behavior therapy represents endogenous serotonin therapy.

The second caveat is that behavior therapy is an effective treatment for a variety of anxiety disorders, including specific and social phobias,<sup>7</sup> panic disorder with agoraphobia,<sup>8</sup> and post-traumatic stress disorder (van Etten M, Taylor S. Manuscript submitted). Behavior therapy is used in much the same way in treating each of these disorders. The main elements of treatment consist of providing prolonged exposure to fear-evoking stimuli (either in vivo or in imaginato) while limiting avoidance and escape behaviors. In these disorders, dysregulations in other neurotransmitter systems (e.g., noradrenergic and GABA systems<sup>1,9</sup>) appear to play a more important role than serotonin dysregulation.<sup>1</sup> Accordingly, it seems likely that behavior therapy is broad-based in its effects and probably normalizes functioning in a variety of neurotransmitter systems. Behavior therapy may be best regarded as endogenous polytransmitter therapy.

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#### Antidepressant Effects of Nicotine

**Sir:** I was surprised and chagrined to read the article “Antidepressant Effect of Transdermal Nicotine Patches in Non-smoking Patients With Major Depression” by Dr. Salín-Pascual and associates<sup>1</sup> in the *Journal*.

It is hardly a medical mystery that nicotine provides improvement in mood for smokers. For any physician with a modicum of clinical experience, this mood elevation has been reported by most smokers and is often given as a reason for the difficulty in stopping smoking. For any psychiatrist with a modicum of clinical experience, it is no medical mystery that patients with serious and acute episodes of mental illness have special difficulty in smoking cessation. Many patients with dys-

phoria, depression, and demoralization have stated that cigarette smoking gives them a lift in mood.

It is also well known that nicotine is a highly addicting drug. Most probably, it takes more than 4 days for a normal adult to become habituated to nicotine, but one might be concerned that vulnerable persons, such as those suffering from major depression, might develop tolerance much more quickly than those without a major mental illness. Since major depression is such a devastating illness and the suffering is so great, a patient experiencing this distress may be sufficiently desperate for relief that he/she might turn to any substance that offered some relief, including nicotine. A patient would possibly be more likely to do this especially after being exposed to the “benefits” of nicotine in a research study where he/she may feel that nicotine use has received the “blessing” of the researchers.

Did those 10 nonsmoking patients in the Salín-Pascual et al. study remain nonsmokers after their exposure to the mood-elevating properties of nicotine? Did any of these vulnerable outpatients with major depression turn to smoking as a primary or adjunctive way to alleviate the pain of their depression?

Have the news media and cigarette manufacturers in either the United States or abroad become aware of the study by Salín-Pascual and colleagues? Will this study be reported in the mass media and make more difficult the major efforts to reduce smoking and create a smoke-free environment which has been found to be so much healthier for all of us? Will cigarette manufacturers use this study to bolster the “benefits of smoking?” Will ads appear, especially in Third World countries whose trade with the United States is, in part at least, dependent upon purchasing cigarettes from the American tobacco industry, touting the antidepressant benefits of nicotine and smoking?

The above questions raise in my mind some of the many ethical issues about such research. The neurobiology and neuropharmacology of nicotine as well as of all abused substances are of great interest to every one of us; the kind of research reported in the study by Salín-Pascual et al., however, seems unnecessary in light of current, common knowledge about the effects of nicotine on human beings and, particularly, on human beings suffering from a depressed mood.

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#### Dr. Salín-Pascual Replies

**Sir:** I thank Dr. James W. Hawkins for his interest in our paper.<sup>1</sup> About his concern with the 10 nonsmoking patients we reported, we have followed them, and none of them are using nicotine through either cigarettes or other replacement forms (patches or gum). It has been shown that nicotine patches as a replacement for nicotine addiction do not produce the same feeling as smoking a cigarette. The pharmacologic signal in smoking is an on-off type, where people who inhale the smoke clearly perceive that the nicotine is in their system.<sup>2,3</sup> Nicotine patches provide a different type of signal, which is the reason this kind of device is useful only for alleviating withdrawal symptoms. In a different study (Unpublished data), we used normal volunteers to evaluate sleep changes after 4 continuous

days with nicotine patches. Only one volunteer asked for more patches because she felt "more energetic" during those days she wore the patches (a careful interview showed that she had dysthymia). Except for this one instance, no other patient or normal volunteer has abused nicotine patches. One extra limitation for becoming addicted to nicotine patches is the high cost of a single box with 28 patches (around \$50 U.S. currency).

With respect to the impact our research may have on news media and cigarette manufacturers, as far as we know, only one tobacco company has asked for a reprint of a previous paper, the one in which we reported sleep and mood effects related to nicotine in both depressed and normal volunteers.<sup>4</sup> Other than that, only the academic world has been interested in our research.

I am concerned that our research may be misunderstood. I do not recommend the use of nicotine in any form as an antidepressant treatment. On the contrary, I am aware that the relationship between depression and nicotine is a dangerous one, and some recent publications support this statement.<sup>5,6</sup> But I believe that understanding the effects and limitations of nicotine in depression could give insight into the pathophysiology of depression. I do not believe that nicotine is a good antidepressant. Maybe it produces only a short-lasting improvement in mood, but patients need to keep administering more nicotine in order to function and to confront other, perhaps more severe, withdrawal symptoms. Perhaps this is the same kind of relationship that occurs with some insomnia patients when they drink alcohol: the alcohol works at the beginning, but at the end it only increases patients' problems. I believe the type of clinical research that we are involved with could give us some idea about the real antidepressant effects of nicotine, without biasing the facts.

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#### Panic and Paranoia

**Sir:** Galynker and colleagues<sup>1</sup> present four most interesting cases of patients whose panic attacks are accompanied by a variety of psychotic symptoms and in the process alert both clinicians and researchers to what may be an important but neglected phenomenon in the development of psychotic disorders.

Few experiences are more stressful than a panic attack. Stress has been implicated in the exacerbation or onset of schizophrenia.<sup>2</sup> Indeed, it has been estimated that the risk for the development of schizophrenia is increased tenfold among persons with panic attacks compared to the general population.<sup>3</sup> It has also

been reported that panic attacks were a predictor, albeit weak, of the development of schizophrenia in the two waves of interviews conducted in the NIMH Epidemiologic Catchment Area Program.<sup>4</sup>

The work of Reich and colleagues<sup>5,6</sup> may shed some light on these provocative observations. They found that 15 (54%) of 28 panic disorder patients met criteria for paranoid personality disorder.<sup>5</sup> They had earlier described two patients who developed schizoid and paranoid personality features in the course of development of new panic disorders.<sup>6</sup>

These findings suggest that panic might serve as an emotional substrate upon which paranoia might develop. Persons who have panic attacks have a natural tendency to search for explanations of their intensely dysphoric experiences. If these persons already have some tendency toward psychotic thinking,<sup>7</sup> it might be more likely for them to "explain," even to the point of perceiving, their experiences in a psychotic or paranoid way.

The high rates of panic attacks among persons with schizophrenia,<sup>8</sup> which was noted by Galynker et al., has led Siris<sup>9</sup> to propose a treatment strategy for chronic schizophrenia based on using adjunctive medications to reduce the stress engendered by such untreated associated psychiatric syndromes. Such clinical links should also be more aggressively investigated to see what they might offer students of psychotic disorders in the way of etiologic hypotheses. The authors are to be congratulated for bringing their cases to your readers' attention.

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#### Drs. Galynker and Winston Reply

**Sir:** We appreciate Dr. Bermanzohn and colleagues' interest in our report.<sup>1</sup> The relationship between panic attacks, psychosis, and schizophrenia is an intriguing one, and we are grateful to the authors for emphasizing a possible etiologic role of panic attacks in schizophrenia. The overlap between panic attacks and psychosis plus the complexity of underlying neuroanatomical

substrates also underscores the limitations of the currently prevailing categorical approach to psychiatric symptoms, which often disregards such relationships. An alternative dimensional approach emphasizes continuity of psychiatric symptomatology and corresponding neurobiology across diagnostic categories. This dimensional approach could be as valuable in exploring the association between panic and psychosis in a number of psychiatric illnesses as it has been in investigating the relationship between negative and depressive symptoms in schizophrenia and other neuropsychiatric disorders.<sup>2-5</sup>

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## Switching Drug Class After Initial SSRI Failure

**Sir:** The report by Joffe et al.<sup>1</sup> underscores an important issue for the practicing psychiatrist, namely, the appropriate next step for the nonresponder to a serotonin selective reuptake inhibitor (SSRI) antidepressant. Their data from an open-label, non-placebo-controlled database review showed that 51% of patients responded to a second SSRI after experiencing lack of efficacy with their initial SSRI. This response represents an important question to be assessed in controlled trials, and the authors acknowledge that the lack of a placebo-controlled design limits their conclusions.

A considerable debate exists in the psychiatric community regarding appropriate handling of this situation. Other open-label trials have reported improvement after initial SSRI failure: Fava et al.<sup>2</sup> reported that 15 patients who failed to respond to 20 mg/day of fluoxetine (50% reduction in scores on the 21-item Hamilton Rating Scale for Depression) responded to dosages up to 60 to 80 mg/day despite the results of controlled trials<sup>3-5</sup> showing no increased efficacy with increasing doses. In another open-label trial, Joffe and Schuller<sup>6</sup> reported a 68% response rate (marked or complete) after buspirone augmentation of SSRI nonresponders.

In addition to augmentation, other strategies include switching to a different biochemical class. Evidence suggests that agents with mixed serotonin/norepinephrine activity, such as the serotonin-norepinephrine reuptake inhibitors (SNRIs), some tricyclic antidepressants (TCAs), or monoamine oxidase inhibitors (MAOIs), may be more efficacious than SSRIs, most nota-

bly in inpatients,<sup>7,8</sup> and therefore may be appropriate alternatives to the SSRIs. Nelson et al.,<sup>9</sup> in an open-label study, found that patients who received coadministration of desipramine and fluoxetine showed a more robust antidepressant response than a historical control group that received desipramine alone. Other studies have suggested that the SNRI venlafaxine may have greater efficacy than fluoxetine in both inpatient<sup>10</sup> and outpatient settings.<sup>11</sup>

So how should the practitioner treat the nonresponder to an adequate SSRI trial? As Joffe and colleagues<sup>1</sup> point out, placebo-controlled trials of treatment strategies are required before definitive suggestions are available. Currently, however, switching classes and augmentation<sup>12-15</sup> remain the strategies with the most empirical backing if the patient has in fact received an adequate trial of the initial antidepressant.

Treatment guidelines for major depression<sup>13,14</sup> suggest switching biochemical classes of antidepressants or augmentation therapy with lithium or T<sub>3</sub>. Switching classes in the pharmacologic treatment of depression may be analogous to a strategy of switching classes in the treatment of hypertension if the first medication trial is unsuccessful. According to the fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V),<sup>16</sup> one of the options after nonresponse to a drug, as outlined in a treatment algorithm, is to switch to a drug from another class. Kaplan and Gifford<sup>17</sup> state that, of all the options outlined by JNC V, substitution with another agent is perhaps the most productive.

Joffe and colleagues present useful data. However, the clinician and patient should determine the most effective and tolerable alternative to SSRI therapy. Switching the drug class may give some patients the possible advantage of dual noradrenergic and serotonergic activity while minimizing the number of different medications or the necessity for and expense of laboratory studies seen in many augmentation strategies. A double-blind, placebo-controlled study involving treatment of SSRI nonresponders with alternative therapies or placebo is warranted to evaluate the optimal strategies.

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### Nizatidine-Induced Delirium in a Nonagenarian

**Sir:** Central nervous system (CNS) reactions have been associated with histamine H<sub>2</sub> blocker use. Of the 78 cases of H<sub>2</sub> blocker-associated CNS disturbances reported in the literature, 63 cases occurred with cimetidine, 13 with ranitidine, and 2 with famotidine.<sup>1</sup> Thus far, no cases of nizatidine-associated CNS toxicity have been cited. The following case report describes a patient in which nizatidine maintenance induced symptoms of delirium.

**Case report.** Ms. A, a 93-year-old white woman with a history of major depressive disorder, cerebrovascular accident (CVA), hypertension, and hypothyroidism, was admitted to the medical unit with mental status changes (confusion and lethargy). She was receiving sertraline 50 mg/day, enalapril 25 mg/day, and levothyroxine 50 µg/day. At admission, a CT scan revealed that Ms. A had had a second CVA (a small pontine lesion), and in addition, suffered from dyspepsia, for which she was given nizatidine 300 mg/day. Her sertraline was stopped, and once her condition stabilized, she was discharged on her other medications. Two months after her discharge, Ms. A experienced paranoid delusions that her home attendant was spying on her and seeking to steal her money. She also developed visual and tactile hallucinations, agitation, and confusion. Ms. A's SMA-20 was normal, and her symptoms were initially recognized as psychosis but not as delirium. She was started on perphenazine 8 mg/day, had no improvement, and was subse-

quently hospitalized owing to dehydration. After hydration, the patient remained confused and agitated, and she continued to experience visual and tactile hallucinations. Ms. A's neurologic examination showed no focal deficits. Her CBC, SMA-20, thyroid function tests, B<sub>12</sub>, folate, and rapid plasma reagin results were all within normal limits, and her MRI revealed two old infarcts. Three weeks after the onset of paranoid ideation and 1 week after her hospitalization, Ms. A was transferred to the psychiatry service, where a diagnosis of delirium was made. Nizatidine was discontinued, and after 4 days, her paranoid ideation and hallucinations resolved. Perphenazine was discontinued, and Ms. A was then discharged on enalapril and levothyroxine. She has been asymptomatic for 2 months since her discharge.

To our knowledge, this is the first report of delirium or any adverse CNS reaction resulting from nizatidine administration. The delirium occurred at the recommended maintenance dose of 300 mg/day. It is well known that most commercial H<sub>2</sub> blockers are associated with CNS side effects. Histamine is known to have depressant effects on the reticular activating system; however, H<sub>1</sub> receptor blockers appear to be more potent than H<sub>2</sub> receptor blockers in reversing this effect.<sup>2</sup> H<sub>2</sub> blockers also interact with the GABA and cholinergic receptors, although the clinical relevance of these observations remains unclear.<sup>3</sup> The lack of CNS symptomatology in patients receiving nizatidine was assumed to be due to its inability to cross the blood-brain barrier. It is possible that Ms. A's advanced age contributed to the onset of her symptoms, in that blood-brain changes due to aging or CVA may have exposed the patient's brain to nizatidine. In fact, a typical clinical trial with an H<sub>2</sub> blocker included only patients within the age range of 21 to 79 years.<sup>4</sup> The present report can only be considered suggestive, given the multiple comorbidities the patient had. However, as U.S. population demographics continue to shift toward ever greater numbers of octogenarians and nonagenarians, it might be prudent to include these segments of the population in future clinical trials.

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