Agranulocytosis Associated With Lamotrigine

TO THE EDITOR: Lamotrigine has been associated with hematologic side effects, including thrombocytopenia and leukopenia. A recent case report (1) described an 11-year-old girl with neurodevelopmental abnormalities and seizures who was treated with lamotrigine and developed reversible agranulocytosis. We report, to our knowledge, the first case of agranulocytosis associated with lamotrigine treatment in an adult.

Ms. A was a healthy, successful, 30-year-old woman with a psychiatric history of anorexia nervosa and past substance dependence and abuse of opiates, benzodiazepines, stimulants, and alcohol. She had a history of bipolar II disorder with refractory depression; she had experienced multiple ineffective trials of medication and ECT.

Four weeks after beginning treatment with lamotrigine Ms. A was receiving a dose of 100 mg/day. At bedtime we added a low dose of valproic acid, 125 mg/day, and slowly increased the dose to 250 mg/day. In the past a dose of 1250 mg at bedtime given to Ms. A had resulted in a blood level of 103 μg/ml of valproic acid. Her concurrent medications included 2 mg b.i.d. of clonazepam, 150 mg b.i.d. of sustained-release bupropion, and 5 mg of olanzapine at bedtime as needed. Ms. A was briefly hospitalized and was found to have a WBC count of 6,700 cells/mm^3, 42% neutrophils, and an absolute neutrophil count of 2,814 cells/mm^3.

Two weeks after the addition of valproic acid therapy Ms. A continued to fare poorly, and suicidal ideation led to another brief hospitalization. It was noted on admission that her WBC count was 3,200 and her absolute neutrophil count was 446. Two days later her WBC count was 2,600, and her absolute neutrophil count was 580. Lamotrigine therapy was discontinued at this point, and Ms. A was discharged. Two days after discharge her WBC count was 3,300, and her absolute neutrophil count was 1,386. Her mild leukopenia disappeared without further intervention while she was taking 750 mg of valproic acid at night.

This account clearly shows an association of neutropenia and agranulocytosis with lamotrigine therapy; the conditions appeared after a rapid titration of the patient's lamotrigine dose to 100 mg/day. Because valproic acid can increase lamotrigine serum levels as much as 211% (2), it may have contributed to the observed agranulocytosis.

It is unlikely that the other medications the patient was taking were responsible for the agranulocytosis, given its resolution after discontinuation of lamotrigine therapy and continuation of the other medications. However, valproic acid has been documented to cause blood dyscrasias, including neutropenia. And olanzapine has been associated with one case of agranulocytosis (3) and may prolong clozapine-induced neutropenia. This suggests that complex interactions among these drugs may have lowered the threshold for lamotrigine-induced agranulocytosis. Neither bupropion nor any benzodiazepine has been associated with bone marrow suppression.

Lamotrigine may be an important option in the treatment of bipolar depression and rapid cycling. Given that many common medications have been associated with agranulocytosis, such as trazodone, cimetidine, and the penicillins, it is unlikely that the two current reports mandate any current change in drug monitoring.

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High Doses of Levothyroxine for Refractory Rapid Cycling

TO THE EDITOR: Rapid-cycling bipolar disorder is notoriously difficult to treat (1). Hypothyroidism has been associated with rapid cycling in patients with bipolar disorder (2). High doses of levothyroxine (supranormal doses that elevate serum thyroxine levels above normal) have been reported effective in the treatment of refractory rapid cycling in preliminary studies (3). In this case a patient with severe treatment-resistant rapid-cycling bipolar disorder was successfully treated with high doses of levothyroxine, as demonstrated by an unplanned on-off-on trial.

Ms. A was a 36-year-old married woman who was disabled by bipolar disorder. A rapid-cycling pattern began in her teens and included hypomanias and depressions characterized by low-energy auditory hallucinations and suicidality. The rapid cycling was unrelated to the effects of antidepressant medications. After her initial hospitalization in 1991 following a suicide attempt, she required multiple hospitalizations despite treatment with fluoxetine, lithium, various antipsychotics, valproic acid, and carbamazepine. There was no history of primary thyroid disease, although Ms. A was taking liothyronine when she was referred to me in 1994.

Her rapid cycling, which occurred every few days to every few weeks, continued despite a treatment regimen of 200 mg/day of clozapine, 1000 mg b.i.d. of valproic acid in therapeutic doses, and 0.15 mg/day of levothyroxine. The results of tests of her thyroid function were normal.

After Ms. A's levothyroxine dose was increased to 0.25 mg/day in 1995 in an effort to treat her rapid cycling, she had a marked decrease in the frequency and severity of her cyclic episodes. She was proud that she "set her record" for staying out of the hospital. Olanzapine and verapamil therapy were tried, but there was little effect. She was maintained in a mildly hyperthyroid state; she had an increased resting heart rate of 120 bpm and a mild tremor. In 1998 Ms. A had a slightly elevated free thyroxine index of 3.9 ng/dl and a decreased thyroid-stimulating hormone (TSH) level of 0.02 mU/ml.

In March 1999 her internist insisted that her levothyroxine dose be decreased to 0.1 mg/day because of concern that her hyperthyroid condition was interfering with management of her newly diagnosed non-insulin-dependent diabetes mellitus and placing her at risk for osteoporosis.

Within several weeks Ms. A developed severe psychotic depression and suicidality, requiring her first hospitalization in 4 years. Her TSH level was elevated, at 10.05 mU/ml, and her free thyroxine index was normal at 2.7 ng/dl. She cycled between depression and hypomania every few days in the hospital. With the approval of a consulting endocrinologist and the agreement of her internist, her dose of levothyroxine was again increased to 0.25 mg/day. Ms. A began to improve within a week and was discharged from the hospital after 14 days.

For the last 7 months she has remained in a nearly euthymic state, with perhaps mild euphoria and much improved functioning, except for a brief period of recurrent cycling that remitted relatively quickly after we increased her levothyroxine dose to 0.3 mg/day. Ms. A continues to be mildly hyperthyroidal; she has a high-normal free thyroxine level of 1.5 ng/dl and a decreased TSH level of less than 0.1 mU/ml.

This case represents, in a sense, an accident of nature that allowed a test in a clinical setting of the efficacy of high doses of levothyroxine for rapid-cycling bipolar disorder in an on-off-on design. The patient's clinical course was clearly consistent with the hypothesis that such treatment is efficacious. Risks such as tachycardia, tremor, diaphoresis, and possibly osteoporosis must be considered. But for carefully selected patients with refractory rapid cycling who are closely monitored, the potential benefits of high doses of levothyroxine may outweigh the risks (4).

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Delirium With Autoimmune Thyroiditis Induced by Interferon Alpha

TO THE EDITOR: Interferon alpha (INF-α), which is antiviral, immunomodulatory, and antiproliferative, is currently used to treat carcinomas and chronic viral infections. Although it is established in the psychiatric field that INF-α often causes a depressive state (1), a large-scale clinical study has indicated a risk of thyroid abnormalities from INF-α treatment (2). We encountered a patient who exhibited confusional delirium due to autoimmune thyroiditis after treatment with INF-α.

Ms. A, a 23-year-old woman with a 6-month history of INF-α therapy after a right nephrectomy for renal cell carcinoma, had no apparent psychiatric history. Ten days after the cessation of INF-α treatment, with confirmation that there was no recurrence of carcinoma in the abdominal region on magnetic resonance imaging, she developed delirium with a fluctuating level of consciousness and psychomotor excitement and was brought to a psychiatrist by her parents. She was immediately admitted to a psychiatric unit.

Although a brain computerized tomography scan did not reveal any signs of metastases, the results of laboratory tests showed abnormal thyroid function: a thyroid-stimulating hormone (TSH) level of 53.97 μU/ml, free triiodothyronine level of 2.24 pg/ml, free thyroxine level of 3.6 pg/ml, a positive microsomal test result of X409600, a positive antithyroid peroxidase antibody test result of 465 U/ml, and a positive antithyroglobulin antibody test result of 3.7 U/ml. There were no abnormal test results for liver and kidney function. Echo examination revealed that the size of Ms. A's thyroid gland was within normal limits. She had not been diagnosed with thyroid dysfunction before the current admission. Thyroid hormone replacement therapy was initiated on the seventh day of admission. Her TSH level returned to normal in 3 weeks, and her delirium gradually improved with thyroid hormone replacement therapy and without the use of neuroleptics. After recovery from the episode Ms. A could recall nothing from the first 10 days of admission.

In this case the effect of INF-α itself on the central nervous system was not held responsible for the patient's delirium because it did not appear during INF-α treatment but 10 days after treatment ceased and because thyroid hormone replacement therapy improved the patient's symptoms. The thyroid side effect of INF-α treatment, which often requires long-term thyroid replacement therapy even after the cessation of treatment, is reported to appear frequently after 4 months of INF-α therapy because of an enhanced autoimmune mechanism (2).

Acquired hypothyroidism is reported to cause three types of psychiatric conditions that are historically categorized as myxedema madness (3): the hallucinatory-paranoid state, depression, and delirium (4). For this reason we considered the patient's delirium to have been induced indirectly by autoimmunological processes in the thyroid gland due to repeated INF-α administration. Although immunosuppressants, including corticosteroids, cyclosporin A (5), and FK506 (6), are well known to cause delirium, the present case represents a possibility that INF-α, which is an immunoactivator, causes delirium by means of thyroid autoimmunological toxicity. Psychiatrists should consider the possible existence of a thyroid abnormality in patients with neuropsychiatric disorders induced by INF-α.

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γ-Hydroxybutyrate Withdrawal and Chloral Hydrate

TO THE EDITOR: γ-Hydroxybutyrate, a natural catabolite of γ-aminobutyric acid (GABA), is sold illegally as a euphoriant (1). An overdose of this drug of abuse can cause coma and death (2). Reports of severe and difficult-to-treat withdrawal syndromes are also emerging (3). We describe a case of γ-hydroxybutyrate withdrawal symptoms abruptly interrupted by chloral hydrate therapy.

Ms. A, a 20-year-old woman, came to the emergency room requesting help in discontinuing γ-hydroxybutyrate. Initially a casual user, she had escalated her use of γ-hydroxybutyrate to every few hours around the clock over the prior 4 months. Over several weeks she had lost 20 lb, and her mood had deteriorated into crying spells. Although she had experimented with other illicit substances, she had used only γ-hydroxybutyrate and marijuana in the previous 2 weeks.

At her admission examination Ms. A's pulse of 114 bpm was the only remarkable physical or neurological finding. A mental status examination found no notable abnormality in cognition, thought processing, or thought content. The results of her laboratory tests uncovered only a urine drug screening that was positive for benzodiazepines after she received a dose of lorazepam.

By the second hospital day Ms. A's mental status had begun to deteriorate. She responded continuously to hallucinations in all sensory modalities. She did not sleep and was oriented only to person. Doses of lorazepam and haloperidol, each up to 10 mg over 24 hours, had no clear effect on her insomnia, irritability, and hallucinations. Her persistent tachycardia was never higher than at admission. She developed mild diaphoresis, dilated pupils, and a moderate resting tremor.

After Ms. A had 5 nights without sleep, little food intake, and no improvement in her dramatically high levels of delirium and psychosis, consideration was even given to general anesthesia. Before more extreme measures were taken we initiated a trial of chloral hydrate. After receiving 1500 mg, Ms. A fell asleep and slept almost 24 hours, during which she took two more doses of chloral hydrate, 1000 mg, as soon as she roused during that period.

The next morning Ms. A was alert, fully oriented, amnestic for the period since admission, and free of hallucinations. She slept well the next few nights while taking chloral hydrate. During a brief recurrence of much milder hallucinations she responded minimally to a dose of haloperidol, but by discharge, after a 10-day hospitalization, they had disappeared, and she was sleeping well.

γ-Hydroxybutyrate withdrawal can develop rapidly and resist pharmacologic interventions, including high doses of benzodiazepines. In this case chloral hydrate appeared to rapidly reduce levels of delirium and psychosis, perhaps by its effect on the severe insomnia seen during γ-hydroxybutyrate withdrawal. Chloral hydrate is rapidly metabolized into trichloroethanol, the active form, which has an unknown mechanism of action. In the brain, γ-hydroxybutyrate receptors have been identified, and γ-hydroxybutyrate has been found to affect dopamine release. However, little else is clear about its effects. In summary, this increasingly popular drug of abuse has dangerous characteristics, and effective treatments for acute related problems are lacking. Chloral hydrate may have some specific efficacy for γ-hydroxybutyrate withdrawal symptoms.

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Citalopram and Haloperidol for Psychotic Depression

TO THE EDITOR: Although the antidepressant-antipsychotic treatment combination has been found to be distinctly superior to antidepressant or antipsychotic therapy alone for psychotic depression (1, 2), reports on the efficacy of the combination of a selective serotonin reuptake inhibitor (SSRI) with a neuroleptic in the treatment of psychotic depression (3) are rare. We describe an apparent antidepressant response to combined treatment with citalopram and an antipsychotic in patients with psychotic depression.

We observed seven patients (five men and two women; mean age=36.7 years, SD=13.8, range=26–61) who met the DSM-IV criteria for a major depressive episode with psychotic features; six had major depressive disorder (four of these with a single episode and two with recurrent episodes), and one had bipolar I disorder. The essential psychotic features of these patients were auditory hallucinations and nihilistic, poverty, and persecutory delusions. Written informed consent was obtained from the subjects after complete description of the study. They were treated with citalopram, 20 mg/day p.o., and haloperidol, 4 mg/day p.o. The doses of haloperidol were increased to 5–9 mg/day in six patients with poor response during the first week, and the doses of citalopram were increased to 30–40 mg/day in five patients with poor response during the second week. Both the citalopram and haloperidol doses were increased in four patients. Two patients were being treated with mood stabilizers (lithium or carbamazepine) before entering the study. No other psychotropic drug was administered except triazolam (0.25–0.50 mg/day).

The Montgomery-Åsberg Depression Rating Scale (4) and the Standardized Assessment of Patients with Depressive Disorders items for psychotic symptoms and signs (score range=0–14) (5) were administered at baseline and weekly for 7 weeks. Clinical Global Impression (CGI) severity ratings were

performed at baseline and after 7, 21, 35, and 49 days. All patients completed the 7-week trial and showed a greater than 50% improvement in scores on the Montgomery-Åsberg Depression Rating Scale at 7 weeks, as well as a reduction in scores on the Standardized Assessment of Patients with Depressive Disorders and the CGI severity scale to 0–2 and 1–2, respectively. All patients were considered responders. Overall clinical improvement was observed during the fourth week for depressive symptoms and during the third or fourth week for psychotic symptoms. Perceptual disability was restored to a more normal state, and later delusional thought waned. Cotreatment with mood stabilizers produced a similar response. Three patients reported nausea (treated for 7 weeks and for 10 and 13 days, respectively, with the antidyspepsia drugs sucralfate and metoclopramide at 10–20 mg/day on an as-needed basis), and three patients reported sedation. Mild stiffness was found in four patients.

To our knowledge, this is the first description of the efficacy and safety of the SSRI citalopram in combination with haloperidol in the treatment of psychotic depression, for which response to placebo is almost absent. Although a larger study group and controlled studies are needed, the efficacy of citalopram may be similar to that of the tricyclics in combined antidepressant-antipsychotic treatment of psychotic depression.

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Psychological Defense Styles and Childhood Sexual Abuse

TO THE EDITOR: The article by Sarah E. Romans, M.D., F.R.A.N.Z.C.P., et al. (1) is a valuable contribution to the literature on the effects of childhood traumatic experiences. As the authors noted, very few investigations have studied a nonclinical population.

This study found that childhood sexual abuse—even including intercourse—was not related to higher levels of dissociation. This conclusion should be understood in a larger context. Our findings (2, 3) suggest that early onset and chronicity of childhood trauma are related to the development of dissociation, and the current study did not address these factors. On a theoretical basis, some younger children are believed to have a high capacity to dissociate and maintain that high level only through repeated traumatization. In a community population with relatively low levels of psychiatric illness or disability, one might suspect that many women who were sexually abused suffered relatively limited abuse, for which they may have compensated. In clinical populations one would be more likely to find the types of psychological damage (perhaps including dissociation) that result from chronic traumatization beginning at an early age.

Despite its limitations, this study is an important first step. It is critical to study nonclinical populations to determine what psychiatric problems develop from what kind of life experiences. Just as important, it must be determined what protective mechanisms exist that may protect traumatized children from suffering ongoing psychological damage from their experiences.

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Adenosine and Antidepressant Effects of Sleep Deprivation

TO THE EDITOR: Joseph Wu, M.D., et al. (1) elegantly showed that 1) depressed patients who responded to sleep deprivation had higher relative pretreatment metabolic rates in the medial prefrontal cortex, ventral anterior cingulate, and posterior subcallosal cortex than nonresponders and normal volunteers and that 2) metabolic rates in the medial prefrontal cortex and frontal pole significantly decreased after sleep deprivation in responders. The authors suggested that dopaminergic and serotonergic systems may be involved in the effects of sleep deprivation.

We propose that the inhibitory neuromodulator adenosine may underlie the findings of this study. Adenosine inhibits excitatory neurotransmission and overall neuronal activity by acting on adenosine A1 receptors, which are widely distributed in the mammalian brain (2). Adenosine's pivotal role in sleep modulation is strongly supported by the subjective and EEG-defined arousal produced by its antagonists, caffeine and theophylline, as well as by the fact that extracellular adenosine concentration is linked to neuronal metabolic activity (3). Regarding sleep deprivation specifically, it is noteworthy that 1) adenosine levels progressively increase after sustained, prolonged wakefulness in cats (3), 2) A1 receptor agonists mimic the electroencephalographic effects of sleep deprivation in rats (4), and 3) caffeine suppresses recovery sleep after deprivation (3). Therefore, the reduced metabolic rates observed in responders after sleep deprivation (1) are consistent with neuronal inhibition secondary to increases in extracellular adenosine. In addition, higher baseline metabolic rates in these patients may reflect a deficient adenosinergic inhibitory tone.

Additionally, Dr. Wu et al. (1) wondered if "the metabolic correlates of the antidepressant response to sleep deprivation…also characterize response to other forms of treatment such as antidepressant medications, ECT…." Again, seizures produce massive release of adenosine up to concentrations that may produce suppression of epileptic activity (5), and cAMP, which is thought to increase after treatment with antidepressants (6), can be released and degraded, elevating extracellular adenosine levels (2).

Finally, if adenosine contributes to the antidepressant effects of sleep deprivation, adenosine agonists, which are not yet available for clinical use, would also produce rapid antidepressant effects in a subset of patients.

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Dr. Wu and Colleagues Reply

TO THE EDITOR: We appreciate the suggestion that 1) "a deficient adenosinergic inhibitory tone" at baseline accounts for the higher local metabolic rates in responders than in nonresponders and comparison subjects and 2) "increases in extracellular adenosine" account for the reduced metabolic rates observed in responders after sleep deprivation. Whether this interesting adenosine hypothesis will weather the tests of time remains to be seen.

If adenosine inhibits the local cerebral glucose metabolic rate, then the present patterns of relative local cerebral glucose metabolic rates could possibly fit a model of 1) loss of adenosinergic tone at baseline in depressed responders or 2) augmentation of adenosinergic function with sleep deprivation in responders. However, insofar as the administration of caffeine mimics "deficient adenosinergic inhibitory tone," its effects on functional brain imaging are complex and not necessarily consistent with the baseline patterns of local cerebral glucose metabolic rates in responders and nonresponders to sleep deprivation. Caffeine increases the local cerebral glucose metabolic rate throughout the brain but decreases cerebral blood flow at the same time, inducing a relative brain hypoperfusion (1–3). Administration of caffeine to normal volunteers does reduce slow-wave activity during non-REM sleep and prolongs sleep latency (4), both of which are characteristic of the sleep of depressed patients, suggesting that some depressed patients might have deficient adenosinergic tone.

In addition, adenosine is only one of many proposed "endogenous sleep-promoting substances," including prostaglandin D_2, interleukin-1, or muramyl peptides, which may accumulate during sleep deprivation and promote sleep (5–7). Any of these other substances could also theoretically act in the fashion proposed for adenosine.

We welcome speculation about the mechanisms of the antidepressant effects of sleep deprivation, particularly neurochemical changes or gene expression, which may lead to new antidepressant medications. Sleep deprivation is one of the easiest and most well-documented experimental antidepressant treatments known.

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Measuring Dopamine D_2 Receptors

TO THE EDITOR: Nora D. Volkow, M.D., et al. (1) used [^{11}C]raclopride and positron emission tomography (PET) to show differences in the striatal dopamine system between subjects who rated the effects of intravenous methylphenidate as pleasant and subjects who rated the effects as unpleasant. They concluded that the subjects in the first group had fewer striatal dopamine 2 (D_2) receptors and that this may be a predisposing factor to drug addiction. However, the method they used does not measure D_2 receptor density.

It has been shown by their group (2) and others (3–5) that the binding of [^{11}C]raclopride depends on the level of endogenous dopamine present at the time of the scan. They incorrectly stated that the [^{11}C]raclopride distribution volume (sometimes also referred to as binding potential) equals B_{max}/

K_D, the ratio of total D_2 receptor density to the dissociation constant of radiotracer and receptor. In fact, the distribution volume, as they calculated it, is more properly expressed as

$$B_{max}/K_D(1 + N_f/K_D^d)$$

where N_f is the concentration of free dopamine and K_D^d is the affinity of dopamine for the D_2 receptor (6).

This does not invalidate their result; however, the conclusion can only be that they showed a difference in the striatal dopamine system between the two groups of individuals, rather than a difference in dopamine receptor density. The former is a somewhat weak conclusion, as it does not necessarily imply an intrinsic or inherited difference in dopamine receptor numbers.

The brain is never in a "baseline" state, and a PET scan is a measure of the neurometabolic response to the experience of undergoing a PET scan, which may include varying degrees of anxiety and discomfort in different individuals. For example, one could imagine that subjects who are more anxious than others have a greater release of dopamine during PET scanning, which would affect the [^{11}C]raclopride distribution volume. In short, it is not possible to measure D_2 receptor density with [^{11}C]raclopride with a single PET scan, although it can be done by using two scans with injections of radiotracer at different specific activity levels (7). Therefore, the theory that D_2 receptor density is related to the risk of addiction is not supported by this PET study.

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Dr. Volkow and Colleagues Reply

TO THE EDITOR: Dr. Dagher is correct in pointing out that when [^{11}C]raclopride is used to measure D_2 receptors, elevated D_2 receptor occupancy by dopamine—which can masquerade as a decrease in receptor levels—presents a potential confounding variable. Since our experimental design did not allow us to exclude this possibility, we should have pointed out this limitation and used the term "D_2 receptor availability" rather than "D_2 receptor levels." However, what follows is evidence that the differences in D_2 receptor availability between subjects who reported the effects of methylphenidate as pleasant and those who reported them as unpleasant reflect differences in D_2 receptor levels.

To start with, [^{11}C]raclopride is unlikely to be sensitive to day-to-day fluctuations of mental state as encountered during a PET experiment (i.e., differences in levels of anxiety and discomfort), as evidenced by its reproducibility when subjects are tested weeks (1) or months (2) apart.

To indirectly assess if the low D_2 receptor availability was due to lower D_2 receptors levels and not higher D_2 receptor occupancy by dopamine, we measured the correlation (Pearson's product-moment) between D_2 receptor availability and the changes in [^{11}C]raclopride binding induced by 0.5 mg/kg of intravenous methylphenidate, which we had previously determined in these subjects (3). Because methylphenidate increases dopamine levels by blocking dopamine transporters (not by dopamine release) (4), the accumulation is a function of the amount of dopamine released at baseline, and hence the measure of methylphenidate-induced dopamine changes can be used as an indicator of baseline dopamine release. Measures of D_2 receptor availability were significantly correlated with the changes in raclopride binding (baseline minus methylphenidate) ($r=0.55$, $df=22$, $p<0.007$). The lower the D_2 receptor availability at baseline, the lower the dopamine changes, and vice versa. This is a strong indication that subjects with low D_2 receptor availability did not have enhanced synaptic dopamine (and thus enhanced D_2 receptor occupancy by dopamine) and those with high D_2 receptor availability did not have decreased dopamine release (and decreased D_2 receptor occupancy). Therefore, these results suggest that the differences in D_2 receptor availability reflect differences in D_2 receptor levels and support the involvement of D_2 receptors as one of the molecular targets that modulates vulnerability to drug addiction.

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Serotonin 2A Receptor Polymorphisms and [^{3}H]Ketanserin Binding

TO THE EDITOR: The report by Gustavo Turecki, M.D., Ph.D., and colleagues (1), showing higher than normal [^{3}H]ketanserin binding in the prefrontal cortex of suicide victims, extends the evidence for an involvement of the serotonin 2A (5-HT_{2A}) receptor in suicide and mood disorders. However, the finding of an association between the level of [^{3}H]ketanserin binding and genetic variation of the receptor in the 22 brains studied conflicts with existing data. In two larger studies no relationship existed between prefrontal cortex [^{3}H]ketanserin binding and either the T102C polymorphism (2) or the linked A-1438G polymorphism (3) (N=125 and N=122, respectively). As such, any effect of these genotypes on 5-HT_{2A} receptor expression must be considered unproved, and since both polymorphisms are silent, their functional significance remains obscure (4).

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Dr. Turecki and Colleagues Reply

TO THE EDITOR: In his letter Dr. Harrison points out the discrepancies between our findings—which suggested a relationship between variation in the 5-HT_{2A} receptor gene (5HTR2A) and the level of [^{3}H]ketanserin 5-HT_{2A} receptor binding in the prefrontal cortex—and two other studies by authors who failed to observe such a relationship. A possible explanation for this inconsistency may be related to the characteristics of the patients included in our study, who were of French Canadian origin.

The existence of a founder effect in the French Canadian population has been confirmed by many studies (1). The French Canadian population currently living in Quebec is descended from approximately 7,000 founding individuals who came to "Nouvelle France" before 1760 (2). Because this is a relatively young population (approximately 12 generations), the background linkage disequilibrium is considerable. For instance, studies of unrelated subjects who carry a mutation for oculopharyngeal muscular dystrophy suggest that for a 5-centimorgan interval, 75% of the subjects of French Canadian origin share all alleles (3). These findings have been replicated in analyses conducted with different diseases (4).

Dr. Harrison reminds the reader that the polymorphisms used to investigate genetic variation in our study (and others) are of unknown function. Indeed, the T102C marker is a silent T→C base substitution (5), and the variants at the A-1438G locus present similar basal promoter activity (6). Therefore, it is possible that our positive results with the 5HTR2A polymorphisms investigated may in fact be a consequence of underlying linkage disequilibrium between these markers and a functional genetic variant located in a different coding or regulatory region of the 5HTR2A gene. Furthermore, because of the extent of the linkage disequilibrium observed in French Canadians, this functional variant could be located relatively far from the tested polymorphisms (regulatory sequences and enhancers). If this is the case, the other studies may have failed to detect such an effect because, although testing larger samples, they investigated patients selected from nonisolated, panmictic populations, in which the power to detect associations due to linkage disequilibrium is considerably reduced. Certainly, other explanations may be also proposed for the reported inconsistency. Among these are type I error and the different analytical procedures employed. To better understand these issues, we are in the process of collecting a larger and independent sample of French Canadian suicide cases and will attempt to replicate our previous findings.

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Treatment of Patients With Delirium

TO THE EDITOR: Although we read with great interest the new "Practice Guideline for the Treatment of Patients With Delirium" (1), we strongly disagree on the dose recommendations for haloperidol. It is suggested to start with "1–2 mg every 2–4 hours as needed" and to titrate to higher doses in severely agitated patients because "bolus intravenous haloperidol doses exceeding 50 mg with total daily doses up to 500 mg…were associated with minimal effects on heart rate, respiratory rate, blood pressure, and pulmonary artery pressure and minimal extrapyramidal side effects" (1). Furthermore, the suggestion of a case-control study (Riker et al., 1994) that started "with a bolus dose of 10 mg [haloperidol intravenously] followed by continuous infusion at 5–10 mg/hour" is given without comment.

Although it is unequivocally acknowledged that typical antipsychotics act by means of blockade of brain dopamine D_2 receptors, there is as yet no consensus as to what extent such a blockade is necessary to exert antipsychotic action. A threshold of 60% has been suggested, whereas a blockade of more than 80% of D_2 receptors might convey only a higher risk for the development of neurological side effects with no further clinical improvement (2). Both [^{11}C]raclopride with positron emission tomography (PET) and [^{123}I]iodobenzamide with single photon emission computed tomography (SPECT) can be used to visualize and quantitatively analyze striatal dopamine D_2 receptors in vivo.

Substantial levels of dopamine D_2 receptor occupancy, ranging from 53% to 74%, were found with doses of 2 mg/day of haloperidol (2). In another PET study (3), 2–5 mg/day of haloperidol led to dose-dependent plasma levels from 0.5 to 5.8 ng/ml and to 53%–88% D_2 receptor blockade. Accordingly, an [^{123}I]iodobenzamide SPECT study also revealed a dose-dependent striatal D_2 receptor occupancy of 63%–85% with 5–20 mg/day of haloperidol (4). In summary, those data suggest that it may not be wise to use daily doses of more than 10 mg of haloperidol. Clinical experience in schizophrenia supports this view. We are aware that the cited data were obtained from patients with schizophrenia. However, it is only fair to assume that nonschizophrenic patients would need approximately the same or even lower doses to establish antipsychotic efficacy. At this level, brain D_2 receptors are most likely already saturated, so patients receiving higher doses are at high risk for more and unnecessary side effects. In cases of severe delirium that is unresponsive to an equivalent of 10 mg/day of haloperidol, one might consider the addition of substances with different mechanisms of action, e.g., glutamatergic or γ-aminobutyric acid medications.

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