Letters to the Editor

In Vivo Serotonin 5-HT_{2A} Receptor Occupancy and Quetiapine

TO THE EDITOR: Quetiapine is a novel atypical antipsychotic drug. Clinical studies report a placebo-level incidence of extrapyramidal side effects and efficacy when quetiapine is used to treat the positive and negative symptoms of schizophrenia (1). Quetiapine shows a differential in vivo affinity for D_2/5-HT_{2A} receptors, which are thought to be predictive of an atypical antipsychotic profile (2). In vivo, low occupancy of striatal D_2 receptors has been reported (3).

We evaluated the in vivo occupancy of 5-HT_{2A} receptors by quetiapine using [^{123}I]5-I-R91150—a novel, highly selective 5-HT_{2A} ligand—for single photon emission computed tomography (SPECT). Two patients with a DSM-IV diagnosis of schizophrenia gave written informed consent before the study began. They had been receiving quetiapine, 300 mg/day, for 7 and 11 weeks, respectively.

Mr. A was a 36-year-old Caucasian man who had previously been treated with haloperidol; he came in for treatment showing marked orofacial dyskinesia. Previously, severe paranoid symptoms had resulted in a 2-year forensic hospital admission after he had been convicted of arson. Mr. A had a Brief Psychiatric Rating Scale score of 24, which did not change with quetiapine treatment. However, his Abnormal Involuntary Movement Scale score decreased from 12 to 4 after 7 weeks of quetiapine treatment.

Mr. B was a 21-year-old Caucasian man who had previously been treated with flupentixol decanoate (40 mg, two per week) for 2 years. This treatment was associated with akathisia, which was controlled with anticholinergic therapy. After he started treatment with quetiapine, both he and his parents reported substantial improvements in his social interaction and peer relations. He obtained part-time work for the first time in 2 years. Ratings were performed before his quetiapine treatment began and on the day of the scan. Mr. B's score on the Scale for the Assessment of Negative Symptoms was 60, which decreased to 23 after treatment with quetiapine. He showed no objective evidence of extrapyramidal symptoms.

This image acquisition was as previously reported (4). A brain-dedicated SME 810 multidetector scanner for SPECT acquired a whole-brain multislice sequence 120 minutes after an intravenous injection of 180 MBq of [^{123}I]5-I-R91150, when corticocerebellar ratio levels were maximal and stable. Region-of-interest templates were fitted to cortical and cerebellar regions for each scanning sequence (by reference to an average brain atlas) and adjusted for brain size. The ratio of activity in cortical areas relative to those in the cerebellum (an area almost devoid of 5-HT_{2A} receptors) provided a measure of regional specific binding to 5-HT_{2A} receptors over time. The degree of competitive occupancy of 5-HT_{2A} receptors by antipsychotic treatment is reflected in the level of decline in the specific binding ratio in drug-treated individuals relative to those in the drug-free state (4). The frontal cortex/cerebellum ratio for Mr. A was 0.94 and for Mr. B, 1.07. These are clearly lower than the ratio of 1.40 (SD=0.05) that was reported in five drug-free healthy subjects (5) but are somewhat higher than the 0.88 (SD=0.09) and 0.87 (SD=0.09) reported in patients treated with risperidone and clozapine, respectively (4). These novel data suggest significant in vivo cortical 5-HT_{2A} blockade by quetiapine (at doses of 300 mg/day) and are consistent with the high ratio of 5-HT_{2A}/D_2 receptor occupancy observed for other atypical antipsychotic drugs.

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Quetiapine and False-Positive Urine Drug Testing for Tricyclic Antidepressants

TO THE EDITOR: Drug interference in laboratory assays is an ongoing problem that requires the combined detection efforts of clinicians and researchers. We report here the finding of new cross-reactivity with the atypical antipsychotic quetiapine in a laboratory assay for urine tricyclic antidepressants.

Mr. A was a 34-year-old, white male veteran with a history of previous treatment-refractory schizoaffective disorder and amphetamine dependence who was admitted to the hospital for an exacerbation of his depressive and psychotic symptoms. He also reported episodes of irritability, racing thoughts, increasing goal-directed activity, and insomnia, but the differential diagnosis between his amphetamine use and a manic component to his schizoaffective disorder had never been clarified. His only prescribed medication at the time of his admission was quetiapine, 600 mg/day.

At Mr. A's hospital admission, a urine sample was submitted for routine toxicology testing, including analysis for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, opiates, methadone, alcohol, and tricyclic antidepressants. The results showed a positive toxicology screening for tricyclic antidepressants, whereas the other toxicology assays on the specimen were all negative. Mr. A denied using tricyclics, but given the possibility that surreptitious use of that drug class might be materially contributing to his ongoing clinical symptoms (1), it was important to rule out drug interference in the assay.

The qualitative urine drug tests used in our laboratory are all homogenous enzyme immunoassays (Diagnostic Reagents, Inc.) and are automated on a Hitachi 911 analyzer. The tricyclic assay uses specific antibodies that detect most tricyclic antidepressants in urine, serum, or plasma. A change in the absorbance value that is equal to or higher than that of the calibrator is interpreted as positive. This assay uses a calibrator of 300 ng/ml of nortriptyline, with the calibrator absorbance value arbitrarily set at zero. Mr. A's urine exhibited a tricyclic assay response of 13.

It was noted that quetiapine is similar in structure to the tricyclic antidepressants and so was suspected as a possible interferent. A 25-mg tablet of quetiapine was dissolved in water and diluted to concentrations of 1–10 μg/ml. Levels below 7 μg/ml yielded negative results in the qualitative assay, whereas levels of 7 μg/ml or more yielded positive readings. Thus, the cross-reactivity of this drug in the assay—defined as the concentration of the calibrator divided by the drug concentration that yields a positive result, multiplied by 100—was 4.3% ([300 ng/ml ÷ 7000 ng/ml] × 100).

Another frequently prescribed atypical antipsychotic—olanzapine—was also tested in the tricyclic antidepressant assay, but this drug exhibited minimal cross-reactivity (0.06%–0.07%).

In summary, patients who are prescribed quetiapine can exhibit false-positive test results in assays for urine tricyclic antidepressants. This information will be submitted to the manufacturer of the assay.

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Meige's Syndrome Associated With Risperidone Therapy

TO THE EDITOR: Risperidone is an atypical antipsychotic that is effective for the positive, negative, and cognitive symptoms of schizophrenia (1). The incidence of extrapyramidal signs has been reported to be low during treatment with a dose of 6 mg/day. We report a case of Meige's disease (2–4), an extrapyramidal syndrome that was secondary to risperidone treatment.

Mr. A was a 43-year-old, single Caucasian male who became psychiatrically ill at age 22 years and had since been taking various neuroleptics. From 1980 to 1996, he was prescribed thioridazine, 50 mg/day. More recently, his thioridazine therapy was changed to treatment with risperidone, 6 mg/day, as a result of an exacerbation of his symptoms. Mr. A then started blinking frequently. Sometime later, he noted episodic blepharospasms that either occurred spontaneously or were triggered by stress. As a result, he had to discontinue vision-dependent activities such as driving. More recently, he sought help for blepharospasms.

During an interview, Mr. A was noted to have intermittent blepharospasms that affected his vision. The more he tried to open his eyes, the more tightly his eyelids closed. He often struggled for about 3–5 minutes to open his eyes.

This patient had Meige's disease that was secondary to his risperidone treatment. Because dopamine-2 blocking agents such as neuroleptics have been known to cause Meige's disease (5), this finding is not surprising. In this case, tardive dystonia was ruled out because he had no other evidence of choreoathetotic movements elsewhere in his body. Spontaneous Meige's disease was ruled out because of the absence of a family history of Parkinson's disease, abnormal facial movements, and concomitant physical illnesses such as multiple sclerosis or autoimmune disorders. It is important to recognize this condition because the withdrawal of antipsychotic drugs may lead to a complete recovery from Meige's disease.

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Paroxetine for Depersonalization Associated With Multiple Sclerosis

TO THE EDITOR: Psychiatric symptoms are often found in patients with multiple sclerosis, even before the typical neurological manifestations of the disease appear (1). A substantial proportion of the patients with multiple sclerosis also suffer from paroxysmal phenomena such as dysarthria, ataxia, tonic seizures, dysesthesias, akinesia, pain, or depersonalization (2).

Mr. A was a 22-year-old student who was seen with paroxysmal depersonalization that had lasted for 6 weeks; he had episodes that lasted from seconds up to 20 minutes. When he was examined, we found left facial dysesthesia, paroxysmal myoclonia, visual impairment, and disturbances of concentration. Oligoclonal banding and multiple periventricular white matter lesions were found with magnetic resonance tomography; possible multiple sclerosis was suggested. Methylprednisolone, given intravenously and tapered orally, however, did not improve his symptoms. Treatment of his paroxysmal depersonalization was begun with carbamazepine, 400 to 600 mg/day; plasma levels of 6–10 mg/liter were achieved. There was a mild improvement in the frequency of his symptoms (from 6–10/day to 2–3/day) and in the severity of his depersonalization attacks.

After 2 months, Mr. A's treatment with carbamazepine had to be stopped because of a rash. His depersonalization worsened, and he had to be treated with valproic acid. However, to achieve an adequate plasma concentration of the drug (more than 50 mg/liter), a dose of 1800 mg/day was necessary; this resulted in marked sedation accompanied by only a slight improvement of his depersonalization symptoms. Therefore, paroxetine was added, 10 mg/day, and his dose was increased weekly to 40 mg/day, whereas his treatment with valproic acid was discontinued. In the third week of his paroxetine treatment, Mr. A's depersonalization attacks started to improve. After 4 months of treatment, they occurred only once or twice a week and had markedly decreased intensity. His social withdrawal disappeared as well, and Mr. A started his leisure activities again. However, the facial dysesthesia, myoclonia, and subjective disturbances of concentration persisted. Because of restlessness and sleep disturbances, his paroxetine dose was reduced to 30 mg/day. Two years after the onset of the disease, an acute relapse with neurological symptoms accompanied by typical changes in magnetic resonance tomographic and CSF findings led to the diagnosis of clinically definite, laboratory-supported multiple sclerosis (3).

Paroxysmal depersonalization, facial dysesthesia, myoclonia, and subjective disturbances of concentration are described as the first symptoms of longitudinally diagnosed multiple sclerosis. Despite reports that paroxysmal phenomena in multiple sclerosis respond to carbamazepine and other anticonvulsants (2), This patient's depersonalization was reduced only a limited degree. Besides the effectiveness of selective serotonin reuptake inhibitors (SSRI) in depersonalization disorder (4), our report emphasizes that depersonalization due to a general medical condition like multiple sclerosis may respond to SSRI treatment as well.

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Using Eye Movement Desensitization and Reprocessing to Reduce Cocaine Cravings

TO THE EDITOR: Eye movement desensitization and reprocessing is intended to eliminate intrusive memories and requires patients to perform alternating eye movements while thinking disturbing thoughts. While it is popular among clinicians, support for eye movement desensitization and reprocessing for posttraumatic stress disorder in well-controlled clinical trials has been limited. In the area of substance abuse treatment, anecdotal reports of reductions in drug cravings and relapse after eye movement desensitization and reprocessing have appeared (1, 2), and adaptations of eye movement desensitization and reprocessing for substance abusers have been made available (unpublished reports by Popky [1996] and Popky et al. [1996]). Currently, there are no controlled studies to support its effectiveness with this population.

We hypothesized that drug cravings, like disturbing thoughts, might be reduced through eye movement desensitization and reprocessing, so we used the procedures described by Popky (unpublished report) to conduct a preliminary evaluation of the effects of eye movement desensitization and reprocessing on cocaine cravings and drug use among opioid addicts who were maintained with methadone. We received the approval of our institutional review board and obtained signed informed consent forms from the subjects.

The subjects were 11 individuals who met the DSM-IV criteria for opiate dependence and were stabilized with therapeutic doses of methadone. The subjects' mean age was 35 years; the group included five men, six women, three African Americans, seven Caucasians, and one Hispanic American. The subjects were referred because of ongoing cocaine cravings and drug use. Eye movement desensitization and reprocessing were offered in three weekly sessions, in addition to the subjects' methadone maintenance, routine urine toxicology screenings, and counseling.

Cravings were assessed at baseline, during each session, and at the 1-month follow-up by using an adaptation of the Yale-Brown Obsessive Compulsive Scale (3), a cocaine craving questionnaire (4), and a level-of-urge scale (unpublished report by Popky). Perceived control over cravings was assessed on a validity-of-cognition scale (5). Cocaine use was assessed by means of self-reports and the urine toxicology screenings that followed each session.

The procedures had limited success in retaining subjects for treatment. Four subjects completed treatment and the 1-month follow-up, six did not complete treatment, and one completed all three treatment sessions but did not return at follow-up. Of the 33 total sessions (three sessions and 11 subjects), in 12% the intensity of the cravings increased, in 40% the cravings decreased, and in 48% no change was seen. Perceived control over the cravings was generally strengthened after each session. Of the four patients who completed treatment, cocaine use decreased for two, remained the same for one, and increased for one.

Overall, the direct effects of eye movement desensitization and reprocessing on the intensity of cocaine cravings and use appear negligible in contrast to the bulk of the research on behavioral treatments for cocaine dependence in this setting, where significant reductions in cocaine use and cravings are often seen (6). We noted that the subjects with higher levels of cocaine cravings and use may be poorly suited for this approach because the three patients with the highest levels of cocaine use and cravings dropped out of treatment. Our findings suggest that eye movement desensitization and reprocessing have limited effects on cocaine cravings or use in this setting.

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Gabapentin Treatment for Insomnia Associated With Alcohol Dependence

TO THE EDITOR: Gabapentin is approved as an anticonvulsant and has also been used to treat chronic pain, restless legs syndrome, bipolar disorder, anxiety disorders (1), and alcohol withdrawal (2). Gabapentin has no known abuse potential, has few side effects, does not require blood monitoring, and does not affect liver metabolism or the excretion of other medications (3). The mechanism of action for gabapentin is unknown. It may influence the synthesis of γ-aminobutyric acid and glutamate (4). These systems are known to modulate anxiety, arousal, and sleep. Gabapentin may also increase deep sleep (stages 3 and 4) by increasing serotonin levels (4). Alcohol-dependent patients commonly complain of insomnia during early recovery, and sleep disturbance has been associated with relapse in alcoholics who are recently abstinent (5).

We used gabapentin to treat 15 of 17 consecutively evaluated alcoholic outpatients who had persistent insomnia despite 4 weeks of abstinence. All patients signed a consent statement (per the Michigan mental health code) before receiving psychotropic medication. One patient discontinued gabapentin treatment after one dose, and another patient refused treatment. The remaining patients included 12 men and three women (aged 24–45 years). Seven patients also abused marijuana, cocaine, or opiates; six had stabilized bipolar disorder, major depression, schizophrenia, or sleep apnea. Their dose of gabapentin was titrated to overall sleep response (mean=953 mg/day, range=200–1500) within 2 weeks. Most patients started to improve with 600 mg at bedtime. While seven patients required a dose of 900–1200 mg/day at bedtime to optimize their sleep quality, one responded to 200 mg/day at bedtime. Three patients took 1500 mg/day in divided doses to maximize sleep quality and reduce daytime anxiety. Neither serious side effects nor tolerance was reported.

All patients remained totally abstinent after 4–6 weeks of follow-up, except two patients who had four or more drinks on one occasion each. Each patient showed improvement on the Sleep Patterns Questionnaire (6), a self-administered measure of insomnia, over the past month; their scores ranged from 0 to 20. Scores on the Sleep Patterns Questionnaire decreased from a mean of 15.9 (SD=2.8) before treatment with gabapentin to 5.9 (SD=3.3) after 4–6 weeks of gabapentin treatment (paired t test: $t=-11.05$, $df=14$, $p<0.001$).

Although our study was limited by small group size, the lack of a control group, short-term outcomes, and the lack of polysomnography, we conclude that gabapentin shows promise as a safe and effective treatment for alcohol-dependent patients with comorbid insomnia during early recovery. Controlled studies are warranted to confirm these preliminary observations.

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Earnings Changes

TO THE EDITOR: The article by Mingliang Zhang, Ph.D., Kathryn M. Rost, Ph.D., and John C. Fortney, Ph.D. (1), provides important insight into the real cost of the treatment of depression for patients, rather than the cost assumed by third-party payers. The authors suggest that the reason for the cost savings for patients treated by psychiatric specialists

over those treated in the general medical sector stems from specialists' "more extensive training and expertise in treating mental health problems" (1, p. 112). Twice the number of patients treated by specialists as patients treated in the general medical sector had treatment in accordance with Agency for Health Care Policy and Research guidelines (2, 3). However, only 48% of the patients treated by specialists had treatment that followed those guidelines. Because the authors did not provide the details of their analysis, we cannot reach a conclusion regarding the meaning of this finding. Which of the guidelines were not followed? What was the use of certain medications, the dosing, the length of treatment, and the like? If 52% of the specialists were not in compliance with the guidelines because they use antidepressants other than those recommended by the Agency for Health Care Policy and Research, the meaning of the authors' finding would be very different from what it would be if the specialists' noncompliance were based on their failure to make patients' drug levels reach accepted therapeutic doses. This is equally true for the 79% of the physicians in the general medical sector who were not in compliance with the guidelines. When training psychiatrists and nonpsychiatrists about the treatment of depression, knowing what they do and do not do would guide the educational endeavor.

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Dr. Rost and Colleagues Reply

TO THE EDITOR: In our article, we reported greater cost savings for patients treated by psychiatric specialists than for those treated in the general medical sector. One explanation for this is that 48% of the community residents treated for depression in the specialty care sector received guideline-concordant care in contrast to 21% of the community residents treated for depression in the primary care setting. In his letter, Dr. Muskin requested further information to identify where the deviations from guideline-concordant care occurred in both sectors. We are happy to provide a further breakdown without extensive statistical comparisons. Specialty care patients were more likely than primary care patients to get any antidepressant medication (64.3% and 53.0%, respectively). Among those who received antidepressant medication, specialty care patients were more likely than primary care patients to be prescribed a guideline-concordant dose (52.8% and 39.4%) and were somewhat more likely to take the medication for a minimum of 8 weeks (75.0% and 70.5%). The remaining difference in guideline-concordant treatment rates was explained by the greater likelihood for specialty care patients to report that they received eight or more counseling visits for depression. The 1992 medication patterns do not adequately represent current primary care medication prescribing patterns, particularly the greater use of newer-generation antidepressants whose limited side effects allow physicians to prescribe therapeutic doses more readily. However, if specialty care's achievement of better outcomes is in part attributable to providing psychotherapy (in combination with medication or independently), we might continue to observe these outcome differences if the study were to be replicated in the current health care environment.

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Clinical Trials and Effectiveness Research

TO THE EDITOR: Kenneth B. Wells, M.D., M.P.H, has made an important contribution with his article (1). It may be helpful to keep the following considerations in mind in interpreting both efficacy and effectiveness studies for both clinical and policy decision making.

Outcomes are most often defined in terms of easy-to-measure markers. Features such as autonomy or authenticity are rarely considered and are also never measured in either type of study. Yet they are most relevant in terms of the utility of given outcomes to individuals, as well as our culture and our society (2–4). More easily measurable outcomes continue to dominate the studies reported even in this *Journal*. Should all outcome studies carry at least an explanation of why the particular outcomes were chosen and why meaningful outcomes were not considered?

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Dr. Wells Replies

TO THE EDITOR: Dr. Bursztajn raises the question of whether the authors of treatment-outcome studies should justify their outcome selection within a broader scheme that includes effects relevant to practice and policy that are difficult to measure. The simple answer is "yes," but this is not a simple question.

Practice and policy decisions involve tradeoffs among treatments and their expected outcomes under conditions of constrained resources, uncertainty, and personal distress. The information required to inform those decisions ideally includes all expected benefits and costs, including respect for individual autonomy and societal implications, of the alternative actions. In addition, one would desire a validated pro-

cess to support the parties in making decisions that reflect their authentic values (from the 1990 book by Bursztajn et al.). Obtaining such data and using them well are the challenging tasks at the heart of both clinical practice and the science of practice. For example, there are known theoretical and technical problems in measuring preferences and reconciling individual and societal perspectives (1). Dr. Bursztajn refers specifically to an ethics outcome (i.e., autonomy) and an attribute of values (i.e., authenticity). These are among other ethics outcomes and values, such as distributive justice, that are seldom considered in treatment outcome studies. How can we develop a broad basis for decisions that include them?

First, the parties in health care and researchers must become more familiar with the range of outcomes of individual and social salience. Such a shared conceptual framework is difficult to accomplish even across two areas, much less several, including clinical, economic, and ethical outcomes. Second, interventions that use scientific data to inform practice must be developed and tested widely, and their implications for these diverse outcomes must be understood. While it is difficult to assess values, it may not be much more difficult than studying quality of life, which is not easy to measure or analyze. Yet smaller studies may not be able to study either type of outcome owing to precision problems. The field can accomplish more, however, by collaborating on fewer studies and studies that have scope and scale or coordinating meta-analyses. It is not clear, however, if diverse investigator groups can or will engage in such planning or if such consolidation of research resources compromises the discovery process.

Meanwhile, studies can achieve progress by improving measures of diverse outcomes and understanding their relationships and determinants. For example, we are assessing the effects of a quality improvement program for depression on clinical, economic, and selected ethical outcomes in the Partners in Care program (2). Tomorrow's clinicians and researchers may need to consider these and broader effects routinely if improved health care information systems enable us to make more richly informed decisions in real time. I hope my recent article represents a step toward the preparation of clinicians and researchers for this agenda and that others, like Dr. Bursztajn, will stimulate discussion as to how best to achieve a useful database and an implementation process for practice decisions.

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