LETTERS TO THE EDITOR

Factors Influencing Adherence in Children and Adolescents Treated With Antipsychotics or Antidepressants

Sir: Although factors influencing adherence often overlap, it is possible to differentiate between factors that are related to the patient, the patient's environment, the treating clinician, and treatment itself.[1] This differentiation may aid the practicing clinician in assessing the various reasons why a particular patient is likely to develop adherence problems. For example, there is a positive correlation between adherence and the patients' feelings of a positive effect of the drug on the illness.[2] On the other hand, weight gain has a strong impact on quality of life,[3,4] and therefore probably on adherence. Especially in children and adolescents, overweight due to second-generation antipsychotics (SGAs) might be even more pronounced compared to adults.[5] SGAs are increasingly prescribed for children and adolescents with neuropsychiatric disorders.[6] Although their specific serotonin and dopamine receptor antagonism offers certain advantages compared to typical antipsychotics, their use has been associated with various adverse effects. Most of these drugs are still prescribed in off-label use,[7] and little is known of drug-associated adverse events in pediatric patients, especially in long-term use. In our study, we investigate adherence in children and adolescents and its relationship to various potential risk factors (age, gender, time since discharge, weight gain, and pharmacologic treatment).

Method. The data derived from a retrospective study investigating demographic characteristics, diagnosis, and medication of all inpatients between August 1, 2002, and August 31, 2004, who were admitted to the Department of Child and Adolescent Psychiatry of Innsbruck Medical University. Seventy inpatients were prescribed drugs for the time after discharge. Data about further drug intake, consultations (psychiatrist or general practitioner), and weight gain were evaluated by follow-up interviews. Twenty-two of the 70 could not be contacted or were not willing to give any further information, and 48 patients were included in the study. Their mean ± SD age was 15.8 ± 1.7 years (range, 10–18 years), 23 (48%) were male, and 25 (52%) were female. According to DSM-IV criteria, 8 (17%) were diagnosed with schizophrenia, 22 (46%) with mood disorders (including adjustment disorders), 11 (23%) with disruptive behavior disorders, and 7 (15%) had other diagnoses (misuse of psychoactive substances, mental retardation, personality disorders, and development disorders). They were treated with antipsychotics (48%, N = 23; risperidone, olanzapine, clozapine, quetiapine, amisulpride, and ziprasidone) and antidepressants (52%, N = 25; citalopram, mirtazapine, fluoxetine, sertraline, escitalopram, trazodone, and venlafaxine).

The effects of age, gender, time since discharge (≤ 6 months, 46%; > 6 months, 54%), weight gain (< 5 kg versus ≥ 5 kg), and pharmacologic treatment (antidepressant versus antipsychotic) on adherence were investigated by means of logistic regression with backward variable selection. The same method was applied to analyze the effects of the above-mentioned variables on weight gain. Odds ratios were calculated to quantify the effect of the potential risk factors. The logistic regression was supplemented by bivariate analyses of the associations between adherence and the individual potential risk factors using Fisher exact test.

Results. Forty-six of 48 patients took part in follow-up consultations. Twenty-two patients continued the drug intake at the point of the interview, 12 had discontinued the drug intake after consulting their psychiatrist or general practitioner, and 12 had discontinued without consulting. These 12 patients were classified as noncompliant.

When considering the effects of age, gender, time since discharge, weight gain, and pharmacologic treatment on adherence one by one, 2 variables were found to significantly increase the probability of nonadherence, namely, antidepressive treatment (p = .017) and diagnostic group (mood disorders versus all other diagnoses, p < .001). However, when investigating the potential risk factors jointly by logistic regression, only the effect of the diagnostic group remained significant (odds ratio = 26.4, p = .003, logistic regression), whereas the significance of antidepressive treatment disappeared (odds ratio = 4.33, p = .122, logistic regression). Obviously, the difference in adherence rate between patients with and without antidepressive treatment is mainly a consequence of the effect of diagnosis on adherence. None of the other variables showed a significant association with adherence. In particular, adherence was not associated with weight gain.

The 48 patients exhibited a mean weight gain of 5.4 kg between discharge and follow-up examination. Patients without any SGA showed a mean increase of 2.4 kg, and patients with antipsychotic medication showed a mean increase of 7.4 kg. Mean ± SD time from discharge to follow-up visit was, for the antipsychotic-free group, 10.0 ± 7.4 months and for the antipsychotic group, 8.5 ± 7.0 months.

Of the risk factors, only antipsychotic treatment had a significant effect on weight gain after adjusting for the effect of other variables (odds ratio = 7.78, p = .005, logistic regression). Patients treated with antipsychotics had an approximately 3 times higher risk of weight gain than patients not treated with antipsychotics.

Discussion. Overweight is socially stigmatizing[8] and has serious effects on physical health that might heavily influence patient adherence. Vieweg et al.[9] found in their review 21 articles linking weight gain and obesity with SGAs among youths. According to our data, we also found significant weight gain with SGAs, but, to some extent unexpected, adherence was favorable even in children and adolescents with overweight, probably due to good physician/patient relationship or to the course of illness itself being positively influenced by the treatment. Due to the low sample size of this preliminary report, separate analysis of single substances was not possible.

In summary, our results suggest a low impact of weight increase on adherence in children and adolescents. Nevertheless, overweight has to be considered as a serious adverse event of antipsychotic treatment. Of course, adherence is an essential condition for positive treatment outcome and has to be promoted in every single patient. Specific diagnostic categories, such as mood disorders, seem to have a negative impact on adherence in youth.

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Risperidone-Induced Tardive Pharyngeal Dystonia Presenting With Persistent Dysphagia: A Case Report

Sir: Tardive dystonia is a rare side effect of long-term antipsychotic use with a prevalence of 0.4% to 4.0% in neuroleptic-treated patients.[1] It involves sustained muscular contraction, which can affect any muscle group in the body. Tardive pharyngeal dystonia presenting as dysphagia has only been anecdotally reported with antipsychotics, particularly the conventional antipsychotics.[2] A case of risperidone-induced tardive pharyngeal dystonia with complete resolution on switch to clozapine is described here.

Case report. Ms. A, a 35-year-old woman, had been diagnosed with DSM-IV-TR paranoid schizophrenia of 3 years' duration. Initially, she was treated with trifluoperazine (15 mg/day) and trihexyphenidyl on an as-needed basis (up to 2 mg/day) for about a year. She exhibited no dystonic movements while on this combination. Subsequently, the patient dis-

continued medications on her own and 6 months later had a psychotic relapse. She was then successfully treated with risperidone (4 mg/day).

Five months after starting risperidone, Ms. A started experiencing difficulty in swallowing solid and semi-solid food. She had no difficulty in swallowing liquids, but other kinds of food would tend to get stuck in her throat. Her appetite decreased significantly, and she lost about 14 lb (6 kg). A neurologic examination revealed no abnormalities, and no other abnormal movements or extrapyramidal signs were evident. Ms. A had no prior or family history of dystonias. Gastroenterology and otolaryngology specialists were consulted, but no local pathology could be ascertained. Findings of an endoscopy and a barium swallow study were unremarkable. For the next 6 months, the patient was treated with various medications prescribed by the specialists, but she continued to experience dysphagia.

With no relief in the dysphagia, the possibility of risperidone-induced pharyngeal dystonia was considered. Risperidone was subsequently discontinued, and the patient had sequential trials of trihexyphenidyl, promethazine, and clonazepam but had no improvement in the dysphagia. Hence, the possibility of "tardive" presentation of the pharyngeal dystonia was considered, and the patient was then started on clozapine 25 mg/day, which was increased to 75 mg/day over 3 weeks. Six weeks after starting clozapine, Ms. A had complete resolution of the dysphagia without any additional medications from other specialists.

This patient met the operational criteria for the diagnosis of tardive dystonia as spelled out by Adityanjee and colleagues.[1] Most cases of antipsychotic-induced dysphagia are acute in nature and occur shortly after initiating treatment with antipsychotics.[3–5] There are 2 reports of insidious-onset dysphagia with risperidone suggestive of tardive dystonia.[6,7] In 1 case, the presentation was described as tardive dyskinesia,[6] while in the other case, it was labeled as "prolonged dysphagia," but not formally diagnosed as tardive dystonia.[7] Whereas a reduction of the dose of risperidone from 4 mg/day to 3 mg/day led to resolution of the dystonia in the first case, discontinuation of risperidone and its substitution with olanzapine provided symptomatic relief in the second case. Tardive dyskinesia leading to dysphagia has been described with conventional antipsychotics, but most of these patients also exhibit dyskinetic movements involving other body regions.[8] Tardive dystonia, though now recognized as distinct from tardive dyskinesia, remains underdiagnosed because of the overlap of signs and its frequent co-occurrence with the other tardive syndromes.[1]

Clozapine has been used to treat antipsychotic-induced tardive dystonia, with some investigators suggesting that tardive dystonia may selectively respond to clozapine.[1,2,9] Botulinum toxin has also been used to treat antipsychotic-induced tardive dystonia.[10] That modality, though more effective than clozapine in some patients, is also associated with dysphagia and may not be suitable for tardive pharyngeal dystonia.[10] As dysphagia can present with a choking sensation, it may be misdiagnosed as exacerbation of anxiety or as a symptom of a somatoform disorder. Hence, a high index of suspicion is desirable in diagnosing antipsychotic-induced pharyngeal dystonia not only to avoid the potential complications of poor nutrition, weight loss, and possible aspiration, but also to curtail extensive diagnostic testing and unfruitful medication trials.

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Aripiprazole in Prodromal Psychosis: A Case Report

Sir: Prodrome of psychosis has been of clinical and research interest in recent times because of its implications in early treatment of psychosis. The rate of conversion of prodrome to psychosis varies from 15% to 54%, as shown in multiple studies.[1,2] Controlled trials have shown that risperidone[3] and olanzapine[4] have been effective in preventing this transition. Aripiprazole has been shown to be efficacious in treatment of schizophrenia in a systematic review.[5] The data regarding the use of aripiprazole in prodrome are sparse. We hereby present a case of prodromal psychosis that was treated with aripiprazole.

Case report. Mr. A, a 17-year-old student, presented in 2007 with a gradual and distinct change in personality of 15 months' duration, characterized by social withdrawal, impaired concentration, and avoiding sunlight, which he found "excessive and unbearable." At times, his surroundings would seem "unreal" or different to him. He would hear voices lasting for brief periods (5–10 minutes) once a week, which were calling out his name or threatening him. He reported an unusual sensation in his head, which he described as having a "brainstorm." He also reported at one occasion that he was weeping, though he did not feel sad. He did not attribute this weeping to an external agency. On a few occasions, he expressed feelings of being unique that were not delusional. He had the feeling that things were different, but could not elaborate further.

Two months before presentation he showed further deterioration in self-care. On outpatient assessment, he did not fulfill the criteria for any syndromal psychiatric diagnosis. He was admitted to the hospital for complete evaluation. Physical examination showed a body mass index (BMI) of 28 kg/m². All his laboratory findings were within normal limits. There was no history of substance abuse. Personal and family histories were also not contributory.

The Comprehensive Assessment of At-Risk Mental State (CAARMS)[6] was administered. On the basis of his score, Mr. A qualified for the diagnosis of attenuated positive symptom syndrome (APSS), subthreshold frequency, as per the PACE clinic criteria.[6] Treatment options, including the potential for side effects, were discussed with the patient and his family. In view of concerns regarding weight gain, aripiprazole was started, which was initiated at 15 mg/day and gradually increased to 30 mg/day. Over a period of 3 to 4 weeks, he reported substantial improvement and no longer fulfilled the criteria for APSS. He tolerated the medication well and reported no side effects.

This case report clearly depicts that prodrome can be reliably diagnosed using standard criteria. As the case shows, the symptoms can be distressing and impairing enough to require treatment. However, the long-term treatment with the currently recommended agents may carry risk of metabolic side effects. This patient with prodromal symptoms was started on aripiprazole in view of his having a high BMI. Treatment resulted in good control of his symptoms, and his condition improved well. These findings suggest that the use of drugs such as aripiprazole may prove to be safe and effective in the treatment of prodromal psychosis.

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Valproate for Treatment of Agitation in Neurosyphilis: A Case Report

Sir: The incidence of syphilis is low worldwide; however, its reemergence has been documented even in developed countries.[1] Developing countries like India and underdeveloped countries continue to have syphilis outbreaks on occasion.[2] Neurosyphilis with concurrent human immunodeficiency virus infection has raised fears of its recrudescence.[3] Patients with the later stages of syphilis, especially neurosyphilis, may present with symptoms of virtually any psychiatric disorder.[4] Here we report an interesting case of neurosyphilis presented to our psychiatric outpatient service.

Case report. Mr. A, a 55-year-old married man who lacked formal education and came from a lower socioeconomic, rural background, reported to our institute in November 2006 with an acute-onset illness of 1 year's duration characterized by irritable mood, restlessness, grandiose ideations, jocularity, disinhibition, decreased sleep, and demanding behavior in the initial 6 months followed by irritability, suspiciousness, and abusive, assaultive, and hallucinatory behavior (talking to self and smiling to self) for the next 5 months. In the last month, the patient had cognitive deficits (poor attention and concentration, immediate and recent memory deficits, impaired calculation, impulsivity, inability to recognize family members, and geographical disorientation), unprovoked aggression, agitation, unsteady gait, dysarthria, double incontinence, and inability to perform activities of daily living. He had received no treatment for the above symptoms. He had family history of chronic psychosis in a first-degree relative, personal history of high-risk sexual behavior, and nicotine dependence, and there was no significant past psychiatric/medical history. Premorbid personality was well adjusted.

On general physical examination, Mr. A had positive cortical release signs, brisk deep tendon reflexes, unsteady gait, dysarthria, and coarse tremors. Mental state evaluation revealed poor personal care; non–goal-directed restlessness and agitation; blunted affect; irrelevant speech; hallucinatory behavior; disorientation to time, place, and person; impaired attention and concentration; and impaired immediate and recent memory.

The patient was started on risperidone 2 mg/day, which was increased further to 3 mg/day for control of agitation and behavioral problems. Opinion from a neurologist was sought regarding his delirium. His serum and cerebrospinal fluid Venereal Disease Research Laboratory tests were positive in 1:16 and 1:2 dilutions, respectively. Trepanoma pallidum particle agglutination was positive in 1:20,480 dilutions. Computed tomography scan of the brain showed significant cortical atrophy with ex vacuo dilatation and subcortical hypodensities. Findings of other laboratory investigations were within normal limits. The diagnosis of neurosyphilis was made, and intravenous crystalline penicillin was started.

During treatment with risperidone 3 mg/day for 4 weeks, there was improvement in his psychotic symptoms, but there was no improvement in his agitation; hence, quetiapine 50 mg/day was started, which was increased to 400 mg/day because his agitation remained uncontrolled. The patient's agitation was not reduced during 4 weeks' treatment with quetiapine 400 mg/day, during which time he required frequent parenteral haloperidol 5 to 10 mg (at least once every 2–3 days) for management of agitation. He was then started on valproate 400 mg twice a day. There was marked reduction in the agitation and behavioral problems within 2 weeks, and the improvement was maintained throughout his stay in the hospital. At the time of discharge, Mr. A's behavioral problems and agitation had been reduced significantly, but his cognitive deficits remained the same.

Risperidone and quetiapine have been used in neurosyphilis for treating behavioral symptoms.[5] However, in the present case both of the newer antipsychotics were ineffective in controlling behavioral symptoms. Valproate has been used successfully in treating agitation in dementias,[6] delirium,[7] and organic brain syndrome.[8] In the present case, also valproate was able to decrease the agitation. There is evidence to suggest that valproate can bring down agitation very rapidly.[9] This case report suggests that valproate can be used for controlling agitation in neurosyphilis.

The authors report no financial affiliation or other relationship relevant to the subject of this letter.

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Improvement of Neuropsychiatric Symptoms in Multiple Sclerosis Subsequent to High-Dose Corticosteroid Treatment

Sir: Multiple sclerosis is an autoimmune inflammatory demyelinating disease that involves different central nervous system structures. In addition to typical clinical features, e.g., optic neuritis, sensory abnormalities, and cerebellar signs, symptoms may include neuropsychiatric manifestations.[1] The

most common neuropsychiatric symptoms are depression, agitation, and apathy, whereas hallucinations and delusion are rather exceptional.[1] The medication treatment of psychiatric symptoms in patients with multiple sclerosis can present a challenge to physicians, especially in cases of psychosis. We report the case of a patient with pure psychotic presentation of multiple sclerosis whose symptoms improved after high-dose corticosteroid therapy.

Case report. Mr. A, a 31-year old male patient, was admitted to the hospital in 2006 with a 3-month history of optical hallucinations and delusions. No history of psychiatric or neurologic illness, drug abuse, seizures, or brain injury existed. An outpatient medication trial with risperidone 5 mg/day for 4 weeks failed. To improve ongoing symptoms, we started him on treatment with olanzapine 10 mg/day. After 1 week, no melioration occurred; therefore, we raised the dose of olanzapine to 20 mg/day and added amisulpride 600 mg/day.

About 2 weeks later, a neurologic workup was initiated. Results of the Expanded Disability Status Scale,[2] laboratory data (blood counts, electrolyte levels, serum vitamin B_{12} level, folic acid levels, thyroid hormone levels, and liver function test findings), and findings of a drug screening were unremarkable. An electroencephalogram showed alpha rhythm with focal abnormalities in the left temporal region of the left hemisphere. Magnetic resonance imaging examination revealed multiple high–signal intensity punctate white matter lesions. Although no lesion was enhanced with gadolinium contrast, the mainly periventricular localized lesions were highly suspicious of demyelinating disease. Analysis of cerebrospinal fluid confirmed oligoclonal bands. Subsequent to examination, neurologic consultants diagnosed him with multiple sclerosis.

Since neuroleptic medication was ineffective, treatment with olanzapine and amisulpride was stopped after $4^{1}/_{2}$ weeks. Due to ongoing symptoms, neurologists decided to start a 3-day course of corticosteroids (1000 mg/day i.v). Although corticosteroids potentially exacerbate psychosis,[3] the patient's status gradually improved within the next few weeks. Currently, 16 weeks later, he is free of symptoms. The temporal relationship between initiation of high-dose corticosteroid therapy and symptomatic improvement argues against a natural course and implies that improvement was related to corticosteroid application.

Neuropsychiatric symptoms in multiple sclerosis are a known phenomenon, and in rare cases multiple sclerosis displays first with psychiatric symptoms.[1,4] However, medication treatment of psychosis in patients with multiple sclerosis can present a challenge to physicians, especially in cases of psychosis. Antipsychotic agents are often ineffective, and only few systematic studies of their use in multiple sclerosis exist.[5] On the other hand, the mainstream therapy for multiple sclerosis includes corticosteroids. Usually, the propensity of corticosteroids to elicit psychosis argues against their use in psychiatric patients.[4] In our case, however, neuroleptics failed, even though they were administered in an optimally monitored regimen, whereas corticosteroids improved symptoms.

This case highlights 2 different points. First, psychiatrists and neurologists need to include multiple sclerosis in their differential diagnosis in patients with therapy-resistant psychotic complaints. Second, corticosteroids may ameliorate psychotic symptoms in multiple sclerosis.

The discrepancy between ineffectiveness of neuroleptics and effectiveness of immunomodulatory substances, e.g., cortico-

steroids, theoretically may be based on the autoimmune inflammatory demyelinating pathophysiology in multiple sclerosis. To elucidate effects of corticosteroid treatment of psychosis in multiple sclerosis in detail, further controlled trials are needed.

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Exacerbation of Obsessions With Modafinil in 2 Patients With Medication-Responsive Obsessive-Compulsive Disorder

Sir: Two patients with medication-responsive obsessive-compulsive disorder (OCD) whose obsessions recurred abruptly after the addition of modafinil and abated abruptly after the cessation of modafinil were presented. Our observation is consistent with the findings that modafinil might cause an increase in the activity of the cingulate cortex,[1,2] enhancing the increased activation demonstrated in OCD patients and leading to an exacerbation of symptoms in some.

Case reports. Mr. A, a 47-year-old man, had suffered from OCD for 25 years when he began to take modafinil in June 2006. His symptoms had been controlled and not clinically distressing with a regimen of paroxetine 60 mg, clomipramine 300 mg, and risperidone 3 mg daily for 2 years. Obsessions and compulsions recurred on the first day he took 100 mg of modafinil and were severely aggravated on the second day. He continued to take modafinil 100 mg daily for an additional 2 days (4 days total). Obsessive-compulsive symptoms improved abruptly on the fifth day when he stopped taking modafinil.

Ms. B, a 57-year-old woman, had a 20-year history of OCD when she began to take modafinil in February 2006. Her symptoms had been under control and not clinically distressing for 1 year with a regimen of paroxetine 60 mg, trazodone 200 mg, and olanzapine 15 mg daily. Obsessions and compulsions recurred to a severe degree on the first day she took 100 mg of modafinil. She continued to take modafinil 100 mg daily for 6 additional days (i.e., she took modafinil for a total of 7 days). Obsessive-compulsive symptoms improved suddenly on the eighth day when she stopped taking modafinil.

Neither of the patients experienced any distressing life event, had any medical/neurologic condition, used illicit substances and/or alcohol or any drug other than those prescribed for OCD. Both patients were given modafinil because of excessive daytime sleepiness. Wakefulness was provided during modafinil use; however, it might have been the result of the severe anxiety due to the recurring obsessions. Clinical diagnoses were made according to DSM-IV. The patients were not assessed with any clinical scale such as The Yale-Brown Obsessive Compulsive Scale or the Hamilton Rating Scale for Depression because they were undergoing routine clinical follow-up while taking modafinil.

The mechanism of action of modafinil is not clear. At pharmacologically relevant doses, modafinil does not bind to receptors for norepinephrine, serotonin, dopamine, γ-aminobutyric acid, adenosine, histamine-3, melatonin, or benzodiazepines.[3] There is no published report of obsessions occuring during modafinil use. However, anxiety, agitation, emotional lability, and even psychosis have been reported in modafinil users.[3,4]

Numerous studies have suggested that OCD patients have a hypermetabolism in the cingulate cortex,[5–8] and cingulotomy remains a viable treatment option for patients with severe treatment-refractory OCD.[9–11] Chronic anterior capsular electrostimulation in OCD patients has resulted in decreased metabolic activity, especially in the subgenual anterior cingulate.[12] Compared with placebo, modafinil administration has been associated with significantly greater activation in the anterior cingulate cortex using functional magnetic resonance imaging during a working memory task in chronic schizophrenic patients.[1] The cingulate cortex has been activated in rats given high doses of modafinil.[2] Therefore, a substance activating the cingulate may result in obsessions. Our observation suggests that modafinil causes an increase in the activity of the cingulate cortex, enhancing the increased activation demonstrated in OCD patients and leading to an exacerbation of symptoms in some.

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Serotonin Syndrome With Paroxetine Overdose: A Case Report

Sir: Serotonin syndrome can be a serious complication of treatment with selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and other serotonergic medications. The syndrome is characterized by the sudden onset of cognitive/behavioral changes (e.g., confusion, agitation, lethargy, coma), autonomic instability (e.g., hyperthermia, tachycardia, diaphoresis, nausea, vomiting, diarrhea, dilated pupils), and neuromuscular changes (e.g., myoclonus, hyperreflexia, rigidity, trismus). The syndrome usually occurs when 2 or more serotonergic drugs are inadvertently administered or through overdose; it rarely occurs at therapeutic doses of a single drug.[1,2] We report a case of an 18-year-old woman who developed serotonin syndrome resulting from overdose of paroxetine.

Case report. Ms. A, an 18-year-old female patient, was admitted in 2007 for altered mental status and agitation. Her psychiatric history was notable for major depressive disorder (DSM-IV criteria), for which she had begun treatment with paroxetine (20 mg/day) 1 week before admission. Ten hours before admission, she had taken 9 tablets of paroxetine (180 mg) after an argument with her boyfriend. She was found at home by her parents, was noted to be very agitated, and was brought immediately to the emergency department. Twelve pills remained in the prescription box (it had included 28 pills when the prescription was filled). It was stated that she had not taken any other medications or other substances for 3 weeks.

On admission, the patient was confused, disoriented, and agitated. After gastric lavage did not result in recovery of pill fragments, charcoal was administered. Her physical examination was significant for tachycardia (110 beats/minute), hypertension (150/80 mm Hg), tachypnea (22 breaths/minute),

elevated body temperature (38.1°C), and generalized anxiousness. Neurologic examination was positive for hyperreflexia, particularly of the lower extremities, and her laboratory results revealed no abnormalities. Computerized tomography of the head showed normal results.

Serotonin syndrome was considered after ruling out infection and cerebrovascular factors as possible etiologies. Paroxetine was stopped, and the patient was aggressively hydrated with intravenous fluids. She was administered 1 dose of alprazolam (2 mg p.o.) and was started on 18 mg/day of cyproheptadine in 3 divided doses. Within 24 hours, the patient's mental status had improved. Treatment was continued with cyproheptadine and intravenous fluids. By the second day on this treatment regimen, the patient's function returned to baseline, and she was discharged from the hospital with psychiatric follow-up.

This case presents a rare incidence of serotonin syndrome occurring after overdose of paroxetine. As such, it highlights the importance for physicians to have a lowered threshold to make the diagnosis when presented with an agitated or confused patient known to be on serotonin-modifying drugs.

Paroxetine[3] is an SSRI with anxiolytic properties, and it is one of the most frequently prescribed antidepressants. It is approved for the treatment of generalized anxiety disorder, depression, panic disorder, and social anxiety disorder. Therapeutic doses range from 10 mg/day to a maximum of 60 mg/day; our patient was on 20 mg/day. Common side effects with paroxetine use are nausea, constipation, diarrhea, yawning, and impotence. An adverse effect of paroxetine, as with other SSRIs, is the serotonin syndrome. The symptoms are protean and can easily be missed.[1] Serotonin syndrome is thought to occur as a result of excess stimulation of the serotonin-1A ($5-HT_{1A}$) and possibly the $5-HT_2$ receptor.[4]

The diagnosis of serotonin syndrome is made on a clinical basis. There are no specific laboratory findings, and blood 5-HT levels are not useful because it is the local concentration at nerve terminals that is responsible for the physiologic effects.[5,6] A strong clinical suspicion, known exposure to serotonergic agents, demonstration of specific signs and symptoms, and exclusion of other medical and psychiatric conditions are required for the diagnosis. The clinical presentation is usually marked by the triad of cognitive/behavioral changes (e.g., confusion, agitation, lethargy, coma), autonomic instability (e.g., hyperthermia, tachycardia, diaphoresis, nausea, vomiting, diarrhea, dilated pupils), and neuromuscular changes (e.g., myoclonus, hyperreflexia, rigidity, trismus).

Key differential diagnoses to the serotonin syndrome are the other potentially fatal hyperthermic syndromes: neuroleptic malignant syndrome (NMS) and malignant hyperthermia.[1] However, important points in history and physical examination facilitate the distinction between the three. NMS is an idiosyncratic reaction to several antipsychotic drugs, e.g., phenothiazines such as chlorpromazine and butyrophenones such as haloperidol.[7] It is thought to be due to dopamine receptor blockade or removal of exogenous dopaminergic agonists. It usually starts with muscular rigidity followed by hyperthermia and altered consciousness. Unlike the serotonin syndrome, NMS is exclusively caused by dopaminergic drugs and symptoms develop over days and resolve over days to weeks.[1,7] In the serotonin syndrome, the onset and resolution of symptoms occur within hours. Most patients present within 6 hours of increasing dosage, starting a new drug, or taking an overdose.[1] A history of neuroleptic usage combined with the presence of bradykinesia or ''lead pipe'' rigidity on examination distinguish the syndrome from that caused by serotonin excess.[7]

Malignant hyperthermia is a life-threatening condition that results from a genetic susceptibility to volatile anesthetics such as halothane and neuromuscular-blocking drugs such as succinylcholine. It is due to an abnormally increased release of calcium from the sarcoplasmic reticulum, which is often caused by an inherited mutation in the RYR1 gene.[6] The syndrome occurs within minutes of exposure to the anesthetic agents, unlike serotonin syndrome, and presents with muscular rigidity, a hypermetabolic state reflecting increased oxygen consumption and increased carbon dioxide production, metabolic acidosis, and hyperthermia.[8] The onset of symptoms, history of exposure to anesthetic agents, family history, and physical examination positive for skin mottling and hyporeflexia may distinguish malignant hyperthermia from serotonin syndrome.

No specific antidote exists for serotonergic toxicity. Successful management relies upon prevention, early recognition, and supportive care. Prevention is based on knowledge of pharmacology and avoidance of potential drug interactions between 2 serotonergic medications. Specifically, pharmacology and clinical experience have taught us that combinations of serotonergic medications should be avoided and that at least 2 to 4 weeks should pass between discontinuation of an MAOI and initiation of another serotonergic agent.[5,9,10] Early recognition involves a high index of suspicion for the diagnosis in any patient taking serotonergic medication who presents with the constellation of signs and symptoms described above. Acute management is based on 2 simple principles: discontinuation of all serotonergic medications and provision of necessary supportive care. Severe forms of the syndrome may require aggressive measures, including neuromuscular-blocking agents, mechanical ventilation, benzodiazepines (for sedation), and external cooling.[11]

In addition to supportive care and discontinuation of offending medications, there also may be a role for pharmacologic therapy in the acute management of serotonin syndrome. Specific agents have included benzodiazepines and nonspecific serotonin receptor blockers such as cyproheptadine, chlorpromazine, methysergide, and propranolol. Each of these agents has been credited with shortening the syndrome's duration.[12] Benzodiazepines are not recommended as first-line therapy but might have protective effects via inhibition of serotonergic neurotransmission.[13] As a first-generation antihistamine, cyproheptadine also has antagonist properties at $5-HT_{1A}$ and $5-HT_2$ receptors. While no randomized controlled trials have been conducted to evaluate fully the efficacy of cyproheptadine, its use in the treatment of serotonin syndrome has been documented.[10,14]

Paroxetine by itself has rarely been shown to cause the serotonin syndrome. It is indispensable that physicians are familiar with the signs and symptoms of serotonin syndrome and should suspect it in anyone with altered mental status who is taking serotonin-modifying drugs. Owing to its variable manifestations, the illness can easily be missed while the patient is subjected to a battery of unnecessary tests. In addition, the offending agent would continue to be administered, leading to an exacerbation of the syndrome with hazardous consequences.

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Alcohol and Drug Problems and Their Relationship to Sexual Impulsivity Among Female Internal Medicine Outpatients

Sir: In the literature, there is a general consensus that alcohol and/or drug use heighten the probability of sexual impulsivity. In this regard, there are findings in the areas of homosexuality and/or infection with human immunodeficiency virus. Beyond this literature, there are also alcohol studies that have examined specific variables related to sexual impulsivity, predominantly in nonclinical populations. For example, among college students, researchers have confirmed relationships between alcohol use and a lower likelihood of inquiring if new partners had sexually transmitted diseases,[1] unwanted sexual intercourse,[2] high-risk sexual behaviors,[3] unplanned and unprotected sex,[4] and a lower likelihood of condom use.[5] Studies have also examined community samples and confirmed relationships between alcohol use and multiple partners, premarital sex, and transactional sex (i.e., sex for money) in China[6]; forced sex, transactional sex, and *greater* condom use in South Africa[7]; unprotected sex, multiple sexual partners, and transactional sex in Botswana[8]; and a greater likelihood of herpes infection.[9] These types of relationships have been examined in clinical samples as well. For example, among women beginning alcohol treatment,

Mckay[10] found *no* patterns with condom use or nonuse. In contrast, Breen and colleagues[11] found among ecstasy users that comorbid alcohol use was related to sex with a greater number of partners as well as a lesser likelihood of practicing safe sex. In addition, Stein and colleagues[12] found among intravenous drug users with alcohol problems that alcohol use predicted risk-taking behaviors with regard to sex.

Enhanced sexual impulsivity has been reported with drugs other than alcohol as well. For example, Simbayi and colleagues[13] found among a South African community sample that methamphetamine use was associated with unprotected intercourse and relations with multiple partners. Raj and colleagues[14] found among detoxification patients that cocaine use was associated with being sexually active as well as transactional sex. Finally, Kingree and Betz[15] found among African American males in juvenile detention that marijuana use was associated with no prior discussion of sexual risks as well as nonuse of condoms.

In this study, we examined relationships between self-reported alcohol and drug problems, and 13 variables related to sexuality in a sample of female internal medicine outpatients.

Method. Participants were female outpatients, aged 18 years or older, who presented for routine medical care at an ambulatory center in which residents in the Department of Internal Medicine function as the primary providers. The sample was one of convenience. Exclusion criteria, which were determined by recruiters, were cognitive, psychiatric, or medical impairment that would preclude the successful completion of a survey.

Participants (N = 76) ranged in age from 18 to 75 (mean = 42.64, SD = 15.16) years. Most (85.5%, N = 65) were white, with 11.8% (N = 9) being African American, 1.3% (N = 1) Native American, and 1.3% (N = 1) Asian. The majority had attained a high school diploma (68.4%, N = 52); 11.8% (N = 9) reported a bachelor's degree and 6.6% (N = 5) a graduate degree. While most participants (71.6%, 53/74) had been married, only 24.3% (18/74) of the sample was currently married; 5.4% (4/74) were separated, 29.7% (22/74) were divorced, and 12.2% (9/74) were widowed.

Each participant completed a 4-page survey. The cover page of the survey contained the various elements of informed consent, and completion of the survey was assumed to function as informed consent. The booklet explored (1) demographic information (i.e., age, race, marital status, and highest level of completed education), (2) alcohol and drug history (i.e., "Have you ever had a problem with alcohol?" and "Have you ever had a problem with drugs?" with yes/no response options), and (3) the sexual history (i.e., age of menarche; age of first intercourse; number of pregnancies, live births, births outside of marriage, miscarriages, and abortions; number of different lifetime sexual partners; number of treatments for a sexually transmitted disease; homosexual experiences; and history of rape by a stranger, date, or partner). This study was approved by the institutional review boards of both the community hospital that sponsors the internal medicine residency and the university and was conducted from July 2005 to June 2006.

Results. Nine participants (11.8%) reported having had a problem with alcohol and 8 (10.5%) with drugs. The simple correlations between alcohol or substance abuse and the sexuality variables are presented in Table 1.

Discussion. For participants endorsing a history of alcohol problems, there were statistically significant positive correlations with a later age at menarche, being raped by a stranger,

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Table 1. Correlations Between Self-Reported Alcohol or Drug Abuse Problem and the Sexuality-Related Variables in a Sample of Female Internal Medicine Outpatients (N = 76)

Sexuality-Related Variables	Alcohol Abuse (N = 9)	Drug Abuse (N = 8)
Age at menarche	0.27*	0.02
Age at first sexual intercourse	–0.21	–0.17
Total number of pregnancies	0.02	0.04
Total number of births	–0.09	0.00
Total number of births outside marriage	0.00	0.24*
Total number of miscarriages	0.04	0.07
Total number of abortions	–0.14	–0.18
Total number of different sexual partners	0.23	0.36**
Total number of times treated for a sexually transmitted disease	0.15	–0.02
Ever been raped by a stranger	0.02	0.04
Ever been raped during a date	0.37**	–0.07
Ever been raped by a partner	0.20	–0.02
Ever had same-sex sexual experience	0.50***	0.41***

*p < .05, 2-tailed.
**p < .01, 2-tailed.
***p < .001, 2-tailed.

and having had same-sex experiences. Likewise, for participants endorsing a history of drug problems, there were statistically significant positive correlations with the total number of births outside of marriage, the total number of different sexual partners, and having had same-sex experiences. Clearly, these data confirm relationships between alcohol and/or drug use and specific sexuality-related behaviors, reflecting the general theme in the literature.

In comparison with previous studies in this area, our sexuality variables for examination were broad and somewhat different. The majority of previous studies have examined *high-risk* sexual behaviors, including the lack of use of condoms, unsafe sex, multiple partners, and transactional sex. In this study, we focused more on sexual *impulsivity* and its possible aftermaths (e.g., pregnancies). Despite the differing sexuality variables under study, the general theme of impulsivity appears consistent both in our study and in the studies of others.

There are a number of potential limitations to this study including the self-report nature of the data, global queries about alcohol and drug problems, small sample size, and use of a female sample. However, this is one of the few studies to examine a number of sexuality variables in relationship to alcohol and substance abuse as well as to use a primary care sample for study. Future studies might clarify these data, explore temporal relationships between alcohol/drug usage and sexual impulsivity, and examine the role of personality dysfunction as a moderating variable. In addition, the role of same-sex experiences warrants further investigation. Regardless, we can conclude that alcohol and drugs may have a potentially detrimental effect on sexual regulation in many individuals.

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