Subjective Experiences During Dopamine Depletion

TO THE EDITOR: A paradigm that induces acute dopamine depletion with the drug alphamethylpara tyrosine (AMPT), a reversible inhibitor of tyrosine hydroxylase, has been used successfully to assess the occupancy of striatal dopamine D_2 receptors by endogenous dopamine in vivo (1). Here we describe the dramatic subjective experiences induced by acute dopamine depletion in one healthy volunteer. They included a whole spectrum of psychiatric symptoms and highlighted the contribution of the dopaminergic system to diverse major psychiatric disorders.

In our study, dopamine depletion was achieved by oral administration of 4.5 g AMPT in 25 hours, as described earlier (1). Striatal D_2 receptors were assessed at baseline and after acute dopamine depletion by using the bolus/constant infusion [^{123}I]IBZM technique (1). Acquisition, reconstruction, and analysis of the single photon emission computed tomography data were performed as described previously (2).

Mr. A was a healthy, extraverted, very well functioning 21-year-old medical student without even minor psychological difficulties or psychiatric disorders in his family. His Global Assessment of Functioning Scale score was 97. Written informed consent was obtained from Mr. A. We will describe the spontaneous reported subjective experiences after he started the first dose of 750 mg AMPT at t=0 hours (1).

After 7 hours, Mr. A felt more distance between himself and his environment. Stimuli had less impact; visual and audible stimuli were less sharp. He experienced a loss of motivation and tiredness. After 18 hours, he had difficulty waking up and increasing tiredness; environmental stimuli seemed dull. He had less fluency of speech. After 20 hours, he felt confused. He felt tense before his appointment and had an urge to check his watch in an obsessive way.

After 24 hours, Mr. A had inner restlessness, flight of ideas; his ideas seemed inflicted, and he could not remember them. He felt a loss of control over his ideas. After 28 hours, he felt ashamed, frightened, anxious, and depressed. He was afraid that the situation would continue. At that time, blepharospasm, mask face, and tremor were noted. After 30 hours, he was tired and slept 11 hours. After 42 hours, he had poor concentration. In the next hours, he returned to normal.

The striatal-to-nonspecific binding ratio was 27% higher after Mr. A took AMPT compared to the baseline situation, indicating severe acute dopamine depletion (1).

During increasing dopamine depletion in this case, a range of subjective experiences appeared and disappeared consecutively. These experiences resembled negative symptoms, obsessive-compulsive symptoms, thought disorders, and anxiety and depressive symptoms and highlight the importance of the role of dopamine in major psychiatric disorders. In former studies, AMPT was found to lower mood, induce fatigue, decrease subjective alertness, and/or induce extrapyramidal symptoms in some healthy individuals (reviewed in reference 3).

Since the subjective experiences due to acute dopamine depletion could be dramatic, we believe that subjects participating in dopamine-depletion studies should be well informed about possible temporarily—but intense—side effects.

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Intravenous Quetiapine Abuse

TO THE EDITOR: There are recent reports in the literature describing the intranasal abuse of quetiapine among jail inmates, who may obtain it by reporting malingering psychotic symptoms and who refer to it as "quell" (1).

Ms. A was a 34-year-old woman with a history of polysubstance dependence (alcohol, cannabis, and cocaine), depressive episodes associated with multiple suicide attempts, and borderline personality disorder who was incarcerated after conviction on charges of physical assault and possession of controlled substances. She had a history of incarceration on multiple occasions for similar charges. She complained of difficulty sleeping, poor impulse control, irritability, and depressed mood. For these symptoms, she was given oral quetiapine, 600 mg at bedtime. On one occasion, she took the pills provided to her but did not ingest them. Instead, she crushed the two 300-mg tablets, dissolved them in water, boiled them, drew the solution through a cotton swab, and while lying in bed, covered by blankets, intravenously injected the solution.

Twelve hours later, she was awoken by facility guards who found the syringe she used still in place on her arm. She informed the guards that she had intravenously injected herself with quetiapine the previous evening and became rapidly sedated, falling asleep before she could remove the syringe. She additionally admitted to previous intranasal abuse of crushed quetiapine tablets. Apart from "the best sleep I ever had," she described no dysphoric, euphoric, or other effects.

This description lends support to findings by other investigators of an increased risk of abuse of prescription medication in individuals who have a history of substance abuse or dependence (2). It is conceivable that such a progression from the use of quetiapine to its abuse either intranasally or intravenously is more prevalent than is currently assumed. This may be particularly apt in settings in which the prescription of sedative agents, such as benzodiazepines, barbiturates, and stimulants, is decreasing secondary to concerns of abuse and resale, e.g., prison settings and substance abuse treatment programs and among school-age children. The calming and sedating effects of quetiapine, which make it useful in

clinical practice, also make it a substance of abuse and confer "street value" on it by the same token.

Quetiapine treatment has been demonstrated to be associated with prolonging abstinence and decreasing the number of hospitalizations in patients with alcohol dependence and posttraumatic stress disorder (3). This is hypothesized to be related to the impact of quetiapine on improving disturbed sleep but may also be related to a direct action of quetiapine in reducing the use of alcohol. The awareness of the "extra-antipsychotic" effects of quetiapine provides potential areas for further clinical research for understanding the treatment of substance abuse and anxiety disorders.

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Complications From Olanzapine in a Mentally Healthy Patient

TO THE EDITOR: Existing literature regarding atypical antipsychotics and weight gain has focused on their use in populations with acute or chronic psychotic illness. Some suggest that weight gain in this population may be due to impaired self-monitoring of food intake unrelated to treatment, making it unclear if the same applies to patients without psychotic illness (1). Weight gain in this population increases the probability of additional problems, such as hyperlipidemia, hypertension, and diabetes. We describe the case of a man without mental illness who developed multiple metabolic complications after inadvertently taking olanzapine for 2 years.

Mr. A, a 36-year-old man with chronic seasonal allergies, was given a prescription for cetirizine, 10 mg b.i.d., to be taken on an as-needed basis for his allergy symptoms. As the result of a retail pharmacy error, he received olanzapine at the same dosage. He took olanzapine for 2 years, refilling the prescription automatically outside his primary pharmacy. He had no preexisting illnesses other than seasonal allergies and sickle cell trait. He had no history of mental illness.

During treatment, Mr. A's weight increased 45 lb. Associated with this weight gain, he developed hyperlipidemia, hypertension, and sleep apnea, requiring treatment. His total cholesterol level increased from 258 to 274 mg/dl, and his triglyceride level increased from 87 to 152 mg/dl, requiring treatment with simvastatin, 10 mg/day. His diastolic blood pressure increased from 79 to 98 mm Hg requiring treatment with combination irbesartan/hydrochlorothiazide at 150 mg/day and 12.5 mg/day, respectively, and amlodipine, 10 mg/day. A formal sleep study revealed severe obstructive sleep apnea requiring treatment with continuous positive airway pressure.

The error was discovered 2 years later when Mr. A's primary care provider declined to write a prescription for his "allergy" medication, at which time the olanzapine was stopped.

Previous studies of weight gain and the use of olanzapine have evaluated mentally ill subjects. Early experience in treatment with antipsychotic medication has suggested that weight gain indicated a positive treatment response (2). A systematic review of treatment data shows that most antipsychotics are associated with some weight gain, with clozapine and olanzapine identified as most likely to produce significant weight gain (2). This case suggests that the weight gain associated with the use of olanzapine is not linked to underlying psychotic illness but to medication use alone. Recent literature supports aggressive health monitoring of schizophrenic patients (3). With an increasing trend to use atypical antipsychotics for illnesses from bipolar disorder to treatment-resistant depression, careful monitoring of weight gain and its associated effects is essential, regardless of the indication.

(The views expressed in this letter are those of the authors and do not reflect the official policy or position of the Department of the Navy, the Department of Defense, or the United States government.)

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Antidepressant Adherence and Suicide Risk in Depressed Youth

TO THE EDITOR: The lack of adequate data on treatment adherence may be what is hampering the full understanding of the relationship between the use of selective serotonin reuptake inhibitor (SSRI) or newer-generation antidepressants and the risk of suicide in depressed children/adolescents. The clinical trial data have been analyzed and reanalyzed to answer the following question: do depressed children/adolescents treated with SSRIs and newer-generation antidepressants have a greater risk of suicide than those treated with placebo? However, adequate data do not exist to examine whether adherence mediates the relationship between antidepressant use and the risk of suicide.

This suggested mediating role of medication adherence is supported by an examination of the correlation between multiple-dose plasma elimination half-lives of the various antidepressants (venlafaxine, fluvoxamine, paroxetine, sertraline, mirtazapine, citalopram, and fluoxetine) and the risk ratio for