

Obesity and Mood Disorders: The Complex Problem of Insight

Sir: McElroy et al.¹ recently conducted an interesting and complete review about the relationship between mood disorders and obesity. The authors highlighted the epidemiologic and pathophysiologic links between obesity, depression, and bipolar disorder, especially in obese patients seeking weight loss treatment. Indeed, it is common that obese patients experience comorbid depressive disorders, as well as anxiety disorders and several Axis II disorders. Nevertheless, psychiatric symptoms and psychological distress often remain hidden, and consequently untreated, even in clinical populations of obese patients.

In fact, in a sample of 168 consecutive obese subjects presenting to the University of Florence outpatient clinic (Florence, Italy) for diagnosis and treatment of obesity, clinically relevant depression (diagnosed through the Structured Clinical Interview for DSM-IV² and the Beck Depression Inventory [BDI],³ routinely used during the initial assessment of obese patients) was present in 35 subjects (20.8%). The mean \pm SD BDI score of the whole sample was 14.4 ± 9.5 ; the range was 0 to 42. Lifetime and current Axis I diagnoses were present in 100 (59.5%) and 70 subjects (41.6%), respectively. Among currently depressed obese patients, only 14 (20.0%) had been previously diagnosed and treated for their depressive illness, even though the mean \pm SD duration of depressive symptoms reported by the patients was 8.7 ± 2.4 months. Among lifetime Axis I–diagnosed patients, only 31 (31.0%) had been treated for their psychiatric illness, mostly with symptomatic drugs (i.e., benzodiazepines) prescribed by general practitioners.

Data obtained from our sample seem to suggest that the majority of obese patients who present with a current or lifetime Axis I psychiatric diagnosis do not seek the help of a psychiatrist. The presence of a depressive disorder, even if clinically relevant, is often discovered only during the psychiatric screening routinely performed in the context of an integrated approach. In our experience, obese patients asking for weight loss treatment cannot identify the presence of psychological distress or psychiatric symptoms. Moreover, patients tend to underrecognize depressive symptoms, considering “sadness” and poor quality of life as normal consequences of obesity itself.

This difficulty in exploring emotions or mood state (alexithymia) is commonly described in obese subjects⁴ and may contribute to the maintenance of depressive illness. Alexithymia, which literally means “no words for emotions,” is a set of cognitive-emotional deficits that includes the inability to identify and express emotions and affects, and avoidance in coping with conflicts and reporting emotions.⁵ There is empirical evidence suggesting a relationship between alexithymia and obesity, and this construct is often described in obese or eating disordered subjects with psychopathologic characteristics.^{6,7} Several studies particularly support the hypothesis that alexithymia is specifically associated with eating disorders in obese subjects, being a significant predictor of emotional eating and depression.⁷ Paradoxically, obese subjects, who are at greater risk of psychiatric comorbidity than nonobese subjects, are also unable to express their psychological distress and, as clearly shown by our data, do not seek the help of a psychiatrist.

As McElroy and colleagues conclude, the presence of depression in obese subjects is associated with a greater body mass index and a poorer outcome of weight loss treatment.¹ Our findings suggest for the first time that the majority of obese patients suffering from psychiatric disorders do not directly consult mental health professionals. These data may not be gen-

eralizable to all settings. However, we support the routine performance of a psychiatric screening in every obese subject seeking weight loss treatment.

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

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Diabetes Mellitus During Olanzapine and Quetiapine Treatment in Japan

Sir: In their report “The Incidence of Hyperglycemia in Patients Treated With Olanzapine,” Misawa et al.¹ present very interesting but also very disturbing data on dysregulation of glucose metabolism associated with treatment of 2 atypical antipsychotics, olanzapine and quetiapine. I would like to comment on some aspects of their report.

Misawa et al. report that within 10 months after the introduction of olanzapine in Japan, 9 schizophrenic patients were reported to have developed severe diabetes mellitus and diabetic coma, resulting in 2 deaths. In the literature, 3 cases have been described so far of fatal glucose disturbances during treatment with olanzapine.^{2–4} Details about the prescription rate and the estimated incidence in Japan of this severe, in some cases fatal, complication of olanzapine treatment would be very welcome indeed.

Misawa et al. also report that in the 19 months after introduction of quetiapine, 13 patients developed severe diabetes mellitus and diabetic coma, resulting in the death of 1 patient. To my knowledge, this is the first report in the literature of a

fatal complication of diabetes mellitus associated with quetiapine.⁵⁻⁹

The 5 new cases described by Misawa and colleagues, 3 with hyperglycemia and 2 with diabetes mellitus, raise a question and some comment.

First, I find their use of the words *hyperglycemia* and *diabetes mellitus* confusing. Three of the new cases showed, at the time of the diagnosis of disturbed glucose metabolism, a random, nonfasting glucose level above 200 mg/dL, described by the authors as "temporary hyperglycemia." However, according to the World Health Organization guidelines,¹⁰ a random glucose level above 200 mg/dL is suggestive of the diagnosis of diabetes, with only a second confirmatory blood determination required for the diagnosis. For case 1, Misawa et al. first state that diabetes mellitus was diagnosed, but they continue on to state that "hyperglycemia did not improve after discontinuation of olanzapine."^{10(p444)} My suggestion is that the 3 cases of "temporary hyperglycemia" were suffering from reversible diabetes mellitus, type 2, and that case 1 was suffering from irreversible diabetes mellitus, type 2.

Second, case 1 showed diabetic hyperglycemia that did not improve on discontinuation of olanzapine. In other words, case 1 had not only irreversible but also iatrogenic diabetes mellitus, type 2. If I am correct that all 5 of the new cases of hyperglycemia were in fact cases of diabetes mellitus, it would follow that 1 out of 5 patients, i.e., 20% of the new cases, had irreversible diabetes mellitus. This percentage corresponds very well with the 20.7% that has been found in a study of 53 cases of new onset of clozapine-associated diabetes mellitus.¹¹

Third, a point of consideration is the little impact that 3 well-known risk factors for the development of diabetes mellitus, type 2, showed in this population. Advanced age (> 50 years), obesity (body mass index > 30), and positive family history were present in only 1 patient each. In a concerted effort to confront the problem of glucose disturbances in the treatment of schizophrenia, a consensus development conference was recently organized by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity. The monitoring protocol has just been published,¹² recommending screening based mainly on the risk factors obesity, family history, and hypertension (age is not separately mentioned). More specifically, a consideration of metabolic risks when starting atypical antipsychotic therapy is recommended. The report by Misawa et al. suggests that the well-known risk factors supply inadequate information for a fair assessment of the risk involved in treating schizophrenic patients with atypical antipsychotics. In the context of the increased prevalence and severity of disturbed glucose metabolism in schizophrenia, this suggestion would be, if confirmed, a particularly worrisome one.

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Drs. Misawa and Fujii Reply

Sir: Olanzapine, which has been shown to be effective in the treatment of schizophrenia with fewer extrapyramidal side effects than typical antipsychotics, is widely used in Japan.

However, olanzapine was contraindicated for patients with diabetes or a history of diabetes due to a letter from the pharmaceutical company warning that 9 cases treated with olanzapine had developed severe hyperglycemia and diabetic coma and that 2 of the 9 patients had died. The 2 cases who died were men with schizophrenia who did not have a past history of diabetes. One of the 2 cases, in his twenties, had been found to have obesity and hyperphagia before treatment with olanzapine. He began to seriously overconsume soft drinks during olanzapine therapy and died of severe hyperglycemia 48 days after the initiation of olanzapine treatment.¹ The other patient, in his thirties, had been found to have obesity and hyperphagia and to be overconsuming soft drinks before treatment with olanzapine. His overconsumption of soft drinks became more pronounced during olanzapine therapy, and he died of severe hyperglycemia 19 days after the initiation of olanzapine treatment.¹

Quetiapine was also contraindicated for patients with diabetes or a history of diabetes due to a letter from the pharmaceutical company warning that 13 cases treated with quetiapine had developed severe hyperglycemia and diabetic coma and that 1 of the 13 patients had died. There are no published reports of a fatal complication of diabetes with quetiapine in any of the established English-language journals. The patient who died in Japan, who was in his fifties, had shown no clear evidence of having either obesity or hyperphagia before starting quetiapine therapy. He had gained weight and ingested excessive soft drinks after starting quetiapine therapy. Due to diabetic coma, quetiapine was discontinued 293 days after initiation, but the patient died 2 days later.

Table 1 shows the backgrounds of the 3 cases who died of severe hyperglycemia with olanzapine or quetiapine in Japan.

Table 1. Characteristics of the 3 Cases Who Died of Severe Hyperglycemia Associated With Atypical Antipsychotics in Japan

| Characteristic | Case 1 | Case 2 | Case 3 |
|---------------------------------------|------------|------------|------------|
| Antipsychotic | Olanzapine | Olanzapine | Quetiapine |
| Age, y | 20s | 30s | 50s |
| Gender | Male | Male | Male |
| Obesity ^a | + | + | - |
| Duration of treatment, d ^b | 48 | 19 | 295 |
| Excessive soft drink consumption | + | + | + |

^aPresence of obesity before commencing treatment with olanzapine or quetiapine.

^bFrom commencing treatment with olanzapine or quetiapine until time of death.

Symbols: + = present, - = absent.

All 3 patients were found to have been drinking too many sugar-containing soft drinks and may have been suffering from soft drink ketosis. Soft drink ketosis is induced by a vicious circle in which overconsumption of soft drinks leads to hyperglycemia and hyperglycemia leads to more severe hyperglycemia through glucose toxicity.² The atypical antipsychotics olanzapine and quetiapine may encourage the formation of such a vicious circle. Soft drink ketosis occurs frequently in young males, and the background of the 3 patients who died is similar to that of patients suffering from soft drink ketosis.¹ Soft drink ketosis is often reported in Japan, although there are few reports in Europe and America.¹ This may be because of some racial difference in glucose tolerance. However, we think there are schizophrenia patients who tend to overconsume sugar-containing soft drinks in all parts of the world and would suggest that overconsumption of soft drinks is a possible risk factor for severe diabetic complications associated with atypical antipsychotics.

Next, we reply to Dr. Cohen's question and comment on the 5 cases.

First, we distinguished between hyperglycemia and diabetes mellitus. We defined hyperglycemia as a fasting glucose level of ≥ 126 mg/dL or a random glucose level of ≥ 200 mg/dL. If hyperglycemia appeared again in a glucose test on another day, we diagnosed diabetes mellitus. This definition was in accordance with the Japan Diabetes Society guidelines.³ Cases 3, 4, and 5 were found to fulfill the conditions for hyperglycemia on 1 occasion only, so they did not fit the criteria for the diagnosis of diabetes mellitus. In cases 1 and 2, hyperglycemia appeared on 2 separate occasions, so we diagnosed them with diabetes mellitus.

Second, Koller et al.⁴ defined new-onset diabetes associated with clozapine as a fasting glucose level of ≥ 126 mg/dL, a random glucose level of ≥ 200 mg/dL, or an elevated glycosylated hemoglobin A_{1c} level; the presence of metabolic acidosis or ketosis; or physician institution of antidiabetic medication. All 5 cases in our study had a diagnosis of diabetes mellitus if we use Koller and colleagues' criteria or the World Health Organization guidelines.⁵ Consequently, the results of our study indicate a ratio of irreversible diabetes mellitus of 20%, and this corresponds well with the 20.7% presented by Koller et al. Incidentally, Koller and Doraiswamy⁶ found in a separate study that the ratio of irreversible diabetes mellitus with olanzapine is 21%.

Third, as Dr. Cohen described, the typical risk factors for type 2 diabetes do not seem to apply to diabetes arising from treatment for schizophrenia. Obesity is one of the risk factors, but there is no clear evidence of obesity or substantial weight gain in about 25% of cases who have diabetes mellitus associated with atypical antipsychotics.^{4,6} About half of the cases have

no family history of diabetes.^{4,6} The mean age (about 40 years) is considerably less than that which is typical for patients with type 2 diabetes.^{4,6}

A large-scale prospective study is needed to verify the facts concerning the important questions of irreversibility, risk factors, and severe complications of diabetes mellitus associated with atypical antipsychotics.

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

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A Case of Complex Movement Disorder Induced by Fluoxetine With Management of Dystonia by Botulinum Toxin Type A

Sir: Selective serotonin reuptake inhibitors (SSRIs) have been associated with movement disorders such as akathisia, dystonia, dyskinesia, and parkinsonism.¹⁻³ We present a case of fluoxetine-induced de novo complex movement disorder characterized by orofacial dyskinesia, jaw-closing dystonia, bruxism, and parkinsonism. Focal injections of botulinum toxin type A (BTX-A) were required to treat the dystonic features. To the best of our knowledge, the use of BTX-A for the management of SSRI-induced dystonia has not been previously reported.

Case report. Mr. A, a 77-year-old, right-handed, white man, presented with a 1-month history of new-onset abnormal orofacial movements and parkinsonism. The involuntary orofacial movements were characterized by stereotypic movements involving buccal, lingual, and masticatory muscles (chewing, lip-smacking, and low-amplitude, random tongue writhing). Tongue protrusion was absent. Significant teeth clenching (bruxism) and difficulty with jaw opening (jaw-closing dystonia) were also present. The patient's symptoms were exacerbated by fatigue, stress, and emotional extremes. Akathisia was absent. No choreoathetoid or dystonic movements were found in other facial or body regions. Signs and symptoms of parkinsonism were predominantly right-sided and included bradykinetic gait, upper extremity postural tremor, slow finger taps, and diminished arm swing.

Mr. A's neurologic and psychiatric history was significant for bilateral sensorineural hearing loss, depression, headache, and radicular neuropathy of the right hip and leg. Other medical problems included benign prostatic hypertrophy, erectile dysfunction, gastroesophageal reflux disease, hyperlipidemia, hypertension, hypothyroidism, left bundle-branch block, macular degeneration, postprandial sweating, renal calculi, and urinary incontinence. Mr. A denied any personal or family history of movement disorders, past exposure to dopamine receptor blocking agents (DRBAs) or lithium, dentures or recent dental procedures, or facial trauma.

Mr. A had been treated with fluoxetine 20 mg daily for the past 6 years. The onset of his abnormal orofacial movements occurred within several days after an increase of fluoxetine dose from 20 to 40 mg daily. Other medication changes included initiation of modafinil (2 months prior to the fluoxetine dose increase) for excessive fatigue and sildenafil for erectile dysfunction. The orofacial dyskinesia and mandibular dystonia resulted in jaw pain, embarrassment in social settings, and modest interference with speech. There was minimal impairment of voluntary chewing or ability to eat. Bruxism was inaudible and occurred during the day and night, resulting in jaw pain. Mr. A's laboratory values were within normal limits, and no evidence of serotonin syndrome was present. Fluoxetine was discontinued, and the orofacial dyskinesia and parkinsonism resolved within 2 months. However, jaw-closing dystonia and bruxism persisted.

Serial treatment with BTX-A (Botox; Allergan, Irvine, Calif.) was initiated. The initial BTX-A injections consisted of 30 units each in the right and left masseters. Within 3 weeks, the jaw dystonia improved, but bruxism persisted. No jaw weakness was reported. Subsequently, over the next year, Mr. A was maintained on BTX-A injections every 12 weeks (30 units in both the right and left masseters and temporalis) for management of jaw dystonia.

The signs and symptoms of our patient fulfill the DSM-IV⁴ criteria for medication-induced movement disorder not otherwise specified. The Naranjo Adverse Drug Reaction Probability Scale,⁵ a reliable and valid causality tool, was administered, and a score of 8 was obtained, which indicates a strong probable relationship between fluoxetine dosage increase and the onset of complex movement disorder. Spontaneous orofacial dyskinesia cannot be excluded but is unlikely, due to the temporal relationship of the symptoms with fluoxetine dosage changes. The pathophysiologic mechanism for fluoxetine-induced movement disorders remains unknown but probably relates to direct or indirect interactions between the serotonin and dopamine pathways within the basal ganglia.^{6,7} This case highlights the complex mechanism of SSRI-induced movement disorders. The acute onset and rapid resolution of dyskinesias upon fluoxetine withdrawal indicate a subacute pathogenic process (e.g., increased serotonergic activity) as opposed to persistent alteration of neurotransmitter or receptor function as has been implicated in DRBA-induced tardive dyskinesia. However, the persistence of focal dystonia suggests persistent changes within the basal ganglia.

The temporal correlation between the fluoxetine dose increase and the onset of abnormal orofacial movements and subsequent improvement of dyskinesia and parkinsonism upon drug discontinuation suggests a strong relationship with fluoxetine levels; this is supported by the high score on the Naranjo Adverse Drug Reaction Probability Scale. Alternatively, modafinil may have contributed to the development of dyskinesias, as these symptoms have been noted to develop in 1% of patients treated with modafinil.⁸ However, in this case, the Naranjo Adverse Drug Reaction Probability Scale score

associated with modafinil treatment was very low (i.e., 3) and indicates a low probability of a relationship.

Several oral agents (e.g., antimuscarinic agents, benzodiazepines) can be used for the management of drug-induced dystonia. However, these orally administered drugs are often associated with significant systemic side effects, particularly in the elderly, and improvement is often suboptimal. For the management of focal dystonias, botulinum toxin injections have become a powerful therapeutic tool.⁹ The most common adverse effect to be expected is focal weakness due to excessive dose or unwanted diffusion of toxin into adjacent muscles.

This report illustrates that SSRI-induced de novo movement disorders may be characterized by a complex of multiple clinical phenotypes. We also believe this is the first report on the use of BTX-A for the treatment of SSRI-induced dystonia.

Dr. Swope has been a speaker for Allergan. Dr. Chen reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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New Onset of Diabetes Mellitus With Ziprasidone: A Case Report

Sir: To the best of our knowledge, only 1 case has been reported in the literature of diabetes and pancreatitis associated with the use of ziprasidone.¹ This report describes a case of diabetes mellitus in a patient treated with ziprasidone.

Case report. Mr. A, a 36-year-old Spanish man, had a DSM-IV diagnosis of schizophrenia paranoid type, first diagnosed in 1986. From the time of his first psychotic episode, he

was successfully treated with different regimens of conventional antipsychotics such as haloperidol, perphenazine, and fluphenazine until late 1999, and from then, due to extrapyramidal symptoms, he was treated with atypical antipsychotics.

In June 2001, due to excessive parkinsonian side effects, the patient was switched to olanzapine 20 mg/day after being treated for 1 year with 6 mg/day of risperidone. While Mr. A was treated with olanzapine (June 2001–July 2002), he experienced a significant weight gain of 33 lb (body mass index [BMI] = 36.5 in July 2002) from his baseline weight of 219.8 lb in June 2001. An extensive blood workup was performed with no significant findings other than elevated cholesterol (up to 235 mg/dL) and triglycerides (up to 260 mg/dL).

Due to Mr. A's weight gain, a trial of ziprasidone (titrated up to 160 mg/day) was initiated in July 2002. Blood tests were repeated monthly, and all parameters normalized within 3 months of treatment. The patient's weight was markedly decreased to 190 lb (BMI = 27.1) by December 2002, yet a routine follow-up blood chemistry (January 2003) showed an elevated fasting glucose level of 145 mg/dL with the rest of the parameters within normal limits. Monthly controls showed progressive increases of serum glucose levels up to 375 mg/dL with clinical correlates of diabetes, as well as an abnormal lipid profile (cholesterol level of 250 mg/dL and triglycerides of 300 mg/dL) despite good diet control. Metformin 1000 mg/day was initiated. Ziprasidone was discontinued in April 2003, and the patient was then switched to quetiapine up to 700 mg/day.

Blood chemistry tests were continued on a monthly basis, confirming a normalization of the glucose levels as well as the lipid profile by July 2003, at which time the patient was off metformin treatment and in good metabolic control.

The association between schizophrenia and diabetes has been reported elsewhere.² With the development of atypical antipsychotics, there has been a progressive increase in their use over the older antipsychotics. Adverse effects such as weight gain as well as glucose and lipid metabolism abnormalities associated with the use of atypical antipsychotics have increasingly gained the attention of clinicians and researchers over the past few years.^{3,4}

To the best of our knowledge, this is the first reported case of a potential association between diabetes mellitus and the use of the antipsychotic ziprasidone without the confounding use of other diabetogenic medication or an underlying medical illness. The Western European ethnicity of the patient, the lack of simultaneous use of other diabetogenic medication, the absence of a family history of diabetes, and the fact that the patient's glucose and lipid regulation abnormalities returned to a normal baseline after discontinuation of ziprasidone suggest the potential correlation between the use of ziprasidone and new-onset diabetes in this patient.

Moreover, although weight gain plays a role in peripheral tissue insulin resistance, the patient's weight loss to below his baseline weight suggests a different insulin resistance mechanism than the one associated with weight gain during ziprasidone treatment.

The increasing data in the literature showing the relationship of new-onset diabetes and lipid abnormalities with the use of the majority of the atypical antipsychotics make it advisable to perform regular basal glucose level and lipid profiles at the beginning as well as later in the course of treatment with this group of drugs.

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Olanzapine-Induced Hyperprolactinemia and Galactorrhea Reversed With Addition of Bromocriptine: A Case Report

Sir: Olanzapine has been suggested as an antipsychotic without sustained hyperprolactinemic effects and has been reported to result in decreased prolactin levels in patients who have experienced hyperprolactinemia with other atypical antipsychotic medications.^{1–3} We report here on a patient who experienced good efficacy with a switch from clozapine to olanzapine, but developed sustained olanzapine-induced hyperprolactinemia and galactorrhea that resolved with the addition of bromocriptine.

Case report. Ms. A, a 28-year-old white woman with schizoaffective disorder (DSM-IV), came to our clinic in 1998 for outpatient treatment of her condition. At that time, she was taking 275 mg/day of clozapine, which had been successfully controlling her previous symptoms of thought broadcasting and paranoia. She had previously failed 2 other antipsychotic trials of trifluoperazine and risperidone in the early 1990s. In fall 2001, reports of successfully switching to olanzapine in clozapine responders,⁴ with the potential for fewer adverse effects, were discussed with the patient. Ms. A requested the change, and a slow cross-titration was successfully completed, without complaints, over several months to 20 mg/day of olanzapine.

Approximately 1 month after completion of the titration, the patient began to develop galactorrhea bilaterally. Her prolactin level was checked and found to be elevated at 43.9 ng/mL (reference range, 3–20 ng/mL) (Table 1). She had no history of hyperprolactinemia or galactorrhea. Olanzapine was subsequently serially decreased to daily doses of 15 mg, 12.5 mg, 10 mg, 7.5 mg, and finally 5 mg over a period of months. During the downward titration, the patient also developed amenorrhea (missed 2 menses). However, her galactorrhea persisted at the 5-mg olanzapine dose, and it was decided at that time to discontinue the medication. She had remained asymptomatic during the entire dosage reduction with no breakthrough psychotic symptoms. The patient's prolactin levels decreased to 34.6 ng/mL during the tapering process and then to 21.5 ng/mL and finally 13.9 ng/mL within a month after olanzapine discontinuation. Her galactorrhea and amenorrhea resolved with return of normal menstrual function after olanzapine discontinuation.

Ms. A was then given an adequate trial of quetiapine. During the titration period of quetiapine, she began to experience symptoms of paranoia and thought broadcasting again. Her pro-

Table 1. Chronologically Ordered Serial Prolactin Levels in a Patient With Olanzapine-Induced Hyperprolactinemia and Galactorrhea^a

| Time of Measurement | Prolactin Level (ng/mL) |
|--|-------------------------|
| Initial with olanzapine | 43.9 |
| Tapering olanzapine | 34.6 |
| < 1 Month after olanzapine discontinuation | 21.5 |
| 1 Month after olanzapine discontinuation | 13.9 |
| 1 Month with 100 mg quetiapine | 16.3 |
| Peak quetiapine dosing (800 mg) after 5 months | 16.6 |
| 3 Weeks after rechallenge with olanzapine | 57.6 |
| First level (9 weeks) after starting bromocriptine | 34.9 |
| Peak prolactin level (11 weeks) after starting bromocriptine | 65.6 |
| Continued titration of bromocriptine (18 weeks) | 37.3 |
| Continued titration of bromocriptine (25 weeks) | 36.1 |
| Continued titration of bromocriptine (27 weeks) | 39.1 |
| Continued titration of bromocriptine (36 weeks) | 30.2 |
| Continued titration of bromocriptine (42 weeks) | 18.6 |
| End bromocriptine titration (47 weeks) | 15.1 |

^aNo pre-olanzapine prolactin level was obtained.

lactin level during treatment with 100 mg/day of quetiapine was 16.3 ng/mL. She obtained only partial symptomatic relief with quetiapine and had excessive sedation at a dose of 800 mg/day, at which time her prolactin level was 16.6 ng/mL. Quetiapine was discontinued after 5 months, and the patient was then given a 6-week trial of aripiprazole up to 30 mg/day, which also failed to give adequate symptomatic relief. No prolactin level was obtained during the aripiprazole trial. At no time during the trials of these medications did Ms. A experience any galactorrhea.

After considering another antipsychotic trial or resumption of clozapine, Ms. A requested to resume olanzapine in spite of the previous adverse effects. At that time, an endocrinology consultation was obtained, and we decided to rechallenge the patient with olanzapine with a plan to add bromocriptine if her galactorrhea and hyperprolactinemia recurred. Within several weeks after resuming olanzapine at 15 mg/day, the patient was again free of psychotic symptoms. As we expected, her galactorrhea returned after 1 month of restarting olanzapine treatment, and her prolactin level reached a peak of 65.6 ng/mL (which occurred during titration with bromocriptine). No amenorrhea was observed during this time period. She was started on treatment with bromocriptine at 1.25 mg daily, and this dose was slowly titrated over a period of months to 5 mg twice per day. Ms. A's galactorrhea began to resolve, and her prolactin levels returned toward normal reference range. At the current dosages of 15 mg of olanzapine and 5 mg b.i.d. of bromocriptine, she is without galactorrhea, and her prolactin level is 15.1 ng/mL. We were observant of the possibility that bromocriptine could worsen psychosis, but she continues to remain symptom free and without impairment in functioning.

Other causes of hyperprolactinemia were ruled out by an endocrinologist, a neurologist, and 2 magnetic resonance imaging

scans. During the period of treatment, the patient was taking venlafaxine 150 mg daily and interferon beta-1b every other day (for multiple sclerosis). Both of these drugs have been known to increase prolactin levels. However, galactorrhea and changes in prolactin levels occurred only with respect to olanzapine dosing.

Olanzapine has been reported to be an alternative treatment in patients who experienced hyperprolactinemia and galactorrhea with other antipsychotic medications.⁵ Our literature review (a PubMed search of publications in English using the keywords *hyperprolactinemia*, *olanzapine*, *galactorrhea*, and *atypical antipsychotics*) found only 3 reported cases of olanzapine-induced galactorrhea.⁶⁻⁸ Moreover, we have found no references describing the successful use of bromocriptine for olanzapine-induced hyperprolactinemia and galactorrhea. Therefore, bromocriptine treatment could be useful in the rare cases of olanzapine-induced hyperprolactinemia and galactorrhea when the patient does not respond to other neuroleptic medications. We also suggest monitoring for worsening of psychosis during use of bromocriptine. Fortunately, this patient showed no worsening of psychosis on treatment with bromocriptine.

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