Venlafaxine-Induced Complex Visual Hallucinations in a 17-Year-Old Boy

Sir: Emslie et al.1,2 recently reported results of 2 controlled studies of venlafaxine in children and adolescents. In one study,1 2 of 169 subjects experienced hallucinations as an adverse event. In the other study,2 1 of 86 patients experienced hallucinations. The nature of these hallucinations was not specified in either article.

The adult literature describes antidepressants with serotonin reuptake–inhibiting properties that are known to cause visual hallucinations.2–17 Complex visual hallucinations can be defined as “organized and clear images of animate items, objects, and scenes over which the subject has little control.”18(p581) In adults, these hallucinations are most often associated with withdrawal of serotonin reuptake inhibitors or with serotonin syndrome.19–24 However, there are descriptions in adults of drug-induced complex visual hallucinations as a result of serotonin reuptake inhibitors.3,18

To date, only 1 case report exists of a patient with venlafaxine-induced visual hallucinations not due to a serotonin syndrome or a withdrawal reaction; the patient in that report had a posterior cerebral artery infarction.4

The following case report describes a depressed and anxious adolescent patient on venlafaxine immediate release (IR) treatment who developed complex visual hallucinations.

Case report. A 17-year-old boy presented in December 2006 with a 6- to 7-month history of increasing depression and anxiety and met DSM-IV criteria for major depressive disorder, moderate, single episode; social phobia; and generalized anxiety disorder. His psychiatric symptoms were comorbid with a diagnosis of migraine headaches that had become worse over the past several months. Furthermore, his episodes of anxiety seemed to co-occur with his migraines. Cognitively, the patient seemed to be of above-average intelligence (although no formal intelligence testing was done), was in honors classes, and received mostly A's and some B's in his private school. The patient was on treatment with eletriptan for migraines, and he was told to take over-the-counter diphenhydramine as needed at night with eletriptan and lamotrigine. The patient seemed to tolerate this well and was given another 37.5-mg tablet in the morning. The patient again developed visual hallucinations, at night with eletriptan and lamotrigine. The patient's symptoms improved within the next few hours, and the patient was told to monitor these symptoms and to temporarily discontinue the venlafaxine. The patient's symptoms improved within the next few hours, and the remainder of the day was uneventful. The patient was given only one 37.5-mg tablet the following day, and he had no reactions to this dose. On the next day, the patient was instructed to take 37.5 mg in the morning and an extra half-tablet of 37.5 mg in the evening for a rechallenge on venlafaxine (which he took at night with eletriptan and lamotrigine). The patient seemed to tolerate this well and was given another 37.5-mg tablet in the morning. The patient again developed visual hallucinations, and the patient was told to go to the emergency department to rule out any other causes for his altered mental status. The patient was observed overnight, and results of his physical examination were unremarkable, with no signs or symptoms of a serotonin syndrome. Results of a chemistry panel and metabolic panel were negative. The patient also had a negative drug screen. Results of an electroencephalogram were normal, and results of magnetic resonance imaging were normal except for a 9-mm cerebellar tonsil ectopia. The patient's symptoms resolved overnight (16–20 hours after the last dose of the medication).

The patient's symptoms never returned in the month after the episode. The patient opted not to try another antidepressant medication and continued with cognitive-behavioral therapy. His anxiety began to improve, and he was able to utilize coping strategies for his anxiety and depression.

This is the first published case description of selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor (SSRI/SNRI)–induced complex visual hallucinations in an adolescent. Consistent with the finding in adults that complex visual hallucinations seem to be more common in people with preexisting neurologic conditions or who are taking other medication,19 this adolescent patient had a history of migraine headaches and was taking diphenhydramine during his first episode of psychosis as well as eletriptan during his second episode of psychosis. The anticholinergic effects of diphenhydramine in conjunction with the increased serotonergic effects of the SNRI may have affected the cholinergic/serotonergic balance that is thought to be the mechanism behind complex visual hallucinations.19 Complex visual hallucinations may be second-
ary to high levels of serotonin and low levels of acetylcholine. Furthermore, the addition of eletriptan prior to the retri
alafaxine may have increased the serotonin levels, which altered the balance of acetylcholine to serotonin. Finally, the patient’s mental status change could have been simply due to higher lev
events. A thorough understanding of antidepressants, with more controlled studies focusing on unique side effect profiles in children and adolescents versus adults treated with antidepressant medications. Safer and Zito reported that children and adolescents experienced more activa
tion and vomiting compared to adults and suggested that chil
24. Parker G, Blennerhassett J. Withdrawal reactions associated with

**REFERENCES**

24. Parker G, Blennerhassett J. Withdrawal reactions associated with
Reliability, Not Overdiagnosis

Sir: The recent Journal article by Zimmerman et al. 1 does not show that bipolar disorder is overdiagnosed, because it mistakes reliability and validity. 2 All the authors showed was that, about half the time, researchers reached different diagnoses than clinicians who had diagnosed bipolar disorder. This merely reflects interrater diagnostic reliability, a long-established issue in epidemiology. 1 The same or lower levels of diagnostic reliability among psychiatrists have been shown for schizophrenia and other psychotic disorders 3 and, in comparisons with lay interviewers, for major depressive and anxiety disorders. 4, 5 For that matter, similar reliability rates have been shown for neurologic illnesses, such as cervical radiculopathy, 6 stroke, 7 and some dementias. 8 There is nothing specific to bipolar disorder or even psychiatry here.

To demonstrate overdiagnosis, the authors needed to use a different design to assess validity, not reliability: beginning with validly diagnosed patients with bipolar disorder (the researchers could use themselves as the gold standard), they could then have assessed past bipolar diagnoses, and then, with a comparison group (such as validly diagnosed unipolar depression), a similar comparison of past bipolar diagnoses could have been made. Such a design has rarely been conducted in bipolar disorder (as compared to schizophrenia and other psychotic disorders) and remains one of the most widely used approaches to assessing diagnostic validity. In short, we addressed the issue of diagnostic reliability and did not present information on the reliability of their diagnostic procedures.

In sum, the authors show some unreliability of bipolar diagnosis, at similar levels to those of most other psychiatric disorders, but they have not demonstrated overdiagnosis.

Dr. Ghaemi has received grant/research support from Pfizer and AstraZeneca. He is not currently on the speakers/advisory boards of any pharmaceutical companies.

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Dr. Zimmerman and Colleagues Reply

Sir: Ghaemi suggests that in our study on the diagnosis of bipolar disorder we confused concepts of reliability and validity. In fact, we discussed issues of both reliability and validity. As we noted in the discussion section of the article: “Any study seeking to determine whether a psychiatric disorder is overdiagnosed will find that some patients with the index condition do not have it on re-interview. Such is the nature of the imperfect reliability of psychiatric diagnosis.” 1(p938) Had we limited our study to rediagnosis alone, Ghaemi’s comment might have merit. However, we did more than this.

Ghaemi failed to note in his comment that we also compared the morbid risk of bipolar disorder in the first-degree relatives of patients whom we diagnosed with bipolar disorder to the risk in patients who were previously diagnosed with bipolar disorder that was not confirmed by an evaluation based on the Structured Clinical Interview for DSM-IV. Family and genetic studies were one of the 5 phases of establishing diagnostic validity recommended nearly 40 years ago by the Washington University group 2 and remains one of the most widely used approaches toward establishing validity. In short, we addressed the issue of validity in our study with family history data.

It is ironic that Ghaemi faults us for suggesting that bipolar disorder was overdiagnosed, as opposed to being unreliable diagnosed, considering that he made similar claims, albeit of underdiagnosis, in a study of prior diagnoses of patients whom he had diagnosed with bipolar disorder. 3 Ghaemi and colleagues titled their article, “Is Bipolar Disorder Still Underdiagnosed?” and, in contrast to our discussion of our study, they did not mention at all the issue of diagnostic reliability and did not present information on the reliability of their diagnostic procedures.

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

REFERENCES

Use of Risperidone Long-Acting Injection to Support Treatment Adherence and Mood Stabilization in Pediatric Bipolar Patients: A Case Series

Sir: Recent studies have suggested that depot formulations of second-generation antipsychotics may be considered for controlling mood episodes in bipolar disorder (BD) patients who have relapsed due to medication nonadherence or failed to respond to standard therapies.1,2 The safety and effectiveness of risperidone long-acting injection (RLAI) have been demonstrated through clinical trials in stable BD adults, and the applicability of RLAI in frequently relapsing patients has also been shown.3,4 Although the U.S. Food and Drug Administration approved oral risperidone in 2007 for use in early-onset BD patients, no study has reported the utility of RLAI in youth.

We describe the use of the RLAI formulation in 3 medication-nonadherent adolescent BD patients. Although oral risperidone was effective in controlling their previous manic episodes, putative nonadherence or refusal led to treatment failure and was the major indication for using an alternative long-acting preparation. After the consent of the parents or responsible guardians was obtained, treatment with RLAI was initiated at the dose of 25 mg every 2 weeks.6

The diagnosis of BD was confirmed with a face-to-face clinical interview and the Diagnostic Interview for Children and Adolescents–DSM-IV version.7 The Clinical Global Impressions scale (CGI)8 was used to rate the symptomatic change relative to baseline, and the Children’s Global Assessment Scale (CGAS)9 was used to measure global functioning. The CGAS score of each BD patient was below 31 at the index timepoint, indicating severe functional impairment. Side effects,10 weight gain, extrapyramidal symptoms (EPS), and adverse events were closely monitored in each clinical visit (Table 1). Electrocardiography, electroencephalography, and magnetic resonance imaging were routinely performed, with negative results, during follow-up in a university-based outpatient unit.

Case 1. Patient 1, an 11-year-old boy, had a history of school phobia at age 6 (which lasted 1 month) and major depressive disorder (MDD) since age 10, which resulted in his dropping out of school.

At the time he dropped out of school, the selective serotonin reuptake inhibitor (SSRI) sertraline was prescribed. Four weeks later, the patient switched to a manic episode, presenting euphoria, increased energy, and daily mood variations; exhibiting bossy behavior and an arrogant attitude; being aggressive toward his parents; and having a decreased need for sleep as well as an increased appetite. The manic symptoms persisted even after discontinuation of sertraline.

Three months after the manic episode began, monotherapy with oral risperidone, dose range 5–1.5 mg/day, was prescribed. Although the patient’s symptoms improved significantly after 2 weeks, he began refusing medication and discontinued all treatment because his brother and his friends belittled him. Because his parents were incapable of controlling his medication adherence, he then used medication irregularly and soon returned to a seriously impaired state.

In September 2006, when the patient was 11 years and 9 months of age, RLAI 25 mg/2 weeks was prescribed, with the family’s consent. After the third RLAI, he showed significant improvement, and after the fifth RLAI, the patient’s aggressive behavior and manic symptoms were controlled, his CGI score had decreased from 6 to 3, and his CGAS score had increased from 31 to 61. Oral risperidone was then substituted for RLAI, and the patient continues to receive treatment with 3 mg/day of oral risperidone.

Case 2. Patient 2, a 14-year-old boy, had a history of attention-deficit/hyperactivity disorder beginning at 5 years of age. When he was 6, after receiving treatment with methylphenidate 20 mg/day, he presented an episode of depression. Sertraline 25 mg/day was prescribed, and he then became more agitated than usual, euphoric, and hyperenergized and had a decreased need for sleep. After medication was discontinued, he presented a second episode of depression. Fluoxetine 20 mg/day was prescribed, and he experienced the same symptoms as he had with sertraline. These symptoms persisted even after discontinuation of the SSRIs. Afterward, he also stole, made obscene gestures in public, and exhibited a sexually embarrassing, hypererotic attitude and aggressiveness, which led the school to expel him.

Case 3. Patient 3, a 14-year-old boy, had a history of bipolar disorder beginning at 8 years of age. When he was 10, he was referred for a psychiatric evaluation. His concerns included bossy behavior and an arrogant attitude; being aggressive toward his parents; and having a decreased need for sleep. The patient was later referred for a face-to-face psychiatric evaluation. At the time he was referred, he was taking oral risperidone, dose range 0.5–1.5 mg/day, for the treatment of his mood disorder. Although his symptoms improved significantly after 2 weeks, he began refusing medication and discontinued all treatment because his brother and his friends belittled him. Because his parents were incapable of controlling his medication adherence, he then used medication irregularly and soon returned to a seriously impaired state.

In September 2006, when the patient was 11 years and 9 months of age, RLAI 25 mg/2 weeks was prescribed, with the family’s consent. After the third RLAI, he showed significant improvement, and after the fifth RLAI, the patient’s aggressive behavior and manic symptoms were controlled, his CGI score had decreased from 6 to 3, and his CGAS score had increased from 31 to 61. Oral risperidone was then substituted for RLAI, and the patient continues to receive treatment with 3 mg/day of oral risperidone.

Table 1. Outcome of Severity Measure, Global Functioning Assessment, and Blood Prolactin and Cholesterol Levels During Risperidone Long-Acting Injection (RLAI) Treatment

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>CGI Score</th>
<th>CGAS Score</th>
<th>Prolactin (ng/mL)</th>
<th>Cholesterol (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-RLAI</td>
<td>6</td>
<td>21</td>
<td>...</td>
<td>98</td>
</tr>
<tr>
<td>1st injection/0 day</td>
<td>5</td>
<td>31</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>2nd injection/15 days</td>
<td>4</td>
<td>41</td>
<td>42.0</td>
<td>...</td>
</tr>
<tr>
<td>3rd injection/30 days</td>
<td>3</td>
<td>51</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>4th injection/45 days</td>
<td>3</td>
<td>51</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>5th injection/60 days</td>
<td>3</td>
<td>61</td>
<td>5.5</td>
<td>134</td>
</tr>
<tr>
<td>Case 2</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pre-RLAI</td>
<td>7</td>
<td>21</td>
<td>18.4</td>
<td>230</td>
</tr>
<tr>
<td>1st injection/0 day</td>
<td>6</td>
<td>35</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>2nd injection/15 days</td>
<td>5</td>
<td>41</td>
<td>...</td>
<td>...</td>
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<td>4</td>
<td>45</td>
<td>...</td>
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<td>5th injection/60 days</td>
<td>3</td>
<td>51</td>
<td>4.9</td>
<td>235</td>
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<tr>
<td>18th injection/255 days</td>
<td>2</td>
<td>71</td>
<td>6.4</td>
<td>105</td>
</tr>
<tr>
<td>Case 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-RLAI</td>
<td>6</td>
<td>31</td>
<td>...</td>
<td>102</td>
</tr>
<tr>
<td>1st injection/0 day</td>
<td>5</td>
<td>41</td>
<td>...</td>
<td>...</td>
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<tr>
<td>2nd injection/15 days</td>
<td>4</td>
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<td>...</td>
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<td>5th injection/60 days</td>
<td>3</td>
<td>61</td>
<td>...</td>
<td>...</td>
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<tr>
<td>12th injection/165 days</td>
<td>2</td>
<td>71</td>
<td>2.5</td>
<td>110</td>
</tr>
</tbody>
</table>

Abbreviations: CGAS = Children's Global Assessment Scale, CGI = Clinical Global Impressions scale.
At age 7, he attained significant control of symptoms using valproic acid 500 mg/day combined with risperidone 1 mg/day; however, these medications were replaced due to weight gain, hyperglycemia, and sedation. From age 8 to age 13, he was treated with oxcarbazepine 900 mg/day, ziprasidone 120 mg/day, lithium 1500 mg/day, haloperidol 2 mg/day, quetiapine 300 mg/day, topiramate 500 mg/day, and divalproate 2000 mg/day, administered either alone or in combination, with no clinical improvement. Finally, he attained significant control of manic symptoms with risperidone 3 mg/day monotherapy, but his parents failed to supervise regular medication use, and from 13 to 14 years of age, he had used medication irregularly.

In May 2007, at 14 years of age, with a critical medical situation (hypothyroidism, hyperglycemia, liver enzymes increase, hypercholesterolemia, and obesity) and severe impairment (CGI score = 7/Cgas score = 25), the patient began treatment with RLA1 25 mg/2 weeks, with his family’s consent. The patient’s externalizing symptoms were controlled after the fifth RLA1, and the patient was readmitted to school. After the tenth RLA1, the patient’s CGI score had decreased to 3, and his CGAS score had increased to 71. He has received monotherapy with RLA1 25 mg/2 weeks for the past 9 months.

Case 3. Patient 3, a 14-year-old boy, had experienced anxiety symptoms with phobic behavior since he was 7 years old, brought on by his father’s death due to human immunodeficiency virus infection complications. The family environment was unstable, with a history of violence, addiction, depression, suicidal attempts, and criminal activities. At 9 years old, after witnessing his stepfather threaten to kill his sister, the patient started to present bizarre behavior, hallucination, sadness, irritability, agitation, and insomnia; cried easily; and had less tolerance with frustration. This condition worsened over the following 2 years, during which he was without treatment.

At 11 years of age, he was diagnosed with MDD that persisted even after treatment with fluoxetine 20 mg/day. However, after 3 months, a transient mixed state occurred, and he then clearly shifted to a manic episode (e.g., euphoria, hyperactivity, talkativeness, and decreased sleep). Significant improvement was observed after treatment with risperidone 2 mg/day combined with carbamazepine 800 mg/day. When he became better, his family failed to supervise the treatment, and after his brothers belittled him, he discontinued the medicines. From the ages of 12 to 14 years, he had used medication irregularly.

In August 2007, when he was 14 years old, with his family’s consent, the patient started treatment with RLA1 25 mg/2 weeks. He improved considerably at school and home, his CGI score decreased from 6 to 3, and his CGAS score increased from 31 to 71. He has been stable for the last 6 months, but due to poor family supervision and the risk of nonadherence, he is kept on monotherapy with RLA1 25 mg/2 weeks.

This case series reports 3 difficult-to-treat youths with BD who benefited from treatment with long-acting risperidone. Psychiatric misdiagnosis, medical comorbidity, a changeable clinical picture, and pharmacologic mood swings are common situations that make BD more cumbersome to manage. Nevertheless, the main reasons for therapeutic failure after definite BD diagnosis were nonadherence and medication refusal.4,11 The prescription of alternative treatment with RLA1 was justifiable in view of the patients’ severe clinical worsening and the effectiveness of the treatment in achieving progressive mood stabilization.4,5

The extent to which the patient continues the agreed-upon mode of treatment under limited supervision when faced with conflicting demands is one of the determinants of therapeutic success. In the clinical setting of youth with BD, there are several types of unwillingness to follow a prescribed course of treatment. First, treatment nonadherence may be related to the disorder itself, because young BD patients may have difficulty engaging in any treatment due to the nature of mood instability and impaired judgment.2,3,6 Second, adherence can be affected by the patient’s insight about his or her illness and the importance of treatment in overcoming it.2,8,12 Understanding the rationale for the treatment, understanding the drug regimen, and having a good relationship with and trust in the clinician are elements that enhance patients’ knowledge about their illness, increasing the success of treatment regimens. The boy in case 1 exemplifies a case of complete failure of adherence, refusing all treatment and rarely coming to appointments with his psychiatrist. This made it difficult for the psychiatrist to adapt the patient’s medication treatment on the basis of his need for it.11,12 Many times, inadequate family functioning also exerts negative influence on BD patients’ treatment adherence.11,12 Cases 2 and 3 illustrate intermittent adherence, in which patients only take medication when their family is more structured or only accept acute treatment, refusing to treat the illness in its entirety.1,11,13 Besides controlling acute manic episodes, the long-acting antipsychotic was found to be helpful in resolving different kinds of nonadherence, facilitating adherence to maintenance treatment with monotherapy.

Another reason patients stop taking medication is the side effects. The subjects tolerated RLA1 well, without significant cognitive complaints or adverse events related to hormones, weight gain, or EPS. The concern about the clinical and metabolic complications of using atypical antipsychotics, such as hyperprolactinemia and hypercholesterolemia, seems not applicable in these cases.13 RLA1 could be safely prescribed for the patient in case 2, even though his medical problems were not controlled.

This new RLA1 has reversed dramatically the therapeutic failure of patients who did not follow the recommended medication regimen. Tracking patients if they are taking medication through long-acting antipsychotics could help clinicians to manage compliance status. Nevertheless, the alliance between the care provider and the young BD patient should be continuously pursued even though a new resource is available.

Dr. Fu-I is a speaker for Abbott and has received support to participate in medical events from Abbott and Janssen-Cilag. Dr. Boarati has received support to participate in medical events from Pfizer. Drs. Stravagognis and Wang have no conflict of interest.

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