## 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.[3–17] 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[25] 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 had no signs of cognitive limitations, but his grades had been falling prior to his presentation because of multiple school absences due to his migraines. The patient's family had no history of neurologic disorders, but his mother had significant anxiety and was being treated with buspirone. All other psychiatric review of systems was negative, including history of manic symptoms.

Prior to his first psychiatric visit, the patient had been treated with topiramate for migraines, but it was quickly discontinued due to the side effect of cognitive dulling. His neurologist began treatment with lamotrigine, which was being titrated to an effective dose. In addition, prior to his psychiatric evaluation, the patient was on treatment with eletriptan, which was taken on Sundays (once per week) for prophylactic migraine control, and a hydrocodone/acetaminophen combination for breakthrough migraine pain control, which was used at a maximum of once daily as needed (patient took this dose maximally about 1 or 2 times per week). The patient also regularly took ibuprofen for his migraines, and he was told to take over-the-counter diphenhydramine as needed at night to help with sleep.

Fluoxetine was presented as the drug of choice based on its effectiveness for the treatment of adolescent depression and anxiety. In addition, cognitive-behavioral therapy was recommended. However, in discussing the case with the patient's neurologist, the neurologist strongly favored a trial of venlafaxine to help with his debilitating migraines, in addition to relieving the anxiety and depression. Although there is no strong evidence supporting the use of venlafaxine in adolescents, this drug remained a treatment option, since the patient was 17 years old and had an adult body habitus (weight greater than 200 pounds).

After a thorough discussion of risks and benefits associated with antidepressant use in adolescents, the patient was started on treatment with venlafaxine IR 37.5 mg daily to treat his depression and anxiety and possibly assist with migraine control. In addition to medication management, the patient agreed to begin weekly cognitive-behavioral therapy.

The dose of 37.5 mg/day was tolerated well with no side effects. After 2 weeks at this dose, the patient's symptoms persisted, and his dose was increased to 37.5 mg twice daily. The patient was given 1 additional evening dose (along with diphenhydramine and lamotrigine), and after he was given his morning dose the next day, he started experiencing visual hallucinations of "bugs crawling" on him and tactile hallucinations of these "bugs." The patient also became disoriented approximately 1 hour later. The patient's family 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, tactile hallucinations, and extreme disorientation with an inability to recognize his mother and sister within 30 to 60 minutes of taking venlafaxine. The patient's visual hallucinations lessened throughout the day, but his disorientation persisted. He was instructed 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,[18] 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.[18] 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 retrial of venlafaxine 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 levels of serotonin secondary to the increase in venlafaxine dose, since the patient seemed to tolerate low doses of venlafaxine.

The presence of visual or tactile hallucinations can suggest an organic etiology. These types of hallucinations can result from a number of causes including infection, substances, autoimmune disorders, posttransplant status, postoperative status, trauma, neoplasm, and organ failure. Turkel and Tavaré[26] found that, of 36 patients exhibiting hallucinations with delirium, visual hallucinations were present in 33 of the patients, and tactile hallucinations were present in 10 of the patients. In the present case, the above organic causes were ruled out after the medical workup in the emergency department. The only insulting agent(s) appeared to be the medications prescribed to the patient. In addition, because the patient's migraines historically were described as severe headaches with nausea and photophobia (no numbness, scintillations, or history of hallucinations), it is unlikely that the migraines are the primary cause of his mental status change.

As well as the preceding possible causes of hallucinations, some reports conclude that patients with a psychotic depression or bipolar disorder may be more inclined to experience medication-induced hallucinations.[18] Although this patient had no history of hallucinations or clear delusions related to depression, his anxiety and fears had a paranoid flavor. He did not experience (nor had a history of) symptoms of grandiosity, decreased need for sleep, pressured speech, flight of ideas, increased involvement in pleasurable activities, or increase in goal-directed activity. The patient's symptoms of disorientation and hallucinations were more consistent with delirium. However, the patient must continue to be monitored to see how his symptoms and diagnosis evolve.

The patient also has a history of adverse reactions to drugs. His parents reported that he had experienced an episode of delirium after waking from anesthesia following a tonsillectomy. The patient had an episode of psychotic symptoms including visual and tactile hallucinations on a different occasion after taking promethazine for vomiting (he thought spiders were crawling on the walls and felt "bugs" crawling on him). Thus, because of promethazine's anticholinergic activity, it may also have contributed to the cholinergic/serotonergic imbalance associated with his psychotic reaction to medication.

It seems most likely that the mechanism for the patient's complex visual hallucinations was related to the disruption in the cholinergic/serotonergic balance. The exact reason why this occurred in this particular patient is still unclear. This case reminds clinicians that they should consider the remote possibilities of SSRI/SNRI-induced psychosis in patients who have risk factors such as central nervous system dysfunction, who are taking additional medications that alter the cholinergic/serotonergic balance, or who may have a clear or subtle underlying psychotic disorder. Additionally, growing evidence exists showing different side effect profiles in children and adolescents versus adults treated with antidepressant medications. Safer and Zito[27] reported that children and adolescents experienced more activation and vomiting compared to adults and suggested that children may be more vulnerable to certain SSRI-induced adverse events. A thorough understanding of antidepressants, with more controlled studies focusing on unique side effect profiles of these medications, could help prescribers and patients feel confident about the medications they use and ways in which they manage adverse events.

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*Parents of the child described in this letter gave written consent for this report to be published.*

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## 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.[2] 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.[3,4] For that matter, similar reliability rates have been shown for neurologic illnesses, such as cervical radiculopathy,[4] stroke,[5] and some dementias.[6] 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 nosology research; in a small sample, we previously implemented that design with a unipolar comparison group and found bipolar disorder to be more often misdiagnosed than unipolar depression, hence proof of underdiagnosis, not overdiagnosis.[7]

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 in the past year has been a member of the speakers bureaus for 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 upon reinterview. 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 unreliably 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.*

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## 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.[1–3] 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.[4,5] 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.

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

| Timepoint | CGI Score | CGAS Score | Prolactin (ng/mL) | Cholesterol (mg/dL) |
|---|---|---|---|---|
| Case 1 | | | | |
| Pre-RLAI | 6 | 21 | … | 98 |
| 1st injection/0 day | 5 | 31 | … | … |
| 2nd injection/15 days | 4 | 41 | 42.0 | … |
| 3rd injection/30 days | 3 | 51 | … | … |
| 4th injection/45 days | 3 | 51 | … | … |
| 5th injection/60 days | 3 | 61 | 5.5 | 134 |
| Case 2 | | | | |
| Pre-RLAI | 7 | 21 | 18.4 | 230 |
| 1st injection/0 day | 6 | 35 | … | … |
| 2nd injection/15 days | 5 | 41 | … | … |
| 3rd injection/30 days | 4 | 41 | … | … |
| 4th injection/45 days | 4 | 45 | … | … |
| 5th injection/60 days | 3 | 51 | 4.9 | 235 |
| 18th injection/255 days | 2 | 71 | 6.4 | 105 |
| Case 3 | | | | |
| Pre-RLAI | 6 | 31 | … | 102 |
| 1st injection/0 day | 5 | 41 | … | … |
| 2nd injection/15 days | 4 | 41 | … | … |
| 3rd injection/30 days | 3 | 51 | 10.3 | … |
| 4th injection/45 days | 3 | 61 | … | … |
| 5th injection/60 days | 3 | 61 | … | … |
| 12th injection/165 days | 2 | 71 | 2.5 | 110 |

Abbreviations: CGAS = Children's Global Assessment Scale, CGI = Clinical Global Impressions scale.

Three months after the manic episode began, monotherapy with oral risperidone, dose range 0.5 to 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.

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 RLAI 25 mg/2 weeks, with his family's consent. The patient's externalizing symptoms were controlled after the fifth RLAI, and the patient was readmitted to school. After the tenth RLAI, the patient's CGI score had decreased to 3, and his CGAS score had increased to 71. He has received monotherapy with RLAI 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, hyperenergy, 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 RLAI 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 RLAI 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 RLAI 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.[11–13] 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.[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 RLAI 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] RLAI could be safely prescribed for the patient in case 2, even though his medical problems were not controlled.

This new RLAI 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. Stravogiannis and Wang have no conflict of interest.*

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