

The mysterious foreign accent

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While treating Ms. D for a suspected psychotic disorder, you learn she has developed a foreign accent. What could be the cause of this unusual symptom?



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CASE Disruptive and withdrawn

Police bring Ms. D, age 33, to our psychiatric facility because of violent behavior at her group home. When confronted for allegedly stealing, she became upset, fought with a housemate, and spat. Six months before coming to our facility she was admitted to a private hospital for psychotic disorder, not otherwise specified (NOS) where she was mute, refused all food and medications, lay in her room, and covered her face with a sheet when someone tried to talk to her.

Ms. D denies having depressive symptoms, sleep disturbance, racing thoughts, thoughts of hurting herself or others, or auditory or visual hallucinations. She complains of poor appetite. Ms. D denies a history of mental illness and says she is not taking any medication. She is upset about being hospitalized and says she will not cooperate with treatment. We cannot obtain her complete psychiatric history but available records indicate that she has 1 previous psychiatric hospitalization for psychotic disorder NOS, and has received trials of haloperidol, lorazepam, diphenhydramine, escitalopram, ziprasidone, and benztropine. Her records do not indicate the dosages of these medications or how she responded to pharmacotherapy.

During her mental status exam, Ms. D is well dressed, covers her hair with a scarf, has no unusual body movements, and responds

to questions appropriately. She describes her mood as “okay” but appears upset and anxious about being in the hospital. She exhibits no overt psychotic symptoms and does not appear to be responding to auditory hallucinations or having delusional thoughts. Her cognitive function is intact and her intelligence is judged to be average with impaired insight and judgment. However, she speaks with a distinct accent that sounds Jamaican; otherwise, her speech is articulate with normal rate and tone. When we ask about her accent, Ms. D, who is African American, does not disclose her ethnicity and seems to be unaware of her accent. We did not question the authenticity of her accent until after we obtained collateral information from her family.

What is your differential diagnosis?

- bipolar disorder NOS
- substance-induced psychosis
- brief psychotic disorder
- psychotic disorder NOS
- delusional disorder

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continued

Clinical Point

Foreign accent syndrome can result from lesions in the brain areas involved in speech production

The authors' observations

Based on the available information, we make a provisional diagnosis of psychotic disorder NOS and Ms. D is admitted involuntarily because of concerns about her safety. She is reluctant to accept any treatment and receives an involuntary probate commitment for 90 days. At admission, Ms. D is evasive, guarded, secretive, and at times hostile. Her physical examination reveals no signs or symptoms of focal neurologic deficits. Laboratory testing, including urine toxicology, is unremarkable. She refuses an MRI. Later testing reveals a critical ammonia level of 143 $\mu\text{g}/\text{dL}$, warranting an axis III diagnosis of asymptomatic hyperammonemia.

HISTORY Paranoia and delusions

Ms. D says she was born and raised in a southern state. She reports that she was born to an Egyptian mother who died during childbirth; her father, who is white, was an ambassador stationed abroad. Ms. D attended school until the 11th grade and was married at age 19 to a Secret Service agent. She says she has a son who was kidnapped by her husband's enemies, rescued by paying ransom, and currently lives with his grandfather. Ms. D is paranoid and fears that her life is in danger. She also believes that she has gluten sensitivity that could discolor and damage her hair, which is why she always keeps a scarf on her head for protection.

Through an Internet search, we find articles about Ms. D's son's kidnapping. The 7-year-old had been missing for weeks when police found him with his mother in safe condition in another state, after Ms. D called her mother to ask for money and a place to stay. The child was taken from Ms. D's custody because of concerns for his safety. We also find Ms. D's mother. Although Ms. D insists her mother is deceased, after some persuasion, she signs a release allowing us to talk to her.

Ms. D's mother reports that her daughter's psychiatric problems began when she was

pregnant. At the time Ms. D did not have a foreign accent. She had started to "talk funny" when her psychiatric symptoms emerged after she married and became pregnant.

How can one acquire a foreign accent?

- becoming immersed in a foreign language
- psychiatric illness
- neurologic illness
- all the above

Foreign accent syndrome

A foreign accent can be acquired by normal phenomena, such as being immersed in a foreign language, or a pathological process,¹ which can include psychiatric (functional) or neurologic illness (organic causes). Foreign accent syndrome (FAS) is a rare speech disorder characterized by the appearance of a new accent, different from the speaker's native language, that is perceived as foreign by the listener and in most cases also by the speaker.² Usually an FAS patient has had no exposure to the accent, although in some cases an old accent has re-emerged.^{3,4}

FAS can result from lesions in brain areas involved in speech production, including precentral gyrus, premotor mid-frontal gyrus, left subcortical prerolandic gyrus, postrolandic gyri, and left parietal area.⁴ Most FAS cases are secondary to a structural lesion in the brain caused by stroke, traumatic brain injury, cerebral hemorrhage, or multiple sclerosis.² There are a few cases in the literature of acquired foreign accent with psychogenic etiology in patients with schizophrenia and bipolar disorder with psychotic features.⁵

TREATMENT Combination therapy

Based on Ms. D's unstable mood, irritability, delusional beliefs, and paranoid ideas, we start divalproex, 500 mg/d titrated to 1,750 mg/d,

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voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: *Skin and subcutaneous tissue disorders* – Angioedema. **DRUG INTERACTIONS: Central Nervous System (CNS)-Active Agents**–The risk of using Pristiq in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when Pristiq is taken in combination with other CNS-active drugs [see *Warnings and Precautions* (5.13)]. **Monoamine Oxidase Inhibitors (MAOIs)**– Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on antidepressants with pharmacological properties similar to Pristiq (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of a MAOI [see *Contraindications* (4.2)]. **Serotonergic Drugs**– Based on the mechanism of action of Pristiq and the potential for serotonin syndrome, caution is advised when Pristiq is coadministered with other drugs that may affect the serotonergic neurotransmitter systems [see *Warnings and Precautions* (5.2)]. **Drugs that Interfere with Hemostasis (eg, NSAIDs, Aspirin, and Warfarin)**– Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Pristiq is initiated or discontinued. **Ethanol**– A clinical study has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Pristiq. **Potential for Other Drugs to Affect Desvenlafaxine-Inhibitors of CYP3A4 (ketoconazole)**– CYP3A4 is a minor pathway for the metabolism of Pristiq. Concomitant use of Pristiq with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq. **Inhibitors of other CYP enzymes**– Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of Pristiq. **Potential for Desvenlafaxine to Affect Other Drugs**– **Drugs metabolized by CYP2D6 (desipramine)**– *In vitro* studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6. Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 can result in higher concentrations of that drug. **Drugs metabolized by CYP3A4 (midazolam)**– *In vitro*, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme. Concomitant use of Pristiq with a drug metabolized by CYP3A4 can result in lower exposures to that drug. **Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9, and 2C19**– *In vitro*, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes. **P-glycoprotein Transporter**– *In vitro*, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of Pristiq are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter. **Electroconvulsive Therapy**– There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment. **USE IN SPECIFIC POPULATIONS: Pregnancy**– Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. **Teratogenic effects**– **Pregnancy Category C**– There are no adequate and well-controlled studies of Pristiq in pregnant women. Therefore, Pristiq should be used during pregnancy only if the potential benefits justify the potential risks. **Non-teratogenic effects**– Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see *Warnings and Precautions* (5.2)]. When treating a pregnant woman with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment [see *Dosage and Administration* (2.2)]. **Labor and Delivery**– The effect of Pristiq on labor and delivery in humans is unknown. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks. **Nursing Mothers**– Desvenlafaxine (0-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Pristiq, a decision should be made whether or not to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Only administer Pristiq to breastfeeding women if the expected benefits outweigh any possible risk. **Pediatric Use**– Safety and effectiveness in the pediatric population have not been established [see *Box Warning and Warnings and Precautions* (5.1)]. Anyone considering the use of Pristiq in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use**– Of the 3,292 patients in clinical studies with Pristiq, 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term, placebo-controlled studies, there was a higher incidence of systolic orthostatic hypotension in patients ≥ 65 years of age compared to patients <65 years of age treated with Pristiq [see *Adverse Reactions* (6)]. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.6)]. If Pristiq is poorly tolerated, every other day dosing can be considered. SSRIs and SNRIs, including Pristiq, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see *Warnings and Precautions* (5.12)]. Greater sensitivity of some older individuals cannot be ruled out. **Renal Impairment**– In subjects with renal impairment the clearance of Pristiq was decreased. In subjects with severe renal impairment (24-hr CrCl < 30 mL/min) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to Pristiq; therefore, dosage adjustment is recommended in these patients [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.6) in the full prescribing information]. **Hepatic Impairment**– The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. The recommended dose in patients with hepatic impairment is 50 mg/day. Dose escalation above 100 mg/day is not recommended [see *Clinical Pharmacology* (12.6)].

OVERDOSAGE: Human Experience with Overdose– There is limited clinical experience with desvenlafaxine succinate overdose in humans. In premarketing clinical studies, no cases of fatal acute overdose of desvenlafaxine were reported. The adverse reactions reported within 5 days of an overdose > 600 mg that were possibly related to Pristiq included headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia. Desvenlafaxine (Pristiq) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Pristiq) is presented below; the identical information can be found in the *Overdose* section of the venlafaxine package insert. In postmarketing experience, overdose with venlafaxine (the parent drug of Pristiq) has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdose may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdose, as opposed to some characteristic(s) of venlafaxine-treated patients, is not clear. Prescriptions for Pristiq should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Management of Overdose**– Treatment should consist of those general measures employed in the management of overdose with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known. In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians Desk Reference (PDR®).

This brief summary is based on Pristiq Prescribing Information W10529C009, revised September 2009.

and risperidone, 3 mg in the morning and 4 mg at bedtime.

The unit psychologist evaluates Ms. D and provides individual psychotherapy, which is mainly supportive and psychoeducational. Ms. D gradually becomes cooperative and friendly. She is not willing to talk about her accent or its origin; however, as her psychiatric symptoms improve, her accent gradually diminishes. The accent never completely resolves, but reduces until it is barely noticeable.

The authors' observations

Ms. D's foreign accent was more prominent when she displayed positive psychotic symptoms, such as delusions and disorganized thinking, and gradually disappeared as her psychotic symptoms improved. Ms. D's case was peculiar because her accent was 1 of the first symptoms before her psychosis fully manifested.

How are FAS and psychosis linked?

Language dysfunction in schizophrenia is common and characterized by derailment and disorganization. Severity of language dysfunction in schizophrenia is directly proportional to overall disease severity.^{6,7} Various hypotheses have suggested the origin of FAS. In patients with FAS secondary to a neurologic disorder, a lesion usually is found in the dominant brain hemisphere, but the cause is not clear in patients with psychosis who have normal MRI findings. One hypothesis by Reeves et al links development of FAS to the functional disconnection between the left dorsolateral prefrontal cortex (DLPFC) and the superior temporal gyrus (STG) during active psychosis.⁵ In normal speech production, electric impulses originate in the DLPFC and are transmitted to STG in Wernicke's area. From there, information goes to Broca's area, which activates the primary motor cortex to pronounce words. In healthy individuals, word generation activates the DLPFC and causes deactivation

Clinical Point

One hypothesis links FAS to functional disconnection between the DLPFC and STG during active psychosis

of the bilateral STG.⁸ In schizophrenia, the left STG fails to deactivate in the presence of activation of the left DLPFC.⁹ Interestingly, STG dysfunction is seen only during active phase of psychosis. Its absence in asymptomatic patients with schizophrenia and bipolar disorder^{10,11} suggest that a foreign accent-like syndrome may be linked to the functional disconnection between the left DLPFC and left STG dysfunction in patients with active psychosis.⁵

Performing functional neuroimaging, including positron-emission tomography, functional MRI, and single-photon emission computed tomography, of patients with FAS could shed more light on the possible link between FAS and psychosis. In a case report of a patient with bipolar disorder who developed FAS, MRI initially showed no structural lesion but a later functional imaging scan revealed a cerebral infarct in the left insular and anterior temporal cortex.²

One of the limitations in Ms. D's case is the lack of neuroimaging studies. For the first few weeks of her hospitalization, it was difficult to communicate with Ms. D. She did not acknowledge her illness and would not cooperate with treatment. She was withdrawn and seemed to experience hysterical mutism, which she perceived as caused by extreme food allergies. Later, as her symptoms continued to improve with pharmacologic and psychotherapeutic interventions, neuroimaging was no longer clinically necessary.

OUTCOME Accent disappears

As Ms. D improves, psychotherapy evolves to gently and carefully challenging her delusions and providing insight-oriented interventions and trauma therapy. As her delusions gradually start to loosen, Ms. D reveals she had been physically and emotionally abused by her husband.

At discharge after 90 days in the hospital, Ms. D's symptoms are well managed and she no longer shows signs of a thought disorder. Her thinking is clear, rational, and logical. She demonstrates incredible insight and appreciation that she needs to stay in treatment and continue to take divalproex and risperidone. Her delusions appear to be completely resolved and she is focused on reuniting with her son. Many of her previous delusions appear to be related to trauma and partly dissociative.

Ms. D contacts the psychologist several months later to report she is doing well in the community, staying in treatment, and working on legal means to reunite with her son. No trace of any foreign accent is detectable in her voice.

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Bottom Line

Newly acquired foreign accent in absence of an organic cause may be an early manifestation of underlying psychosis. Severity of psychosis can correlate with the magnitude of foreign accent syndrome, which can be used to assess a patient's progress and response to treatment.

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Related Resources

- Miller N, Lowit A, O'Sullivan H. What makes acquired foreign accent syndrome foreign? *Journal of Neurolinguistics*. 2006; 19:385-409.
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Drug Brand Names

Benzotropine • Cogentin	Haloperidol • Haldol
Diphenhydramine • Benadryl	Lorazepam • Ativan
Divalproex • Depakote	Risperidone • Risperdal
Escitalopram • Lexapro	Ziprasidone • Geodon

Disclosure

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This supplement to CURRENT PSYCHIATRY was submitted by Asante Communications, LLC; supported by educational grants from Eli Lilly and Company and Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals Inc; and administered by Ortho-McNeil-Janssen Scientific Affairs. It was peer reviewed by CURRENT PSYCHIATRY.