

# A Psychodynamic Understanding of Conversion Nonepileptic Seizures in a Young Woman with Acquired Blindness

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## INTRODUCTION

Ms. G is a 19-year-old African-American female with acquired blindness and a seizure disorder following a ruptured cerebral arteriovenous malformation (AVM) in 2001. She currently lives with her mother, brother, and dog, and attends 10th grade in special education at a public high school.

## HISTORY OF PRESENT ILLNESS

During our first meeting in August of 2007, Ms. G cheerfully described herself as "blind, black, and beautiful." During that first visit, she described her mood as "happy" and denied feeling anxious or depressed. She also denied any obsessive, compulsive, or psychotic symptoms. Initially, she was somewhat dismissive about her occasional "seizure" events. However, when asked, she described them as episodes in which she would clench her teeth then lose consciousness, with a period of confusion and headache afterwards. She linked them to times when she was tired or stressed, and noted that one had occurred the day prior. (She had begun the summer at a camp upstate for the visually impaired, but her mom had to come pick her up early because of seizures.) In this first session, she did not mention the additional diagnosis of nonepileptic seizures (NES) that had been made the month prior at another facility's epilepsy center.

She had been admitted for 3 days of continuous video electroencephalogram (EEG) monitoring. The patient had one event during this time, captured on video, in which she first stated that she felt nauseated. She closed her eyes, fell to one side of the bed, and began to shake her arms and legs in a violent but non-synchronous fashion, moving her head from side to side. The event lasted for ~90 seconds, after which she turned over and grabbed the intravenous pole, coughed and vomited. Within a few seconds she awoke and immediately apologized, becoming tearful. The EEG during the event showed normal background rhythm with movement artifact and no generalized epileptiform activity. The report concluded that she has a "mixed seizure disorder with both true complex partial seizures that secondarily generalize as well as nonepileptic seizures."

In our next session in September 2007, we first broached the topic of NES versus epileptic seizures. Ms. G described her understanding of the latter as events in which she would "pass out," while with NES, she would tend to be "off-balance" and would cry afterwards. She noted her NES to be linked to stress, similar to an "anxiety attack," but also somewhat different. When asked about anxiety attacks, she described feeling that "my nerves bother me," with accompanying shortness of breath and palpitations, lasting ~5 minutes, and with no associated trig-

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Authors' Note: Some minor identifying details have been changed to protect patient confidentiality.

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gers. She described the recent diagnosis of NES as “confusing” and complained that “People cannot tell the difference and keep sending me to the hospital when I don’t need to go!” For example, this had happened the week prior when she had again been sent to the emergency room (ER) on the second day of school, after having an “attack” in the hallway in which she started walking “off-balance” and then slipped to the floor.

## PAST MEDICAL HISTORY

The patient has a remarkable past medical history. She was developmentally normal and healthy until June of 2001, when, at 12 years of age, she presented to the school nurse complaining of a severe headache. Her mom was called but was unable to pick her up because, as Ms. G explains, she “had to work.” Ms. G’s friends helped her home, carrying her full backpack because her neck was “locked to one side.” Ms. G convinced her mom she did not need to go to the ER that night, but when she still had a headache the next morning, along with photophobia and vomiting, she was taken to the hospital. A head computerized tomography (CT) scan revealed a right posterior temporal AVM that had ruptured and bled into her ventricles. She was sent to a different hospital for emergency embolization, then transferred to the Mount Sinai School of Medicine (MSSM) for complete neurosurgical resection.

Over the next 4 months, she remained an inpatient at MSSM and suffered multiple post-op complications. These included hydrocephalus and ventriculoperitoneal (VP) shunt placement, with the need for multiple revisions due to infections, including meningitis and encephalitis. At one point, she developed lactic acidemia and had several small strokes, including in the occipital lobe. The aftermath of all of these complications left her completely blind. During this period, she additionally developed pancreatitis and hepatitis, prompting a metabolic work-up and muscle biopsy with the possible finding of a mitochondrial disorder.

In 2002, Ms. G had the onset of generalized convulsive seizures, initially ~2/year, becoming more frequent over time, but at this point well-controlled on oxcarbazepine and lamotrigine, with occasional breakthrough seizures. Her neurologist described these as partial seizures with vocalization that generalize. Ms. G has a history of status epilepticus with one intubation in the spring of 2003. Her current neurologic exam is

consistent with diffuse central nervous system (CNS) injury, residual bilateral motor weakness and long tract signs.

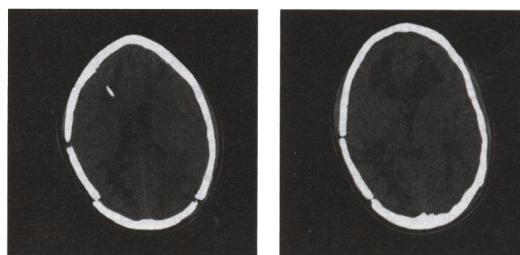
Figure 1 is Ms. G’s non-contrast head CT from October 2001, showing right temporal-parietal craniotomy with right parietal encephalomalacia. The ventricles are dilated with bilateral hypodensities in the periventricular white matter, consistent with edema and hydrocephalus. The VP shunt is seen entering through the right frontal lobe. Figures 2 and 3 contain more recent non-contrast head CT images from March 2007, showing resolution of the acute processes, with residual right parietal encephalomalacia and bilateral frontal white matter hypodensities. Figure 3 additionally shows her current VP shunt, now entering through the left frontal lobe.

Ms. G is currently on a pharmacologic regimen of escitalopram 20 mg/day for anxiety and panic symptoms, lamotrigine 100 mg PO BID and oxcarbazepine 1,200 mg PO BID for seizures, an “enzyme cocktail” (CoQ10, folic acid, vitamins C, B1, B2, E, and K) for her mitochondrial deficiency and an oral contraceptive pill (in case, as her mother states, she were to have a sexual encounter).

## PAST PSYCHIATRIC HISTORY

Ms. G had no past psychiatric history prior to the AVM rupture in May of 2001. After 4 months at MSSM, she was transferred to a rehabilitation center with significant motor deficits and cognitive impairment, in addition to her newly acquired blindness. She also had personality changes, described as being “labile, tearful with inappropriate laughter, and apparently unprovoked screaming.” Her anxiety and panic symptoms were treated with sertraline 50 mg PO QHS. Notes from

**FIGURE 1.**  
Head CT October 2001



CT=computerized tomography.

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that time indicate that she “did not really start talking about what had happened to her...until April of 2002.” After 1 year of inpatient rehab, Ms. G moved back home with her family at 14 years of age. Since then, she has been followed in the MSSM outpatient psychiatry department.

She entered into psychotherapy with a resident physician, Dr. K, who had previously treated Ms. G as an inpatient, providing nice continuity of care. Early psychotherapy focused on adjusting to life as a blind person, Ms. G’s returning to school, and her struggles to navigate adolescence and achieve independence while coping with her memory and motor deficits. These improved significantly over time, although Ms. G continued to have anxiety and panic symptoms, with episodes that were hard to characterize clearly as either panic attacks or partial seizures with panic aura. These declined over time. By 2004 Ms. G was having episodes every 4–5 months, often in the setting of stressful events such as going back to school or going away to camp. Sertraline was discontinued in September 2005.

In June 2006, after nearly four years of psychotherapy with Dr. K, Ms. G’s care was transferred to another psychiatry resident due to Dr. K’s pursuing further training at another institution. Ms. G began attending a new school that fall. She began to have more frequent “seizures” again. Her neurologist felt her symptoms were more consistent with panic attacks and she was started on escitalopram 10 mg/day PO. That year, Ms. G was seen approximately every 2 weeks but was not deeply engaged in therapy.

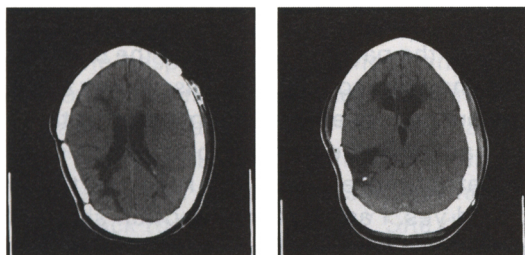
In August of 2007, the patient’s care was transferred to me. On mental status exam, Ms. G presents as a cooperative, friendly, polite, well-groomed, often dramatic, and very well related

young woman, although often younger than her actual age. She wears sunglasses and ambulates with a guide cane quite confidently. Her speech is animated at times; she enjoys telling stories, and was especially prone to do so in the earlier part of the year. Her mood is usually cheerful and her affect is congruently euthymic although often superficial. She tends to dismissively laugh things off, but does become appropriately sad at some moments, much more so recently. Her thought process can vary considerably, from linear to circumstantial, with frank disorganization on some occasions. Her level of insight also varies considerably between and even within sessions. It has been confusing to me in working with her how to understand this degree of fluctuation.

### **SOCIAL, FAMILY, AND EDUCATIONAL HISTORY**

Ms. G was born and raised in New York City by her mother. She has no substance abuse history, and no family history of psychiatric or neurologic disease. She and her mother deny a history of sexual or physical abuse, although one could make a case for emotional neglect by her biological father. He was absent during her younger years and has been inconsistently involved in her life since then. They became close when Ms. G was 12 years of age, although she describes painful memories of waiting up for him all night when he had promised to visit. That year, while she was in the hospital recovering from her neurosurgeries, he was incarcerated, adding to her traumatic losses during that period.

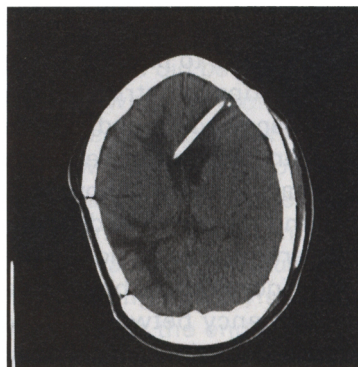
**FIGURE 2.**  
**Head CT March 2007**



CT=computerized tomography.

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**FIGURE 3.**  
**Head CT March 2007, with shunt**



CT=computerized tomography.

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She has attachments to multiple female caregiver figures, including a close relationship with her paternal grandmother. Her relationship with her mother is conflicted in that they are very close, with Ms. G admitting how dependent she is on her, yet she longs for more independence and feels that her mother is too restrictive. Ms. G has had the same home attendant for the past 4 years, Ms. L, to whom the patient is quite attached. Ms. L is with Ms. G for 4 hours everyday after school and brings the patient to her appointments. Ms. G refers to Ms. L as "ma". The patient also has a school paraprofessional who picks her up at home, accompanies her on the bus and throughout the day at school. After school, the patient works several days a week as a cashier in a residential program for the blind, where she makes change with a bill identifier.

Her educational history is notable for the fact that she attended gifted classes in public schools up until the seventh grade. She was a straight-A student throughout. After her illness, she attended a children's hospital where she received physical, occupational, and speech therapy. She had significant short-term memory deficits although relative strength in expressive language. Eventually she entered a high school with an emphasis on occupational training, but was found to be too advanced for the school. Her mom had difficulty finding a school in the public system that was willing to accept Ms. G due to her seizures and blindness. However, she was eventually accepted into a high school and began an Individualized Educational Plan in 2006. She is currently in the 10th grade and will age out of the public school system at 21 years of age. She is not doing well in school, largely due to sporadic attendance because of increasingly frequent seizure events and medical visits. She also misses school at times when her paraprofessional is not able to pick her up.

As part of neuropsychiatric testing back in 2002, Ms. G's IQ range was found to be in the 70s, although on recent testing her Verbal IQ was 88. It is difficult to have a sense of how accurate this is, given her blindness and the difficulty of testing; neither a Performance IQ nor an estimate of pre-morbid intelligence could be obtained. There was a big discrepancy between her Verbal IQ and her Adaptive Behavior composite score; the report notes that "It is likely that her visual impairment along with pseudoseizures...have negatively impacted the development of her adaptive skills."

## COURSE OF TREATMENT

Ms. G was initially assigned to me as one of my caseload patients for supportive therapy and medication management. It became clear early on that the patient was motivated for treatment and wanted to come in more regularly. At her request we began to meet weekly. Early themes included conflict over how much she was allowed to do on her own, her feeling that at times her mother and brother do not listen to her, and her stress about school work. She would tend to minimize or avoid these topics most of the time, however, preferring to enter into "storytelling mode", often talking at great length about boys or people she had met. At times she would offer surprising insights, however, such as noting her own reaction to getting upset, in which she would either become "rude and disrespectful" or "shut down," eg, fall asleep. Despite this, she was avoidant of discussing affect-laden material during this period, and was often superficial, frequently using humor as a defense. She especially would tend to deny or minimize any conflicts with or anger at her mother.

Several months into the year, her mother reported to me on the phone that the patient had had a flurry of what she called "NES" in the past week, now more violent in nature. In one, after kicking and swinging at the air, she threw their dog across the room. This episode lasted ~3 minutes, and afterwards she was tired for hours, with a brief period of altered speech. In another episode, she kicked the wall, was noted to have tongue twisting and appeared to be trying to speak. Another happened at school in which she reportedly sloped over in her chair, with full body shaking, and then later scratched the school nurse. There was no stereotypical pattern that could be elicited in these events.

In the next session, the patient described a dream in which she thought she was going to have a seizure. The dream involved both Ms. L and her mother buying her clothes at a department store, and the patient vomiting on the clothes her mother had picked out. After discussing this and the recent seizure events, she mentioned that her mom had asked her if she would like to see her psychiatrist more often, and reported that she had said yes. I asked her how often she would like to come. She brightened considerably and said "How often can you see me?" We agreed on twice weekly sessions.

In the first "second session" later that week,



the patient wound up discussing her previous attachment to Dr. K. In this session Ms. G expressed real affect to me, crying and taking off her sunglasses, for the first time. She shared the vow she made to herself after Dr. K left not to become attached to any more doctors, and admitted that she had tried not to get too close to the intervening therapist. From this point on, the patient seemed engaged in treatment in a deeper way, more invested and able to examine with more curiosity the connection between her emotions and seizure events. For example, after another attack on the school bus that resulted in an ER visit, she described it as "my mind freezes up and shuts down—and because my mind controls my body, my body collapses."

In subsequent sessions, Ms. G explored memories of being hospitalized at 12 years of age, and how her father left one day, saying he was going home to shower and would come right back. He did not, and she only later learned that he had been incarcerated by overhearing everyone discussing in hushed tones whether or not to tell her. Her mother felt she should know so she would "stop crying," because when Ms. G would cry, her blood pressure would go up and the alarm monitors would sound. These memories raised the idea that Ms. G perceived strong feelings as dangerous.

We have explored her frustration, especially at school, and her feeling that people put pressure on her and expect a lot from her. She worries that she will not meet everyone's expectations and will disappoint people. Ms. G commented that some of her anxiety stems from this, and also from her fear of not doing well on tests. For example, she passed out several times when attempting to take the Regents Exams and is now exempt from them.

In May 2007 she was again hospitalized for repeat video EEG monitoring, which revealed her baseline rhythm. Although she did not have any events during this time, she spent several days in the hospital, missed school, and missed one of our sessions. She did not mention it afterward, and when asked, said that she had "forgotten" about it. Later in the session, she was able to remember the hospital stay, saying it was coming back to her "in pieces." She described the stay as "pitiful and depressing to be in the hospital," commenting that she would rather just forget it. We discussed her general tendency to block out things that are painful.

At one point when her mother had been discussing the possibility of getting a second opinion at another epilepsy center, it emerged that Ms. G was concerned that I was going to send her there for psychiatry as well. She was noticeably relieved when I assured her otherwise, and at the end of that session thanked me and mentioned that she now carries my "voice" around with her in her head, whereas she used to hear Dr. K's voice. I was touched by this strong positive transference and felt the treatment must surely be deepening. At the same time I was puzzled because, although she seemed to be making progress in our work together, she was worsening outside of treatment, with more frequent attacks.

Despite Ms. G's increasing openness to discussing these attacks, her levels of insight continued to fluctuate considerably. Progress was also limited by her often reporting amnesia afterwards for events. She would still often tend to avoid emotionally charged or conflict-laden material. An attack occurred on the way to the dentist to have her wisdom tooth pulled. Ms. G was dismissive later of the possibility she had been scared to go to the dentist, saying, "Oh no, but I love going to the dentist!"

We have addressed her disavowal of anger, even in situations that might typically produce angry feelings. She has commented that in this way she is unlike her mother and brother who are able to "speak their mind." She identifies herself as "sweet" and "with a heart" and says that it is therefore not in her nature to get angry. When asked if she could maintain that identity but still get mad on occasions at people she cares about, she responded that people might not like her if she were to become angry, and besides, if she were to get mad and then anything "bad" were to happen, that "would be a disaster."

In further exploring this, Ms. G linked past experiences in which she did become angry, eg at her father, and had "what my mom then called a seizure." She denied a fear of this happening again, saying that now she never becomes angry. Later in the session, she acknowledged, however, that everyone gets angry at times, and remarked with her head in her hands, "I am stuck!" She seemed to be both laughing and crying. Usually Ms. G transitions easily at the end of sessions, and is very responsive to any cues that the session time is nearing an end. This time, however, it seemed she did not want to leave. On the way out the door, she noted she was off-balance and stated,

"I think I am going to have an anxiety attack." She came back into my office and proceeded to have what appeared to be a panic attack with hyperventilation for ~10–15 minutes, accompanied by weakness, muscle stiffening, and then a fainting-like episode. She slipped to the floor in my office, followed by 2 minutes of full-body convulsive movements similar to the nonepileptic event captured on video EEG last summer. After this, she awoke, asked "Who are you?" and "Where am I?" several times. She continued to be confused, speaking with bizarre, altered speech and childlike behavior and movements—then after several minutes was able to walk out with assistance.

### PSYCHODYNAMIC UNDERSTANDING OF CONVERSION NONEPILEPTIC SEIZURES

Seeing this attack on the floor of my office was a moving experience for me. It speaks to the extraordinary power of the unconscious to shape our thoughts, feelings, and behaviors. Ms. G uses the classic defenses of repression, dissociation and somatization to keep from conscious experience painful conflicts and affects. Conversion is literally that—the conversion of anxiety, unacceptable wishes and feelings into physical symptoms.

Alper has written elsewhere that NES can be a manifestation of the "disparity between the demands of fulfilling a role or self ideal and the needs of the real self."<sup>1</sup> In this case, Ms. G still sees herself as the gifted student she used to be. I believe her inability to accept her negative feelings and current limitations, her conflicted relationship with her mother, her ambivalent desire for independence and pull towards dependency, and, I suspect, her as of yet largely unresolved grief over her loss of vision, all contribute to her symptoms.

It has been an honor and a pleasure to work with Ms. G but also difficult. In reviewing her records and watching videotapes of recent sessions I wondered if maybe I myself had been blinded to some of her limitations. Maybe I have experienced her this year as more cognitively intact than she really is—almost as if I had been enveloped in the defended and rosy universe she projects outwards.

### REMAINING QUESTIONS

My remaining questions include the following. How useful and appropriate is it to approach

this case with a psychodynamic framework, given her cognitive impairments? What is the role of organicity in her presentation of paroxysmal alterations of behavior and memory? How should the fluctuations in her mental status be understood? What should I make of the deepening of therapy sessions, with increasing affective awareness, yet seeming worsening outside of sessions?

At times Ms. G presents as childlike, regressed, or developmentally delayed—yet at other times, as I hope I have demonstrated, she is remarkably insightful and emotionally related; to what extent should this and her mood lability be seen as neurologically determined, and in what ways dynamically and defensively motivated, perhaps dissociative? It is my aim to gradually bring into consciousness, as the patient is able to tolerate, what I believe are her repressed feelings of anger and sadness and to understand how her NES in some cases may serve as a form of avoidance or expression of anxiety-producing and affect-laden situations or conflicts. Is this the best therapeutic approach to take, and how can I proceed without destabilizing her? **CNS**

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### DISCUSSION—DR. ALPER

"The diseased heart is more susceptible to the influence of an affect than a healthy one"—Josef Breuer 1893, *Studies on Hysteria*<sup>1</sup>

This quote comes from a paper published in 1893 that is of critical importance to the history of psychoanalysis and psychoanalytic theory because it first introduced the construct of the dynamic unconscious, as well as the diagnostic concept of conversion.<sup>1</sup>

Freud made his observations regarding the unconscious on the basis of a series of women who presented with "hysterical fits", ie, conversion disorders presenting as nonepileptic seizures (NES).<sup>2</sup> He found a high rate of abuse in this series of women, and initially concluded that there was a connection between abuse and conversion NES. Sometime later, he revised his original theory and suggested that this abuse was fantasized. Freud did not have access to statistics regarding the prevalence of abuse in the general population or in patients with NES. A recent meta-analysis<sup>3</sup> indicated a combined

prevalence of a history of childhood sexual abuse across the studies of 37% in patients with NES versus 16% in controls. Thus, it appears that Freud's original formulation was correct and his later retraction was incorrect.

The Table presents the diagnostic criteria for Conversion Disorder from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.<sup>4</sup> Note criterion "A" includes the term "voluntary," which is important because this differentiates conversion from other psychiatric disorders that can present with events that must be differentiated from conversion NES.<sup>5</sup> Approximately 15% of the population that presents to us for video electroencephalogram (EEG) monitoring has NES. Most of those are conversion NES and they are distinct from other conditions such as attention-deficit/hyperactivity disorder, bipolar disorder, or panic disorder, which can be present with paroxysmal lapses of attention or events that do not involve unconsciously intended voluntary movement.<sup>5</sup>

The psychodynamic concept of conversion is still very much with us. The *DSM-IV* has attempted to exclude psychoanalytical theory, but was not

able to do so in the case of conversion disorder. Note criteria "B" and "C" (Table). The attributions of psychological factors and intentionality are references to the dynamic unconscious. As used in the *DSM-IV*, "intentionally" must imply unconscious intent, because the unconscious nature of the intent to produce the symptoms distinguishes conversion from Factitious Disorders and Malingering. In contrast to Conversion Disorder, the production of intentional symptoms is conscious in Factitious Disorder and Malingering. Yet, the term "intentionally" as used in criterion "C" avoids an explicit reference to conscious versus unconscious intent. I suspect this has to do with an aversion to putting an analytic word like "unconscious" in the diagnostic criteria. Conversion can be viewed as the last redoubt of psychoanalytic theory in the *DSM-IV*, because whether or not it is explicitly acknowledged, the clinical definition of conversion inevitably invokes the fundamental, essential psychoanalytic concept of the dynamic unconscious.

There are inevitable difficulties in attributing conversion symptoms to psychological factors according to criterion "B". Does this mean that epileptic patients have no conflicts or stressors? There is an element of post hoc reasoning that identifies a "psychological factor" and associates it with the conversion nonepileptic event. Criterion "B" also lacks of specificity, with regard to the inclusion of "psychological factors", because patients with physiological epileptic seizures reportedly acknowledge stress in relation to their seizures more often than nonepileptic patients. We looked at the relationship of identified stress to the production of epileptic versus NES<sup>6</sup> and found that 71% of patients with epilepsy acknowledged that their seizures occurred more frequently when they were experiencing psychological stress, compared to 46% of patients with NES. This is consistent with the function that conversion serves in terms of neutralizing anxiety and unpleasant affects.

There is uncertainty regarding our attribution as to whether the intent is conscious versus unconscious, which involves accessing the consciousness of the patient. Also, the diagnostic criteria assume the distinction of conscious from unconscious is categorical. It does not have to be. It could be continuous, whatever that means. However, with all of the difficulties, can this construct of unconscious intent be avoided with regard to diagnosing conversion? I do not

**TABLE.**

**Diagnostic Criteria for 300.11 Conversion Disorder, from the *DSM-IV***

- A. One or more symptoms or deficits affecting voluntary motor or sensory function that suggest a neurological or other general medical condition.
- B. Psychological factors are judged to be associated with the symptom or deficit because the initiation or exacerbation of the symptom or deficit is preceded by conflicts or other stressors.
- C. The symptom or deficit is not intentionally produced or feigned (as in Factitious Disorder or Malingering).
- D. The symptom or deficit cannot, after appropriate investigation, be fully explained by a general medical condition, or by the direct effects of a substance, or as a culturally sanctioned behavior or experience.
- E. The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.
- F. The symptom or deficit is not limited to pain or sexual dysfunction, does not occur exclusively during the course of Somatization Disorder, and is not better accounted for by another mental disorder.

*DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.*

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believe so. The construct of unconscious intent is an important distinction between conversion non-epileptic events and other psychiatric events that present as NES.

Charcot<sup>7</sup> took a view of NES that was strongly criticized at that time. He postulated a biologically determined diathesis existed that permitted the expression of conversion symptoms. He did not view conversion events as the direct expression of a neurological syndrome. He believed that neurologic factors played a permissive, or disinhibiting role, which appears to be pertinent to Ms. G's case. Charcot's idea was initially rejected, however, this view has become more accepted due to observations of non-specific neurological pathology in NES.<sup>8</sup> For example, mild traumatic brain injury is reportedly more common in nonepileptic versus epileptic patients.

Janet<sup>9</sup> introduced the concept of dissociation in conversion which has been viewed as "a description in psychological terms of a process which must rest on neurophysiologic changes". There is an association of NES with epilepsy. The prevalence of epilepsy is ~1% to 2% and increases with age. But the association with NES and epilepsy in the literature is anywhere between 10% and 50%. Even if one assumes the lowest estimate, the association between NES and epilepsy is on the order of 10 times greater than that which would be expected on the basis of chance.

Head trauma and structural lesions are pertinent to this case. Eames<sup>10</sup> reported on a series of patients with anoxia, hypoglycemia, and carbon monoxide exposure, all of which affect the basal ganglia, and developed a scale that operationalized the clinical features of conversion events in this series. Child-like behavior was one of the major criteria for conversion presenting the setting of anoxic or hypoglycemic brain injury identified by Eames,<sup>10</sup> and has been emphasized in the phenomenology of Ms. G's conversion events.

There is a literature that associates injury to the right hemisphere with conversion symptoms. Strokes or other destructive lesions of the frontal lobe or the right parietal lobe, can be associated with anosognosia or neglect. Anosognosia or neglect are concepts that involve acquired tendency for initiating action outside the patient's awareness, and an analogy has been drawn to the neglect syndrome seen in patients with right hemispheric damage. In patients presenting with neurological lesions and NES, we found a predominance of right-sided lesions.<sup>11</sup> Some patients develop NES following

epilepsy surgery, and it has been reported that in these patients the resection relatively more often tends to involve the right than the left hemisphere. The reported right hemisphere predominance of brain structural lesions as well as EEG abnormalities in conversion has been interpreted according to a theory that body image and the awareness of the self involve global processes that may preferentially involve the right hemisphere. One statement of this interpretation is:

"It is known that right hemisphere dysfunction can impair conscious awareness of body parts, neurological deficits (eg, anosognosia), sensory input, and emotional and social cues...In conversion disorder, there may be a restriction in the conscious fields of attention, memory, and emotions, leading to a subconsciously generated behavior through which prior emotional memories resurface and are expressed as somatic symptoms. Right hemisphere lesions may thus impair capacity to 'psychologically handle' painful emotions and, simultaneously, impair awareness of self-features (as in anosognosia) and self-generated behaviors such as conversion symptoms that would otherwise be accessible to consciousness."<sup>11</sup>

Conversion disorder presenting as NES is a clinically and historically significant diagnostic paradigm in psychiatry and neurology. The concept of the dynamic unconscious has an important basis in early observations of patients with conversion NES. The concept that neurologic impairment can permit or facilitate the expression of conversion symptoms, of which Charcot<sup>7</sup> was an early advocate, is the subject of increasing contemporary research interest. **CNS**

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## DISCUSSION—DR. BASCH

Congratulations to Dr. Soffer and Dr. Alper for undertaking the formidable task of elucidating so many complex and confounding issues, not the

(Cont. on page 584)





**NEW**

Introducing  
**A NEW SNRI**  
therapy

for major depressive  
disorder in adults





### IMPORTANT TREATMENT CONSIDERATIONS

PRISTIQ 50 mg is indicated for the treatment of major depressive disorder in adults.

#### **WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS**

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of PRISTIQ or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PRISTIQ is not approved for use in pediatric patients.

#### **Contraindications**

- PRISTIQ is contraindicated in patients with a known hypersensitivity to PRISTIQ or venlafaxine.
- PRISTIQ must not be used concomitantly with an MAOI or within 14 days of stopping an MAOI. Allow 7 days after stopping PRISTIQ before starting an MAOI.

### Warnings and Precautions


- **All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the first few months of treatment and when changing the dose.** Consider changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Families and caregivers of patients being treated with antidepressants should be alerted about the need to monitor patients.**
- Development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including PRISTIQ, particularly with concomitant use of serotonergic drugs, including triptans, and with drugs that impair the metabolism of serotonin (including MAOIs). If concomitant use is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Concomitant use of PRISTIQ with serotonin precursors is not recommended.
- Patients receiving PRISTIQ should have regular monitoring of blood pressure since sustained increases in blood pressure were observed in clinical studies. Pre-existing hypertension should be controlled before starting PRISTIQ. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported. For patients who experience a sustained increase in blood pressure, either dose reduction or discontinuation should be considered.



For major depressive disorder in adults

# New SNRI therapy. From the start: One dose. No titration.

- The major active metabolite of Effexor XR® (venlafaxine HCl)<sup>1</sup>
- One simple 50-mg dose, no need to titrate<sup>1</sup>  
— Dosage adjustment is necessary in patients with severe renal impairment or end-stage renal disease and is recommended when discontinuing therapy
- PRISTIQ may help your patients with depression—emotionally, physically, and functionally<sup>1-3</sup>
- Discontinuation rate due to adverse events was comparable to placebo in clinical studies at 50 mg<sup>1</sup>

New  **Pristiq**<sup>TM</sup>  
desvenlafaxine  
EXTENDED-RELEASE TABLETS

- SSRIs and SNRIs, including PRISTIQ, may increase the risk of bleeding events. Concomitant use of aspirin, NSAIDs, warfarin, and other anticoagulants may add to this risk.
- Mydriasis has been reported in association with PRISTIQ; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.
- PRISTIQ is not approved for use in bipolar depression. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine the risk of bipolar disorder.
- As with all antidepressants, PRISTIQ should be used cautiously in patients with a history or family history of mania or hypomania, or with a history of seizure disorder.
- Caution is advised in administering PRISTIQ to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Increases in blood pressure and small increases in heart rate were observed in clinical studies with PRISTIQ. PRISTIQ has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease.
- Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoprotein) cholesterol, and triglycerides were observed in clinical studies. Measurement of serum lipids should be considered during PRISTIQ treatment.
- On discontinuation, adverse events, some of which may be serious, have been reported with PRISTIQ and other SSRIs and SNRIs. Abrupt discontinuation of PRISTIQ has been associated with the appearance of new symptoms. Patients should be monitored for symptoms when discontinuing treatment. A gradual reduction in dose (by giving 50 mg of PRISTIQ less frequently) rather than abrupt cessation is recommended whenever possible.
- Dosage adjustment (50 mg every other day) is necessary in patients with severe

renal impairment or end-stage renal disease (ESRD). The dose should not be escalated in patients with moderate or severe renal impairment or ESRD.

- Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with PRISTIQ.
- Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including PRISTIQ. Discontinuation of PRISTIQ should be considered in patients with symptomatic hyponatremia.
- Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of PRISTIQ) therapy have been rarely reported.

#### Adverse Reactions

- The most commonly observed adverse reactions in patients taking PRISTIQ vs placebo for MDD in short-term fixed-dose premarketing studies (incidence  $\geq 5\%$  and twice the rate of placebo in the 50-mg dose group) were nausea (22% vs 10%), dizziness (13% vs 5%), hyperhidrosis (10% vs 4%), constipation (9% vs 4%), and decreased appetite (5% vs 2%).

**References:** 1. Pristiq<sup>TM</sup> (desvenlafaxine) Prescribing Information, Wyeth Pharmaceuticals Inc. 2. Data on file, Wyeth Pharmaceuticals Inc. 3. Sheehan DV. Sheehan Disability Scale. In: Rush AJ Jr, Pincus HA, First MB, et al, eds. *Handbook of Psychiatric Measures*. 1st ed. Washington, DC: American Psychiatric Association; 2000:113-115.

Please see brief summary of Prescribing Information on adjacent pages.

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**Pristiq**<sup>TM</sup>  
desvenlafaxine

**Wyeth**<sup>®</sup>

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**BRIEF SUMMARY.** See package insert for full Prescribing Information. For further product information and current package insert, please visit [www.wyeth.com](http://www.wyeth.com) or call our medical communications department toll-free at 1-800-934-5556.

**WARNING: Suicidality and Antidepressant Drugs**

**Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Pristiq or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Pristiq is not approved for use in pediatric patients [see Warnings and Precautions (5.1), Use in Specific Populations (8.4), and Patient Counseling Information (17.1 in the full prescribing information)].**

**INDICATIONS AND USAGE:** Pristiq, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder (MDD).

**CONTRAINDICATIONS: Hypersensitivity**—Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the Pristiq formulation. **Monamine Oxidase Inhibitors**—Pristiq must not be used concomitantly in patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with SNRI or SSRI treatment or with other serotonergic drugs. Based on the half-life of desvenlafaxine, at least 7 days should be allowed after stopping Pristiq before starting an MAOI [see Dosage and Administration (2.5) in the full prescribing information].

**WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk**—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18–24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1 of the full prescribing information. No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [see Warnings and Precautions (5.9) and Dosage and Administration (2.3) in the full prescribing information for a description of the risks of discontinuation of Pristiq]. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. 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. **Screening patients for bipolar disorder**—A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Pristiq is not approved for use in treating bipolar depression. **Serotonin Syndrome**—The development of a potentially life-threatening serotonin syndrome may occur with Pristiq treatment, particularly with concomitant use of other serotonergic drugs (including SSRIs, SNRIs and triptans) and with drugs that impair metabolism of serotonin (including MAOIs). The concomitant use of Pristiq and MAOIs is contraindicated [see Contraindications (4.2)]. If concomitant treatment with Pristiq and an SSRI, another SNRI or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Pristiq with serotonin precursors (such as tryptophan supplements) is not recommended. **Elevated Blood Pressure**—Patients receiving Pristiq should have regular monitoring of blood pressure since dose-dependent increases were observed in clinical studies. Pre-existing hypertension should be controlled before initiating treatment with Pristiq. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with Pristiq. **Sustained hypertension**—Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving Pristiq, either dose reduction or discontinuation should be considered [see Adverse Reactions (6.7)]. Treatment with Pristiq in controlled studies was associated with sustained hypertension, defined as treatment-emergent supine diastolic blood pressure (GDBP)  $\geq 90$  mm Hg and  $\geq 10$  mm Hg above baseline for 3 consecutive on-therapy visits. In clinical studies, regarding the proportion of patients with sustained hypertension, the following rates were observed: placebo (0.5%), Pristiq 50 mg (1.3%), Pristiq 100 mg (0.7%), Pristiq 200 mg (1.1%), and Pristiq 400 mg (2.3%). Analyses of patients in Pristiq controlled studies who met criteria for sustained hypertension revealed a dose-dependent increase in the proportion of patients who developed sustained hypertension.

**Abnormal Bleeding**—SSRIs and SNRIs can increase the risk of bleeding events. Concomitant use of aspirin, other drugs that affect platelet function, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants can add to this risk. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Pristiq and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding. **Narrow-angle Glaucoma**—Mydriasis has been reported in association with Pristiq;

therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored. **Activation of Mania/Hypomania**—During all MDD and VMS (vasomotor symptoms) phase 2 and phase 3 studies, mania was reported for approximately 0.1% of patients treated with Pristiq. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, Pristiq should be used cautiously in patients with a history or family history of mania or hypomania. **Cardiovascular/Cerebrovascular Disease**—Caution is advised in administering Pristiq to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders [see Adverse Reactions (6.7)]. Increases in blood pressure and heart rate were observed in clinical studies with Pristiq. Pristiq has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease. Patients with these diagnoses, except for cerebrovascular disease, were excluded from clinical studies. **Serum Cholesterol and Triglyceride Elevation**—Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoprotein) cholesterol, and triglycerides were observed in the controlled studies. Measurement of serum lipids should be considered during treatment with Pristiq [see Adverse Reactions (6.7)]. **Discontinuation of Treatment with Pristiq**—Discontinuation symptoms have been systematically and prospectively evaluated in patients treated with Pristiq during clinical studies in Major Depressive Disorder. Abrupt discontinuation or dose reduction has been associated with the appearance of new symptoms that include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, fatigue, abnormal dreams, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy. During marketing of SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors) and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Pristiq. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate [see Dosage and Administration (2.4) and Adverse Reactions (6.1) in full prescribing information]. **Renal Impairment**—In patients with moderate or severe renal impairment or end-stage renal disease (ESRD) the clearance of Pristiq was decreased, thus prolonging the elimination half-life of the drug. As a result, there were potentially clinically significant increases in exposures to Pristiq [see Clinical Pharmacology (12.6) in full prescribing information]. Dose adjustment (50 mg every other day) is necessary in patients with severe renal impairment or ESRD. The doses should not be escalated in patients with moderate or severe renal impairment or ESRD [see Dosage and Administration (2.2) in full prescribing information]. **Seizure**—Cases of seizure have been reported in premarketing clinical studies with Pristiq. Pristiq should be prescribed with caution in patients with a seizure disorder. **Hyponatremia**—Hyponatremia can occur as a result of treatment with SSRIs and SNRIs, including Pristiq. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients can be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk [see Use in Specific Populations (8.5) and Clinical Pharmacology (12.6) in full prescribing information]. Discontinuation of Pristiq should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. **Coadministration of Drugs Containing Desvenlafaxine and Venlafaxine**—Desvenlafaxine is the major active metabolite of venlafaxine. Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with Pristiq. **Interstitial Lung Disease and Eosinophilic Pneumonia**—Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of Pristiq) therapy have been rarely reported. The possibility of these adverse events should be considered in patients treated with Pristiq who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of Pristiq should be considered.

**ADVERSE REACTIONS: Clinical Studies Experience:** The most commonly observed adverse reactions in Pristiq-treated MDD patients in short-term fixed-dose studies (incidence  $\geq 5\%$  and at least twice the rate of placebo in the 50- or 100-mg dose groups) were nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders. **Adverse reactions reported as reasons for discontinuation of treatment:** The most common adverse reactions leading to discontinuation in at least 2% of the Pristiq-treated patients in the short-term studies, up to 8 weeks, were nausea (4%), dizziness, headache and vomiting (2% each); in the long-term study, up to 9 months, the most common was vomiting (2%). **Common adverse reactions in placebo-controlled MDD studies:** Table 3 in full PI shows the incidence of common adverse reactions that occurred in  $\geq 2\%$  of Pristiq-treated MDD patients at any dose in the 8-week, placebo-controlled, fixed-dose, premarketing clinical studies. In general, the adverse reactions were most frequent in the first week of treatment. **Cardiac disorders:** Palpitations, Tachycardia, Blood pressure increased; **Gastrointestinal disorders:** Nausea, Dry mouth, Diarrhea, Constipation, Vomiting; **General disorders and administration site conditions:** Fatigue, Chills, Feeling jittery, Asthenia; **Metabolism and nutrition disorders:** Decreased appetite, weight decreased; **Nervous system disorders:** Dizziness, Somnolence, Headache, Tremor, Paraesthesia, Disturbance in attention; **Psychiatric disorders:** Insomnia, Anxiety, Nervousness, Irritability, Abnormal dreams; **Renal and urinary disorders:** Urinary hesitation; **Respiratory, thoracic, and mediastinal disorders:** Yawning; **Skin and subcutaneous tissue disorders:** Hyperhidrosis, Rash; **Special Senses:** Vision blurred; Mydriasis, Tinnitus, Dysgeusia, Vascular Disorders: Hot flush. **Sexual function adverse reactions:** Table 4 shows the incidence of sexual function adverse reactions that occurred in  $\geq 2\%$  of Pristiq-treated MDD patients in any fixed-dose group (8-week, placebo-controlled, fixed and flexible-dose, premarketing clinical studies). **Men Only:** Anorgasmia, Libido decreased, Orgasm abnormal, Ejaculation delayed, Erectile dysfunction, Ejaculation disorder, Ejaculation failure, Sexual dysfunction; **Women Only:** Anorgasmia. **Other adverse reactions observed in premarketing clinical studies:** Other infrequent adverse reactions occurring at an incidence of  $< 2\%$  in MDD patients treated with Pristiq were: **Immune system disorders** – Hypersensitivity. **Investigations** – Liver function test abnormal, blood prolactin increased, **Nervous system disorders** – Convulsion, syncope, extrapyramidal disorder. **Psychiatric disorders** – Depersonalization, hypomania. **Respiratory, thoracic and mediastinal disorders** – Epistaxis. **Vascular disorders** – Orthostatic hypotension. In clinical studies, there were uncommon reports of ischemic cardiac adverse events, including myocardial ischemia, myocardial infarction, and coronary occlusion requiring revascularization; these patients had multiple underlying cardiac risk factors. More patients experienced these events during Pristiq treatment as compared to placebo [see Warnings and Precautions (5.7)]. **Discontinuation events**—Adverse events reported in association with abrupt discontinuation, dose reduction or tapering of treatment in MDD clinical studies at a rate of  $\geq 5\%$  include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, abnormal dreams, fatigue, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy [see Dosage and Administration (2.4) and Warnings and Precautions (5.9) in full prescribing information]. **Laboratory, ECG and vital sign changes observed in MDD clinical studies:** The following changes were observed in placebo-controlled, short-term, premarketing MDD studies with Pristiq. **Lipids**—Elevations in fasting serum total cholesterol, LDL (low density lipoproteins) cholesterol, and triglycerides occurred in the controlled studies. Some of these abnormalities were considered potentially clinically significant [see Warnings and Precautions (5.8)]. **Proteinuria**—Proteinuria, greater than or equal to trace, was observed in the fixed-dose controlled studies (see Table 6 in full prescribing information). This proteinuria was not associated with increases in BUN or creatinine and was generally transient. **ECG changes**—Electrocardiograms were obtained from 1,492 Pristiq-treated patients with major depressive disorder and 984 placebo-treated patients in clinical studies lasting up to 8 weeks. No clinically relevant differences were observed between Pristiq-treated and placebo-treated patients for QT, QTc, PR, and QRS intervals. In a thorough QTc study with prospectively determined criteria, desvenlafaxine did not cause QT prolongation. No difference was observed between placebo and desvenlafaxine treatments for the QRS interval. **Vital sign changes**—Table 7 summarizes the changes that were observed in placebo-controlled, short-term, premarketing studies with Pristiq in patients with MDD (doses 50 to 400 mg). Relative to placebo, Pristiq was associated with mean increase of up to 2.1 mm Hg in systolic blood pressure, 2.3 mm Hg in diastolic blood pressure, and 4.1 bpm with supine pulse. At the final on-therapy assessment in the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to Pristiq during the initial 12-week, open-label phase, there was no statistical difference in mean weight gain between Pristiq- and placebo-treated patients. **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)]. **Monamine 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 an 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** (e.g.,



**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 (O-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, but greater sensitivity of some older individuals cannot be ruled out. 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) in the full prescribing information]. **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. No adjustment in starting dosage is necessary for patients with hepatic impairment.

**OVERDOSAGE: Human Experience with Overdosage-** There is limited clinical experience with desvenlafaxine succinate overdosage 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 *Overdosage* 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 (e.g., 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 overdosage 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 overdosage, as opposed to some characteristic(s) of venlafaxine-treated patients, is not clear. Prescriptions for Pristiq should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. **Management of Overdosage-** Treatment should consist of those general measures employed in the management of overdosage 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 W10529C002, revised April 2008.

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least of which is an attempt to understand epileptic versus nonepileptic seizures. Dr. Soffer has been doing and continues to do an outstanding job with a very complex and difficult case. Since this is a complicated patient with wide ranging issues, I will limit my comments to a few areas, concentrating on some of the obstacles to treatment. Some are the obstacles of everyday therapy, others are magnifications of ordinary obstacles, and some are unique to this patient.

The first obstacle is resistance. The psychoanalytic definition of resistance is the force that constrains the unconscious from becoming conscious, namely, bringing unpleasant, repressed memories into awareness—although the term is often applied more broadly. With Ms. G, issues of intention, awareness, automatic behavior and other mechanisms brought out by Dr. Alper were often perplexing. Some of her seizures may have been her unconscious talking, with her lack of awareness of her anguish at an unconscious level breaking through in the form of a seizure.

The next obstacle concerns transference, the psychoanalytic definition of which is applying past experiences, feelings and memories derived from earlier figures in life, often parents, and then investing them in current figures, such as the therapist. Transference issues make children and adolescents, who are still in a fluid state of personality and character formation, particularly challenging to treat. Ms. G was traumatized at an early age and experienced interferences, which altered her development in ways that influenced any future transference reactions. In addition, her multiple medical problems promoted regression, which retarded and undermined the progression of her normal development, leading to possible transference distortions. These early experiences with family, caretakers, doctors and others would inevitably affect Ms. G's relationship with Dr. Soffer.

The transference is complicated by the fact that the patient is blind. Analysts place their patients on the couch so that they can have a blind experience and blank screen in order to encourage the patient to fantasize or free associate more easily and slip into regressive transference attitudes towards the analyst. Ms. G has a blank screen and responds mainly to audi-

tory cues. Her blank visual screen may be evidenced by her calling her mother "Mom" and her home attendant "Ma." Although Ms. G doesn't see them, she may experience them in a similar way or even fuse them into one parental imago. This may be further projected onto Dr. Soffer. The patient's injury caused regression and may have suspended or fixated her transference connection to her mother and caretakers. These relationships along with the relationship with Dr. Soffer are likely still in formation, further confounding the treatment.

A third obstacle relates to countertransference. In treating a late teenage girl presenting herself as "Black, blind, and beautiful," should one maintain objectivity or a neutral professional stance? And as we know, maintaining a neutral stance sometimes is not in the patient's best interest. How can Dr. Soffer balance her objective stance, apply her psychiatric training, be appropriately empathetic and sympathetic, and, at the same time, proceed in the treatment with ease and effectiveness? It is an extremely difficult line to walk and takes great care and thoughtfulness as well as flexibility on the part of the therapist.

The fourth obstacle is the patient's use of her defenses in a counterproductive way. In her attempt to avoid anxiety and painful affects, she calls on a multitude of intrapsychic mechanisms. As shown by Dr. Soffer, Ms. G has utilized denial, repression, suppression, rationalization, minimization and other defenses, as well as dissociation and somatization, which have been difficult to characterize.

Since the physical and psychological overlap, we are at odds as to how to characterize the patient's symptoms. They may spare her psychic pain and thus prevent her from making progress in the therapy. Should treatment proceed gingerly to avoid prying loose some advantageous mechanisms of defense? If we do not challenge the defense, are we complicit in perpetuating Ms. G's symptoms? Would not nonepileptic seizures be an example of this?

I again congratulate Dr. Soffer for meeting the challenges and frustrations of this difficult and confounding case. **CNS**