

THE PRIMARY CARE COMPANION TO THE JOURNAL OF CLINICAL PSYCHIATRY

VOLUME 2

APRIL 2000

NUMBER 2

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Dissociative Spectrum Disorders in the Primary Care Setting

James L. Elmore, M.D.

Dissociative disorders have a lifetime prevalence of about 10%. Dissociative symptoms may occur in acute stress disorder, posttraumatic stress disorder, somatization disorder, substance abuse, trance and possession trance, Ganser's syndrome, and dissociative identity disorder, as well as in mood disorders, psychoses, and personality disorders. Dissociative symptoms and disorders are observed frequently among patients attending our rural South Carolina community mental health center. Given the prevalence of mental illness in primary care settings and the diagnostic difficulties encountered with dissociative disorders, such illness may be undiagnosed or misdiagnosed in primary care settings.

We developed an intervention model that may be applicable to primary care settings or helpful to primary care physicians. Key points of the intervention are identification of dissociative symptoms, patient and family education, review of the origin of the symptoms as a method of coping with trauma, and supportive reinforcement of cognitive and relaxation skills during follow-up visits. Symptom recognition, Education of the family, Learning new skills, and Follow-up may be remembered by the mnemonic device SELF. We present several cases to illustrate dissociative symptoms and our intervention. Physicians and other professionals using the 4 steps and behavioral approaches will be able to better recognize and triage patients with dissociative symptoms. Behaviors previously thought to be secondary to psychosis or personality disorders may be seen in a new frame of reference, strengthening the therapeutic alliance while reducing distress and acting-out behaviors.

(Primary Care Companion J Clin Psychiatry 2000;2:37-41)

Received Nov. 18, 1999; accepted March 14, 2000. From the Coastal Empire Community Mental Health Center, Beaufort, S.C.

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North American interest in dissociative disorders has surged from the early 1980s to the present. Recent studies in North America found that these disorders have a lifetime prevalence of about 10%; dissociative identity disorder (DID; formerly multiple personality disorder) constitutes only about 1% of that figure.¹ It is estimated that 6% to 10% of the general population experi-

ence episodes of dissociation not secondary to abuse.² The surprisingly high prevalence of dissociative disorders prompts this review.

Coastal Empire Community Mental Health Center (CECMHC), in Beaufort, S.C., serves a 50% white and 50% African American population in a poor, predominately rural part of South Carolina. Many of our center's clients reside on North Carolina's Outer Banks islands and maintain voodoo-derived beliefs in spirits, sorcery, hags (a threatening image that may "ride" an individual), rooting (placing a spell on an individual), and the use of amulets and charms to ward off evil. Voodoo possession, a culturally sanctioned phenomenon occurring in normal individuals, involves trance-like behavior with an alteration of perception, memory, and identity.³ Goodman⁴ holds that glossolalia (speaking in tongues) among religious groups in the region is an artifact of a culturally approved dissociative trance state. Issues of "honor" and a tendency to quickly resort to violence to resolve conflict result in homicide rates among the highest in the United States. The juxtaposition of strong moral-religious and violent, good-versus-evil themes may foster intense conflicting emotions. These issues, combined with high poverty rates and associated early emotional, physical, or sexual abuse or neglect, are associated with the development of dissociative defense mechanisms that may persist throughout individuals' lives.

The frequent occurrence of bizarre symptoms and dangerous acting-out behavior among our patients prompted the development of our approach. Severe acting-out, overt psychosis, or situations involving a danger to self or others may require hospitalization. However, we are often able to manage patients in their natural setting using the SELF (Symptom recognition, Education of the family, Learning new skills, and Follow-up) approach, initiated in the first contact with the patient and/or family.

SYMPTOM RECOGNITION

DSM-IV dissociative disorders are described in Table 1. The DSM-IV⁵ notes that dissociative disorder not otherwise specified (NOS) includes disruption of consciousness, memory, identity, or perception of the environment but does not meet the criteria for any specific dissociative disorder. The affected individual does not have 2 or more distinct personality states or significant amnesia. Dissociative amnesia is an inability to recall important personal information, usually of traumatic nature, that is too exten-

Table 1. General Description of DSM-IV Dissociative Disorders^a

Disorder	Area of Disruption	Description
Dissociative amnesia	Memory	Inability to recall important personal information, usually of a traumatic or stressful nature, too extensive to be explained by ordinary forgetfulness
Dissociative fugue	Memory, identity	Sudden, unexpected travel away from home or one's customary place of work, accompanied by inability to recall one's past and confusion about personal identity or the assumption of a new identity
Dissociative	Identity, memory	Presence of 2 or more distinct identities or personality states that recurrently take control of the identity disorder individual's behavior accompanied by an inability to recall important personal information that is too extensive to be explained by ordinary forgetfulness
Depersonalization disorder	Perception, consciousness	Persistent or recurrent feeling of being detached from one's mental processes or body that is accompanied by intact reality testing

^aAdapted from DSM-IV.⁵

sive to be explained by normal forgetfulness. Amnesia may be localized (surrounding an event), selective (partial), generalized (involving one's entire life), continuous (having a fixed beginning with continuation to the present), or systematized (involving only certain categories of information). The latter 3 types are less common.

Dissociative symptoms occur in acute stress disorder, posttraumatic stress disorder (PTSD), and somatization disorder as well as in alcohol and substance abuse. These dissociative symptoms are usually not manifest within distinct and developed personalities. They may take the form of ego-disruptive behavioral states.⁶ Dissociative disturbances are by definition not due to a substance or a medical condition such as complex partial seizures. They are said to also occur in the face of perceived danger and may begin as early as 6 months of age.⁷

These dissociative disorders encompass dissociation in persons subjected to intense, coercive persuasion. Trance (a state of detachment from one's physical surroundings as in contemplation or daydreaming) and possession trance (replacement of the customary sense of personal identity by a new identity, attributed to the influence of a spirit, power, deity, or other person and associated with stereotyped "involuntary" movements or amnesia) are dissociative phenomena.¹ Loss of consciousness not due to a general medical condition as well as Ganser's syndrome (amnesia and hallucinations of hysterical origin marked by senseless answers to questions and absurd acts) commonly associated with dissociative amnesia or fugue are also included in this diagnostic category.

DID is characterized by the fragmentation of an individual's identity into 2 or more distinct personalities, which recurrently take control of the person's behavior, as well as inability to recall important personal information more extensive than ordinary forgetfulness.⁵ Differential diagnosis in adults includes comorbid disorders, such as somatization disorder, PTSD, seizures, and amnesia. Pseudoseizures and conversion phenomena are both reported to share similar psychological processes with dissociative disorders.^{8,9} Schizophrenia, schizoaffective disorder, and bipolar and unipolar mood disorders must also be ruled out. In fact, dissociative symptoms, disso-

ciative disorder NOS, and DID may all occur in the presence of these diagnoses. Substance abuse populations are reported to have high levels of dissociative experiences, and substance abuse is reported to be high among DID patients.^{10,11}

Ellason et al.,¹² Giese et al.,¹³ and Ganaway¹⁴ all report on the high levels of comorbidity of dissociative disorder NOS and DID with borderline and other personality disorders. Atlas and Wolfson¹⁵ found that borderline adolescents evidenced significant dissociation and depression. These reports suggest that the clinician should be wary of diagnosing discrete dissociative syndromes in the presence of other psychiatric diagnoses.

Dissociative auditory hallucinations, unlike schizophrenic hallucinations, are most often described as "voices in one's head" (rather than outside the individual) talking, arguing, directing, or commenting on one's actions and do not have the "disintegrated quality" and disorganization of schizophrenic hallucinations.¹⁶ In one study,¹⁷ about half of the patients with DID had been diagnosed and treated for schizophrenia. A review of our clinic records confirmed past diagnoses and treatment for both schizoaffective and bipolar disorders among our dissociative patients.

EDUCATION OF PATIENT AND FAMILY

When dissociative features are noted, the patient and family are educated about the symptoms. In our center, these symptoms most commonly involve a dazed or daydreaming state (of which the client is aware or that is observed by others) or a loss of time (the patient may drive or go to a destination without recalling it or knowing why the trip was made) along with other criteria up to and including frank DID features.

Ganaway observed that DID patients "are continually moving in and out of hypnotic trance states."^{14(p208)} He found in a group of 82 individuals that virtually all met special criteria for Spiegel and colleagues' Grade Five Syndrome (highly hypnotizable).¹⁸ The high incidence of trance states ascertained by either history or their emergence in treatment sessions has prompted us to educate

our patients about them in our earliest contacts. Bliss¹⁹ and Butler et al.²⁰ note that the ability to self-induce a trance state is central to development of dissociative symptoms and DID. This is compatible with our clinical experience and supports our cognitive approach with these patients.

Our patients also experience dissociative symptoms in the perceptual area. These include conversion reactions, flashbacks, self-mutilation, depersonalization (feeling outside the self), derealization (setting or people seem unreal), lack of behavioral control such as lashing out at someone without warning, the dissociation of affect (as in acute stress disorder, binge eating, identity confusion or alteration, finding unrecognized possessions, and age regression), and other dissociative symptoms described in the literature.²¹

The origin of the symptoms as a method of coping with past trauma (sexual, physical, or neglect), overwhelming affect, or present boredom, loneliness, interpersonal conflict, or anxiety in a patient's life is explained to the individual and his or her family. We point out that the trance state or other symptoms may be innate or learned and that the patient can, over time, develop more control over these experiences.

Dissociative symptoms may occur in normal individuals in stressful circumstances; these spontaneously improve, but patients may benefit from short-term treatment with an anxiolytic medication. In patients with psychiatric disorders, medication approaches should address the primary disorder. Concurrent diagnoses such as anxiety disorder, depressive disorder, bipolar affective disorder, schizophrenia, or schizoaffective disorder should be managed with anxiolytics, antidepressants, mood stabilizers, or neuroleptics as indicated. For example, our patient in case 1 (see below) was essentially psychotic and self-destructive when interviewed, but benefited remarkably from adequate doses of a neuroleptic medication. Brief psychotherapies for crisis intervention in addition to supportive treatment and medications greatly reduce the anxiety that drives the dissociative symptoms.²²

Dissociative symptoms occur frequently in patients with borderline personality disorder who may be depressed or anxious or experience brief psychotic symptoms, which warrant appropriate medications. Education of the patient and family about the nature of the symptoms and the role of medication will dispel the mystery and sense of helplessness they experience.

LEARNING NEW SKILLS

We educate our patients that they are not "crazy" and can learn to identify the precipitants of trance state or other dissociative phenomena and develop more adaptive coping skills. This involves teaching patients to make a conscious effort to remain in touch with reality and de-

velop new coping skills such as assertion (countering a learned submissive response and expressing his or her own wishes instead), relaxation (a positive use of the autohypnotic trance), and rationalization to deal with stressful situations.

Basic relaxation responses to anxiety include deep inhalation to a count of 4 for 4 breaths. Other self-relaxation approaches include repeating an important word while breathing slowly in and out as well as visualizing a peaceful scene while breathing deeply and quietly.

Ross²² holds that the primary task of the DID patient during childhood is survival through maintaining emotional attachment to an ambivalently held parent-perpetrator by intrapsychic splitting. This is consistent with the development of alternate personalities. The persistence of the attachment need in the adult is seen in the battered spouse who maintains her dependence on the perpetrator at any cost. In treatment, transference and acting out is understood in analytic terms, but cognitive approaches are primary tools. Ross uses the victim-perpetrator-rescuer model and emphasizes that the children identify with the aggressor and, by shifting the bad object inside themselves, feel they potentially have control of the abuse.

Well-defined psychodynamic, cognitive, and hypnotic therapy models for treatment of DID have been developed and described in the literature.^{21,23,24} These approaches comprise integrative techniques, generally involving lengthy dynamic and insight-oriented therapies. Our model differs in offering a structured, brief, crisis-oriented management for the dissociative individual and his or her family.

Clinicians will be aware that these patients often have basic personality issues and conflicts as well as problems with attachment and dependency. However, acute therapy should focus on current stressors, avoiding expression of undue interest in any dramatic symptom presentation. This focus diminishes transference-based elaboration of alternate identities or other dissociative phenomena.

FOLLOW-UP CONTACT

Our follow-up contact consists of brief sessions to determine that symptoms are in remission and to monitor medication effects. We review assertion and relaxation approaches to deal with problems and stress. Recognition and support for progress in dealing with problems is important in these sessions to build confidence. These sessions may be continued at intervals for several months or interrupted with the assurance that the patient may return if necessary.

The physician provides consultation to the patient's social worker, nurse, or other medical professional working with the patient and family as well as ongoing medication management as necessary. Periodic crises with symptom exacerbation are not uncommon; the patient is often strug-

gling with a maladaptive coping style developed over a lifetime. This pattern is recognized in other disorders such as diabetes and congestive heart failure. Undue pessimism is not warranted.

CASE REPORTS

Three cases illustrate our results using the SELF model to engage our patients and modify their behavior over time.

Case 1

A 43-year-old married white woman was treated at CECMHC for DSM-IV major depression and personality disorder NOS, with dependent, borderline, and dissociative features. She had had 4 state hospital admissions in the first year of her treatment in CECMHC because of depressed mood, diminished interest in activities, poor energy, feelings of worthlessness, suicidal ideation, and auditory hallucinations. During a dissociative episode, she slapped her alcoholic husband with no recall of the event. He was actively drinking and had life-threatening liver disease. This along with fear of losing the husband by death and ensuing isolation and financial problems were precipitating factors in the patient's symptomatology.

After 4 years of treatment in our clinic with multiple neuroleptics, minor tranquilizers, antidepressant medications, and supportive management that included participation in an incest group, the patient was noted to have scratches on her extremities that she indicated occurred in a trance state during which she wandered through the woods. She experienced trance states while bowling or during road monotony when driving. Other dissociative phenomena included memory loss for childhood events in general, current time loss, derealization, depersonalization, and periodic behavioral lack of control.

We suggested that she could assume more control of her dissociative symptoms, which began during early sexual abuse by a grandfather, and we described her trances as self-induced hypnotic states that originally protected her from overwhelming trauma. She said our view was reassuring to her, relieving anxiety about the "crazy" nature of the experience, which she recognized was the same state she entered during periods of somnambulism.

We explained to her that several therapies could help her diminish the power of the dissociative responses. She declined participation in group therapy, choosing brief supportive sessions incorporating assertion and relaxation techniques with her case manager and medication (alprazolam, 0.25 mg every 8 hours) monitoring at quarterly intervals. The dissociative symptoms did not resurface during the 3 years since our original discussion.

Case 2

Dissociative symptoms may emerge in the context of active interpersonal or situational difficulties. A demure

42-year-old recently separated black woman with a DSM-IV diagnosis of schizoaffective disorder, bipolar type (symptoms included hypomanic periods, hallucinations, depression, low energy, death wishes, and recent suicide attempt) was taking risperidone, 3 mg twice daily; sertraline, 50 mg daily; and clonazepam, 1 mg twice daily, and presented with a barking, guttural utterance (staccato in nature), yelling obscenities and intimidating remarks ("There's a male demon inside me!").

Between these outbursts, she spoke in a well-modulated voice, expressing concern about her bizarre behavior. We advised that she had charge of the altered state in which the symptoms occurred (a possession trance), and it was suggested that the symptoms would subside. Her altered state was likened to those induced in television performances, under which the hypnotized subjects may engage in behaviors totally unlike their usual demeanors.

Although outbursts occurred initially every few seconds, they abated during our supportive and educational interview, indicating to the patient and her sister (present in the session) how readily the symptoms were modified. Two days later, the patient reported by phone that the symptoms were much improved.

She denied sexual/physical abuse and did not present pervasive, persistent, alternate personalities or other dissociative symptoms subsequent to her possession trance. She resisted group therapy, but continued on treatment with her original medication and in periodic supportive treatment with her case manager with no recurrence of her possession trance. She moved from the area 4 months later. The DSM-IV diagnosis of personality disorder NOS with dependent, avoidant, and dissociative features was added.

If her symptoms had only been secondary to her schizoaffective disorder, the risperidone should have prevented them. A major psychosis should not have remitted so strikingly in one session with supportive and educational approaches.

Case 3

A 33-year-old single black woman who had depressed mood was referred by her probation officer after a charge of shoplifting. The patient stated, "an alternate personality tells me I'm ugly and to hurt myself, drink, take drugs, and steal things." A sutured 6-inch wound on her left shoulder was inflicted at the alternate personality's command. She made the host personality (who presents for treatment over 50% of the time, nearly always bears the legal name, and has certain depressed/anxious features and suffers both psychophysiologic symptoms and time loss or time distortion),²⁵ break a glass in her hand and told her to burn her apartment. The patient saw "a shadow, ghosts, or a man in a tree at night."

The patient denied physical or sexual abuse as a child, although she endorsed many dissociative symptoms, in-

cluding trance states, time loss, depersonalization, the familiar seeming strange, and finding clothes she did not recall purchasing. The patient did not endorse racing thoughts, great confidence or energy, pressure of speech, decreased need for sleep, excessive spending, or irritability, which might suggest a cycling or mixed bipolar state. There was a history of periodic cocaine abuse. A pattern of neglect and isolation in her childhood persisted to the present, and she lived alone in poverty, isolated from her family, enduring her frightening symptoms and the acting out associated with the presence of her alternate personalities.

Because the patient initially had no therapeutic alliance with her psychiatrist and case manager, and because the patient's powerful, sadistic alternate personality could instruct the patient to mutilate herself, we did not initially suggest that the host personality could control the alternate personality or resist her commands. She was advised that she was not "crazy" and could feel better over time. She declined psychoeducational group therapy, but accepted haloperidol, 75 mg intramuscularly every 2 weeks, for her extreme personality fragmentation and mirtazapine, 30 mg daily, for her depression along with supportive management and noted "the medicine makes me [the host personality] strong," although her alternate personality was still present.

Three years later, while she was taking olanzapine, 10 mg daily (because of the onset of tardive dyskinesia on haloperidol), and mirtazapine, 30 mg daily, her dissociative symptoms and depression were in complete remission. She met DSM-IV criteria for personality disorder NOS, with dissociative, borderline, and dependent features.

SUMMARY AND CONCLUSION

Cases similar to those described may be seen in the primary care office or the emergency room. These patients may elect collaborative management in primary care where primary care physicians have good relationships with psychiatrists. Those who have less severe symptoms or presentations related to acute stress or loss may only need the supportive care and patient education that informed primary care clinicians could provide. Spiegel and colleagues¹⁸ note that better outcomes may be expected in individuals with higher levels of ego integration, greater psychological mindedness, and better ability to restrain acting-out impulses.

The 3 patients presented above had limited ego strength and insight and were impulsive, but all remained in supportive and medication therapy over months to years, voicing benefit from their treatment. Patients with dissociative symptoms may be seen by physicians in any specialty; addressing their symptoms using the SELF model reassures the patient and family, enhances trust, and may reduce treatment resistance and acting out.

Drug names: alprazolam (Xanax and others), clonazepam (Klonopin and others), haloperidol (Haldol and others), mirtazapine (Remeron), olanzapine (Zyprexa), risperidone (Risperdal), sertraline (Zoloft).

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Munchausen Syndrome by Proxy: A Clinical Vignette

Robert G. Zylstra, Ed.D., L.C.S.W.; Karl E. Miller, M.D.;
and Walter E. Stephens, M.D.

Munchausen syndrome by proxy is the act of one person fabricating or inducing an illness in another to meet his or her own emotional needs through the treatment process. The diagnosis is poorly understood and controversial. We report here the case of a 6-year-old boy who presented with possible pneumonia, nausea, vomiting, and diarrhea and whose mother was suspected of Munchausen syndrome by proxy.

(*Primary Care Companion J Clin Psychiatry* 2000;2:42-44)

Received Feb. 11, 2000; accepted Feb. 22, 2000. From the Department of Family Medicine, Chattanooga Unit, University of Tennessee College of Medicine, Chattanooga.

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Munchausen syndrome by proxy, the act of one person fabricating or producing an illness in another in order to meet his or her own emotional needs via the treatment process, is a poorly understood and controversial diagnosis. While many refer to it as a psychiatric disorder, described by DSM-IV¹ provisional research criteria as an extreme manifestation of factitious disorder by proxy (Table 1),^{2,3} others argue strongly that it is more accurately described as medical abuse.^{4,5} Proponents of the psychodynamic perspective describe victims as the object used to regulate the perpetrator's "... intensely ambivalent but often destructive relationship with a physician."^{3(pS110)} While acknowledging psychopathologic comorbidity, proponents of the medical abuse position state that perpetrators "... engage in the behavior willingly, not under the influence of some uncontrollable impulse and with full knowledge that it is wrong."^{5(p773)} We describe the case of a 6-year-old boy whose mother was suspected of Munchausen syndrome by proxy.

CASE PRESENTATION

A 6-year-old boy was seen in a physician's office for possible pneumonia. According to his mother, the child had been coughing and wheezing for the past 6 days. In

addition, the mother stated that the child had a temperature of 103.9°F (39.9°C), decreased oral intake for the last 3 days, and decreased urine output for 2 days. The child had been treated with home albuterol nebulizers and antibiotics for 3 days. Over the last 24 hours, the child developed nausea, vomiting, and diarrhea. A sibling in the house had been diagnosed with bronchitis.

The child's past medical history included neurofibromatosis, asthma, seizure disorder, attention-deficit/hyperactivity disorder, and pneumonia. The child had a prior workup that showed negative results for hyperglycemia. Current medications included methylphenidate, 20 mg twice per day; the albuterol nebulizer treatments; and amoxicillin, 250 mg 3 times per day. He had no known drug allergies.

Family history was positive for a mother with neurofibromatosis and insulin-dependent diabetes mellitus. There was also a family history of asthma. The child lived with his parents and 1 sister. There were no smokers in the household, but there was an inside dog. They had central heat, and the boy's immunizations were current.

Physical examination revealed a well-nourished, well-developed, lethargic, and ill-appearing boy who was uncooperative and somnolent during the initial examination. His temperature was 96.5°F (35.8°C), pulse rate was 129 beats per minute, blood pressure was 116/56 mm Hg, and respiratory rate was 28. His eyes had a disconjugate gaze, but the remainder of the HEENT examination was normal. Results of cardiovascular examination were normal, and his lungs were clear to auscultation with no wheezing noted. Although the neurologic examination was difficult to assess secondary to the child's lethargy, he did move all extremities. His skin showed multiple café-au-lait areas and was extremely diaphoretic.

Initial laboratory evaluation revealed a white blood cell count of 16,200/mL (normal range, 3500-10,000/mL), plasma sodium level of 140 mmol/L (normal range, 135-145 mmol/L), plasma chloride level of 106 mmol/L (normal range, 98-107 mmol/L), plasma potassium level of 2.3 mmol/L (normal range, 3.5-5.0 mmol/L), plasma carbon dioxide level of 20 mmol/L (normal range, 22-28 mmol/L), normal serum urea nitrogen and creatinine levels, and a plasma glucose level of 31 mg/dL (normal range, 60-110 mg/dL). Owing to mental status concerns,

a computed tomography scan of the head was performed with normal results. The child was admitted for further evaluation.

Following multiple injections of intravenous (i.v.) glucose during the first 3 hours after admission, the child's blood sugar rose appropriately, only to fall again shortly after the physician left the room. The patient's blood sugar level then normalized for the next 48 hours. On day 3, the child's mother was informed that administration of i.v. glucose was being discontinued. That night, the child's blood sugar level dropped into the high 40s despite repeated attempts to treat with i.v. solutions. Curiously, once the day shift started, the child's blood sugar level again normalized.

Very early the next morning, the child's blood sugar level once again dropped, this time into the 30s, with poor response to appropriate measures. Growth hormone, cortisol, insulin, C peptide, and lactate levels were measured. The child's blood sugar level continued to fluctuate despite aggressive management. Of interest is that at one time during this episode, the i.v. tubing was noted to be leaking. Upon inspection, the tubing had a hole that looked like it was created by a needle.

Once the blood sugar level normalized again, dextrose was removed from the i.v. solution. Without the mother's knowledge, however, the i.v. bag was intentionally mislabeled to suggest ongoing dextrose administration. The child's subsequent blood sugar levels remained normal.

Suspicions that the mother was injecting some of her insulin into the child's i.v. access were triggered by the fact that her son's abnormally low blood sugar levels occurred only when she was in the room. The mother also voiced concern that her child was becoming a diabetic just like her, and the child knew how to perform his own finger prick for glucose monitoring. Behavioral aberrations on the part of the mother were also noted, as evidenced by her remaining curled up in a fetal position on the parent's bed during her child's most severe hypoglycemic episode.

On the fifth day of admission, the mother was removed from the room and the child's blood sugar level subsequently remained normal. Laboratory results received that day from analysis of blood drawn on day 3 showed an insulin level of 9776 $\mu\text{U}/\text{mL}$ (normal range, 5–25 $\mu\text{U}/\text{mL}$) and a C peptide level of 0.5 ng/mL (normal range, 0.8–4.0 ng/mL). The mother subsequently expressed concern about her child's blood sugar level and confessed to covert administration of insulin. The child was removed from the mother's custody and made a full recovery.

DISCUSSION

Although Munchausen syndrome by proxy has alternately been described as "a rare psychiatric disorder"² and "more common than previously believed,"³ it is clearly a

Table 1. DSM-IV Research Criteria for Factitious Disorder by Proxy^a

- A. Intentional production or feigning of physical or psychological signs or symptoms in another person who is under the individual's care.
- B. The motivation for the perpetrator's behavior is to assume the sick role by proxy.
- C. External incentives for the behavior (such as economic gain) are absent.
- D. The behavior is not better accounted for by another mental disorder.

^aAdapted with permission from the American Psychiatric Association.¹

serious and potentially life-threatening situation for the victim, with a mortality rate approaching 10%.⁶ Treatment success rates for perpetrators are notoriously poor.^{3,5}

Perpetrators of Munchausen syndrome by proxy are typically mothers, and the victims are usually their young children, although fathers have been identified as perpetrators, and elderly individuals have been victims. The most common illness presentations are seizures, failure to thrive, vomiting and diarrhea, asthma and allergic reactions, and infections.⁶ These initial assaults are typically compounded by subsequent painful medical procedures performed in an effort to diagnose and treat what appears to be a most perplexing and elusive medical condition.

Typical warning signs of Munchausen syndrome by proxy include^{7,8}

1. Persistent or recurrent illness that cannot be explained
2. Discrepancies between clinical findings and history
3. Symptoms that occur only when the mother (or suspected perpetrator) is present
4. Symptoms or treatment course that is not clinically consistent
5. A working diagnosis that is less plausible than Munchausen syndrome by proxy
6. A mother who welcomes even painful medical tests for her child, is constantly at the bedside, and has previous medical experience, yet seems less concerned than the medical staff about the health of her child
7. Family history of sudden or unexplained infant death

It is important, however, to differentiate Munchausen syndrome by proxy from similar concerns. Munchausen is not to be confused with⁹

1. Anxiety resulting in excessive but nonabusive care for a child
2. Noncompliance resulting in a child's persisting or worsening illness
3. Malingering with the goal of some external gain (e.g., financial benefits)

In attempting to diagnose Munchausen syndrome by proxy, it is helpful to separate the mother (or suspected perpetrator) from the child (or other victim) and evaluate for symptom continuation. This separation may also prove to be an important first step in protecting the victim from further injury, which is of primary importance. While referral to additional treatment specialists may be of value, overall review of the case history by a physician unfamiliar with the patient may help clarify concerns regarding possible abuse. Medical professionals, trained to provide supportive care for patients and their families, are particularly vulnerable to deceitful parents who give the appearance of being exemplary caregivers.

Evaluation of previous medical records for the patient and any siblings may suggest illness patterns. A detailed social history can be helpful in identifying dysfunctional family dynamics, and involvement of a multidisciplinary treatment team can be instrumental in further assessing the situation and initiating any necessary legal action. As always, it is important to carefully and objectively document all findings in the medical record.

Drug names: albuterol (Proventil and others), amoxicillin (Amoxil and others), methylphenidate (Ritalin and others).

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Divalproex Sodium Versus Valproic Acid in Hospital Treatment of Psychotic Disorders

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Background: Approximately 50% of pharmacy prescriptions in the United States are filled with generic drugs, which have improved substantially in quality owing to increased governmental regulations. The remaining medicoeconomic question regards whether or not brand-name medications are worth the price. This study evaluates these questions for the brand-name mood stabilizer divalproex sodium and its generic counterpart, valproic acid.

Method: We conducted a retrospective chart review of all patients who had been taking divalproex and had been switched to valproic acid at 2 local mental health facilities in 1997. Data collected from the inpatient- and day-treatment charts for these 28 patients included dose, duration, side effects, and efficacy (determined using retrospective chart review and the Clinical Global Impressions scale [CGI]) of divalproex sodium compared with valproic acid treatment.

Results: *t* Tests for dependent samples revealed that valproic acid was administered at higher doses than divalproex sodium, but these treatments did not differ in efficacy on the basis of CGI scores. Fisher exact test analyses revealed a trend toward more nausea with valproic acid; also, the combination of nausea, abdominal discomfort, and diarrhea occurred more often in valproic acid-treated patients. There were no differences in the discontinuation of either medicine because of side effects, or in the use of medications to treat gastrointestinal side effects. Efficacy was similar for valproic acid and divalproex sodium. There was no single, significant side effect increase for valproic acid; however, when grouped together, gastrointestinal side effects were statistically significantly increased in valproic acid-treated patients. This appears clinically insignificant because of the lack of difference in drug discontinuation rate or gastrointestinal medication use.

Conclusion: Given these results and that valproic acid is much less expensive than divalproex sodium, valproic acid appears to be a satisfactory substitution for divalproex sodium in the treatment of frequently hospitalized psychotic patients.

(Primary Care Companion J Clin Psychiatry 2000;2:45-48)

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Choosing and tailoring cost-effective pharmacologic treatments for patients has been an area of interest for many years. When treating an individual for a specific condition, the clinician must choose a treatment that will improve the condition, achieving the best clinical outcome at the lowest cost. This approach is necessary to satisfy patients while minimizing the cost of health services. The advent of managed care has increased the emphasis on evaluating the economics of treatment options, which requires a better understanding of available treatment resources.

The use of generics instead of brand-name drugs has contributed to a decrease in medical spending.¹ This medicoeconomic issue has been extensively researched, especially in psychiatry. For example, the use of generic lithium as a treatment for bipolar disorder has saved \$4 billion in the United States.²

The U.S. Food and Drug Administration (FDA) approved valproic acid in 1978 for the treatment of seizure disorder and approved divalproex sodium, its enteric-coated counterpart, in 1986 for the same indication. Few issues were raised in the use of these medications for seizure control; therefore, few studies were performed to compare them when the latter drug was introduced. These drugs had been studied in the past, and their anticonvulsant efficacies were equivalent. One study found valproic acid to be economically superior to divalproex sodium,³ even when their differences in pharmacokinetic and side effect properties were considered.^{4,5}

These differences have raised concerns about the use of valproic acid and divalproex sodium, since the costs of these drugs differ significantly. The cost of drugs is particularly important when treating psychiatric illnesses, which contribute significant and burdensome costs to most health care systems. As with other comparisons of generics and brand-name medications, whether 1 of these 2

mood-stabilizing drugs is more cost effective should be determined.

One recent review found that the side effects of valproic acid are so severe that the expense of divalproex sodium is warranted.⁶ However, a review of the literature provided scarce data comparing valproic acid and divalproex sodium for cost-effectiveness. Therefore, this study was designed to investigate the impact of generic substitution of valproic acid for divalproex sodium at a local state psychiatric hospital and an outpatient continuing day program. The hospital switched from divalproex sodium to valproic acid to cut costs, hoping that valproic acid would be as effective as divalproex sodium. The hospital assumed that the incidence of side effects would be higher with valproic acid, but that these could be ameliorated with lower-cost gastrointestinal (GI) medications. Hypotheses included the following: (1) efficacy would be equivalent in patients who could tolerate therapeutic doses of either medication, (2) effective doses of valproic acid and divalproex sodium would be equal on a per-patient basis, (3) the noncompliance and dropout rates for valproic acid would be higher because of side effects, and (4) valproic acid-treated patients would have a higher concomitant use of GI medications. This study was designed to determine if this generic substitution was worthwhile and cost-effective.

METHOD

A local state psychiatric hospital, Hutchings Psychiatric Center (Syracuse, N.Y.), switched all inpatients who were taking the brand-name drug divalproex sodium to the generic valproic acid in 1997. In addition, intensively treated outpatients treated in the Cattaraugus County Continuing Day Treatment Program (Olean, N.Y.) were also switched. We performed a retrospective chart review of all of the patients who were involved in this switch. Data on dosage, frequency, blood drug levels, adverse effects, use of GI medications, diagnosis, and efficacy were collected. Efficacy was measured on the basis of relapse of symptoms, hospital admission recidivism, and Clinical Global Impressions scale (CGI) scores for each treatment by reviewing all chart notes during the study period. The CGI is a 7-point rating scale ranging from "very much worsened" to "very much improved" and relates to the clinical change of each patient.

Patients switching from divalproex sodium to valproic acid initially received valproic acid at the same dosage and dosing frequency as with divalproex sodium. Doses were usually divided for inpatients. The dosage of valproic acid was then adjusted for each patient on the basis of his or her response. Any use of medications to treat valproic acid-related side effects was noted.

Compliance was near 100%, since most patients were in inpatient wards and drug use was monitored. Blood

Table 1. Demographics of Patients Switched From Divalproex Sodium to Valproic Acid (N = 28)

Variable	N	%
Gender		
Male	11	39.3
Female	17	60.7
DSM-IV diagnosis		
Schizophrenia		
Undifferentiated	5	17.9
Paranoid	4	14.3
Disorganized	2	7.1
Residual	1	3.6
Schizoaffective disorder	8	28.6
Bipolar disorder	5	17.9
Dementia not otherwise specified	1	3.6
Major depressive disorder	2	7.1

levels and discontinuation rates were obtained through chart laboratory sheets and order sheets, yielding a statistical comparison between divalproex sodium and valproic acid treatment. Statistical analyses were performed on the collected data using standard software (StatSoft, Tulsa, Okla.). Dependent t tests and Fisher exact test analyses were run where appropriate.

RESULTS

Charts of 28 patients were reviewed. Eleven (39%) were male and 17 (61%) were female. Table 1 shows patient demographics and DSM-IV diagnoses. Schizoaffective disorder was the most common diagnosis, followed by undifferentiated schizophrenia and bipolar disorder. Patient age ranged from 23 to 75 years (mean \pm SD = 45.64 \pm 13.37 years).

The mean \pm SD dose of divalproex sodium before switching to valproic acid was 1205 \pm 646 mg/day, and the mean dose of valproic acid after switching was 1554 \pm 1021 mg/day; this difference was statistically significant (Table 2). Duration of treatment on divalproex sodium was 0.25 to 60 months (mean = 15.30 \pm 15.79 months). Duration of valproic acid after the switch from divalproex sodium ranged from 0.30 to 12 months (mean = 7.21 \pm 3.90 months). Blood divalproex sodium levels ranged from 32.0 to 107.0 mg/dL (mean = 68.39 \pm 19.94 mg/dL). Blood valproic acid levels after the switch from divalproex sodium ranged from 16.0 to 95.0 mg/dL (mean = 64.36 \pm 19.73 mg/dL). Olanzapine (N = 12), clonazepam (N = 7), and risperidone (N = 5) were the most commonly coprescribed standing medications in this population. Only 10 other standing nonpsychiatric prescriptions were given to these patients, and only 1 of these was a medication for GI problems.

CGI scores were similar for both groups: 2.75 \pm 0.93 and 2.93 \pm 1.05 for divalproex sodium and valproic acid, respectively, revealing insignificant clinical changes with the switch from divalproex sodium to valproic acid. Side effects were minimal when addressed separately. There

Table 2. Dosing and Efficacy of Divalproex Sodium Versus Valproic Acid (N = 28)^a

Variable	Divalproex Sodium	Valproic Acid	t	df	p Value
Dose, mg/d					
mean ± SD ^b	1205 ± 646	1554 ± 1021	-2.07	27	.048
CGI score,					
mean ± SD	2.75 ± 0.93	2.93 ± 1.05	-1.04	27	.305
No. of discontinuations	5	5			1.000 ^c
No. of GI medications prescribed	0	1			.500 ^c

^aAbbreviations: CGI = Clinical Global Impressions scale, GI = gastrointestinal.

^bSignificant difference between divalproex sodium and valproic acid.

^cFisher exact test p value.

was a trend toward increased nausea in valproic acid patients. When all GI side effects were combined, however, there was a significant increase in side effects with valproic acid compared with divalproex sodium (Table 3). Five patients (18%) discontinued divalproex sodium treatment and 5 (18%) stopped valproic acid treatment (no significant difference; see Table 2). No differences were found between groups in concurrent use of GI medications such as antacids (see Table 2).

DISCUSSION

In many fields of medicine, including psychopharmacology, pressures exist to find the best drug for the lowest price. The use of generic drugs is increasing, and the high quality of many generic drugs has been documented. Many new psychopharmacologic agents are not yet available generically, but many of the common mood stabilizers are available as generics, including lithium, carbamazepine, and valproic acid. However, few published studies have compared the brand-name mood stabilizer divalproex sodium with its generic counterpart, valproic acid.⁷⁻⁹ Most clinicians consider divalproex sodium to be the first-line treatment for bipolar disorder, but it is much more expensive than valproic acid. Similarly, divalproex sodium is becoming a first-line medication for use in impulsive and agitated patients, rather than as-needed neuroleptics.

At Hutchings Psychiatric Center in 1998, one hundred 250-mg tablets of divalproex sodium cost \$67.00, whereas one hundred 250-mg tablets of valproic acid cost \$6.00, a 121-fold difference. These data suggest that the cost of divalproex sodium (\$1162.80 per patient per year) is not justified because valproic acid is as effective (at \$133.20 per patient per year). In addition, the side effect profile of valproic acid in this patient sample was statistically worse in some instances, but the difference was clinically less significant in that discontinuations and GI medication use were similar for both drugs. The generic

Table 3. Side Effects of Divalproex Sodium and Valproic Acid (N = 28)^a

Variable	Divalproex Sodium	Valproic Acid	Fisher Exact Test p Value
GI side effects			
Nausea	0	4	.0557
Abdominal discomfort	0	3	.1182
Diarrhea	0	1	.5000
Total GI side effects ^b	0	8	.0022
Sedation	2	0	.4909
Tremors	1	1	.7545
Weight gain	0	0	1.000
Hair loss	1	0	.5000

^aAbbreviation: GI = gastrointestinal.

^bSignificant difference between divalproex sodium and valproic acid.

substitution of valproic acid for divalproex sodium appears clinically acceptable in this population of severely and chronically ill patients.

Significantly higher doses of valproic acid than those of divalproex sodium were required to achieve the same therapeutic response. Valproic acid is metabolized more rapidly than divalproex sodium, which could explain the need for higher doses. However, even at higher doses, treatment with valproic acid is still less expensive than with divalproex sodium because of the difference in price.

This study has some limitations. The sample size is small, and significant differences in clinical improvement and side effect rates may evolve with larger numbers of patients. As with all retrospective reviews, charting may have been incomplete; some mild side effects and clinical changes may have been omitted, which might have obscured differences in CGI scores and side effect ratings.

Blinding of chart reviewers was impossible because the medications were named frequently in the charts. Some patients may have been switched from divalproex sodium to valproic acid early in the treatment course, resulting in a lower efficacy rating for divalproex sodium. This does not seem to have occurred, given the average divalproex sodium treatment of 15 months. Fifteen months with therapeutic blood levels also constitutes a very thorough therapeutic trial. Additionally, many more side effects would be expected in the patients receiving higher doses of valproic acid later in the course of treatment, but this did not occur, showing reasonable tolerability of valproic acid. Noncompliance was not a problem with this population, since most patients were hospitalized. Because valproic acid usually requires multiple doses per day, and because a trend occurred toward increased GI side effects, compliance and effectiveness might be decreased in less severely ill outpatients. A larger sample size, prospective charting, better use of outcome measures and rating scales, and standardization of treatment regimens are improvements that could be instituted in another study, but were not possible because of the retrospective design of this study.

Despite these limitations, this study lends further input to the existing literature in determining the cost-effectiveness of treating patients with valproic acid or divalproex sodium. For example, the above findings replicate those of Sherr and Kelly's prospective study,⁹ in which a similar therapeutic switch maintained efficacy with good tolerability. Similarly, we hypothesized that divalproex sodium and valproic acid would be equally effective and that valproic acid would have a higher rate of side effects. This hypothesis was partially correct: valproic acid and divalproex sodium appear to have equivalent efficacy in the treatment of hospitalized, chronically psychotic patients. Surprisingly, contrary to the literature, the side effect profile of valproic acid does not appear clinically significantly different since discontinuation rates in the 2 groups were similar. The results of this study suggest that valproic acid is an adequate generic or substitutive agent for the treatment of inpatient psychiatric patients: it costs less than divalproex sodium and produces a similar treatment outcome.

Drug names: carbamazepine (Tegretol and others), clonazepam (Klonopin and others), divalproex sodium (Depakote), lithium (Eskalith and others), olanzapine (Zyprexa), risperidone (Risperdal), valproic acid (Depakene and others).

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Psychiatric and Somatic Markers of Anxiety: Identification and Pharmacologic Treatment

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Anxiety disorders are widely prevalent but insufficiently recognized and inadequately treated in primary care practice. The annual costs of morbidity and mortality of these disorders approach \$50 billion, substantially more than costs for schizophrenia or all affective disorders combined. Somatization of anxiety contributes to the challenges of making an accurate diagnosis and to the indirect costs associated with delaying appropriate treatment. Pharmacologic interventions give clinicians the necessary tools to treat anxiety safely and effectively. Former therapeutic choices were limited to benzodiazepines, buspirone, and older antidepressants, but newer anxiolytic agents have become available. The selective serotonin reuptake inhibitors and agents with dual reuptake inhibition, such as venlafaxine XR, are optimizing therapy and yielding less risk for serious adverse events, greater safety in long-term therapy, and opportunity for improved patient compliance. These newer antidepressants provide substantial efficacy in patients with comorbid anxiety and depression, commonly seen in the primary care setting.

(*Primary Care Companion J Clin Psychiatry* 2000;2:49-54)

Received March 13, 2000; accepted March 20, 2000. From the Department of Psychiatry, Arizona Health Sciences Center, Tucson.

Supported by an unrestricted educational grant from Wyeth-Ayerst Laboratories, Philadelphia, Pa.

Financial disclosure: Dr. Gelenberg has received grant/research support from Bristol-Myers Squibb, Organon, Pfizer, Lilly Research Laboratories, Janssen, Merck Sharp & Dohme, SmithKline Beecham, Wyeth-Ayerst, Hoechst Marion Roussel, and Forest Laboratories; is on the speakers' bureaus for Bristol-Myers Squibb, Pfizer, SmithKline Beecham, Janssen, Lilly, Forest Laboratories, and Parke-Davis; has stock or other ownership interest in Pfizer, Warner-Lambert, and Eli Lilly; and has received consultant fees from Eli Lilly, SCIOS, Forest Laboratories, Parke-Davis, Pfizer, Janus Pharmaceuticals, Best Practice, and Bristol-Myers Squibb.

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Anxiety disorders are a diverse range of psychiatric conditions (Table 1) characterized by clinically significant levels of worry, apprehension, or panic that occur in the absence of or out of proportion to specific causes (such as physical danger or public speaking) that are normally associated with such feelings.¹⁻³ The emotional distress of anxiety is often accompanied by specific physical symptoms associated with a state of autonomic arousal, such as sweating, dizziness, and shortness of breath (most notable in patients with panic attacks), or more generalized somatic complaints, such as insomnia, restlessness, and muscle aches (commonly found in patients with generalized anxiety disorder [GAD]).¹⁻³ Other primary anxiety disorders include phobic disorders (social or specific), obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and acute stress disorder. In addition, many medical conditions are associated with anxiety, particularly among older patients; these include neurologic conditions, thyroid dysfunction, and cardiovascular disease.^{1,4} Drug use or abuse, including benzodiazepine (BZD) and alcohol withdrawal or intoxication, also have been linked to clinically significant anxiety that should be distinguished carefully from medically related causes¹ before a course of treatment is considered.

It is estimated that approximately 27 million Americans have an anxiety disorder at some time in their lives.⁵ In a recent screening study conducted in the United States,⁶ the lifetime prevalence of a diagnosable anxiety disorder was 23.9% in a primary care setting. This figure concurs with data from the National Comorbidity Survey,⁷ which showed a lifetime prevalence of 24.9%. Among the categories of anxiety disorders,¹ specific phobias appear to be the most common, with a lifetime prevalence of 9.8%, and OCD is the least common, with a lifetime prevalence of 2.3%.⁶ In general, the prevalence of anxiety disorders is higher in people younger than 65 years than in their older counterparts. Rates are also higher in women than in men, although the difference is much less pronounced for OCD, in which the rates in men are almost equal to those in women.⁸

Appropriate screening, diagnosis, and treatment are particularly important because a large proportion of patients with anxiety disorders will be seen initially by a generalist physician in the primary care setting.⁶ These patients often present a number of clinical challenges. In

Table 1. DSM-IV Classification of Anxiety Disorders^a

Panic disorder (with or without agoraphobia)
Agoraphobia without a history of panic disorder
Specific phobia
Social phobia
Obsessive-compulsive disorder
Generalized anxiety disorder
Posttraumatic stress disorder or acute stress disorder
Anxiety disorder due to a general medical condition or substance-induced anxiety disorder
Anxiety disorder not otherwise specified

^aFrom the American Psychiatric Association.¹

general, patients with anxiety fare substantially worse than patients with other psychiatric conditions, such as depression, even when they receive an accurate diagnosis and appropriate treatment.⁹ Because both anxiety and depression commonly manifest as nonspecific distress (e.g., mild sleep or appetite disturbances), it is not unusual for anxious patients seen in the primary care setting to receive a misdiagnosis of depression.^{6,10} This finding is further complicated by the fact that patients with long-standing anxiety may develop symptoms of depression over time.⁹ However, anxiety disorders generally can be distinguished from depressive states. In anxiety states, increased vasomotor responsiveness, as well as panic attacks, phobias, derealization, and perceptual dysfunctions, are frequently seen.⁹ In contrast, the general affect in depression is mostly negative, often associated with loss of interest and pleasure (anhedonia), hopelessness, emotional withdrawal, and fatigue.¹⁰ However, as we shall see, the diagnostic distinction between anxiety disorders and depression has become less important as the treatments have become more similar.

SOMATIZATION OF ANXIETY AMONG PRIMARY CARE PATIENTS

Somatization refers to the phenomenon in which patients experience and express their feelings or emotions through physical complaints and distress.¹¹ This phenomenon may result from a variety of cultural, familial, and personal circumstances, including biases against expressing psychological discomfort.¹² Patients may fear being stigmatized if they are labeled with a psychiatric disorder, or they may be concerned about their physician's response to nonsomatic complaints.¹³ Although the term *somatization* is generally used, it needs to be differentiated from *somatization disorder*, which is recognized as a distinct clinical psychiatric disorder.¹ A study in 425 primary care patients found that anxiety disorders were associated with a significantly higher rate of comorbid somatization disorder than that observed in the absence of anxiety disorders.⁶

Symptoms typically associated with somatization of anxiety and other psychiatric disorders include abdominal

pain, dyspepsia, chest pain, fatigue, dizziness, insomnia, and headache.^{12,14,15} Such symptoms, occurring either alone or in various combinations, are among the most common reasons for nearly half of all primary care visits among the general population.¹⁵ A study in 1000 primary care patients found that at least 1 of these symptoms was reported by 38% of the patients, but in only 16% did the symptoms correlate with an organic disease over a 3-year period.¹⁴ Other data, also derived from a primary care population, suggested a strong association between the number of medically unexplained symptoms experienced by patients and the likelihood of a concurrent anxiety or depressive disorder.¹⁵ For example, if 7% of patients with 2 or 3 physical symptoms were found to have a diagnosable anxiety disorder, the incidence almost doubled (13%) in those with 4 or 5 somatic complaints and increased to 48% in patients with 9 or more physical symptoms.¹⁵

In the primary care setting, somatization of anxiety has important implications for identifying patients who have an anxiety disorder. It has been estimated that as many as 53% of patients who meet the criteria for a psychiatric disorder may receive an incorrect diagnosis in this setting.¹⁶ Clinicians may falsely attribute the somatic complaints to an underlying medical condition or, when diagnostic tests reveal no organic cause for the symptoms, may fail to look for a psychiatric cause. In a study conducted in Great Britain,¹⁷ primary care physicians were able to diagnose anxiety, depression, or both significantly more often in patients who had psychiatric symptoms than in patients who had only somatic complaints. A similar study in the United States showed that only 22% of anxious or depressed patients with somatic manifestations received correct diagnoses by their family physicians, compared with 77% of patients who had psychiatric symptoms.¹⁸ These data suggest that patients' somatic complaints may often lead to an overlooked diagnosis of anxiety as the primary source of the discomfort.

Another confounding factor in the timely and accurate diagnosis of anxiety is the high rate of medical and psychiatric comorbidity in patients with anxiety. Depression may occur in as many as 60% of patients with GAD or panic disorder.¹⁹ In some cases, this comorbidity may manifest as mixed anxiety-depression, a condition that is characterized by subsyndromal levels of both anxiety and depression.¹ Comorbid anxiety and depression is associated with significantly greater psychopathology and early withdrawal from treatment than either disorder alone.¹⁹ In addition, coexisting depression and anxiety portends a worse prognosis, with less robust responses to treatment and a greater risk of suicide, than either disorder alone.^{6,20}

Aside from the presence of unexplained somatic complaints and the high rate of psychiatric comorbidities, anxiety is also frequently associated with comorbid medical illnesses. Anxiety itself may be a factor in provoking or maintaining medical conditions or diseases.¹³ A survey

of primary care patients found that those who experienced panic attacks had a significantly higher rate of hypertension than those who did not.¹³ Left untreated, anxiety may prolong or worsen a medical illness.²¹

Not surprisingly, undiagnosed or misdiagnosed anxiety is a major contributor to high use of health care resources and excessive health care costs, even after adjusting for comorbid medical conditions.²² Data collected in 1990 indicated that the total costs of anxiety disorders in the United States, including direct costs for hospitalizations and professional services and indirect costs related to morbidity and mortality, reached approximately \$46 billion, one third of the total cost for all mental disorders.²³ These costs associated with anxiety disorders were higher than those for schizophrenia (\$32 billion), affective disorders (\$30 billion), and other combined mental disorders (\$38 billion). The greatest proportion of the cost of anxiety (nearly three quarters) is attributed to lost or reduced productivity, and the remainder is attributed to the direct costs of medical treatment.⁵

Somatization also contributes to the high cost of anxiety. Medical workups can be extensive and delay treatment of symptoms. Anxious patients may undergo unnecessary tests or procedures and be referred to various medical specialists before an appropriate psychiatric consultation is sought or a diagnosis is made.¹³ High users of health care resources are substantially more likely to have an underlying anxiety disorder: as many as 40% have a lifetime history of GAD, and 20% have somatization disorder.²⁴ High medical-resource utilization and overall costs may be especially problematic in patients with panic disorder because of the somatic symptoms such as tachycardia and hypertension associated with a panic attack. These patients are often referred for costly cardiovascular or neurologic tests such as Holter monitoring, exercise testing, angiography, magnetic resonance imaging, or electroencephalography.¹² In addition, the use of health care resources and loss of productivity are significantly higher in patients with an anxiety disorder and a comorbid medical or psychiatric condition.²⁵ Therefore, prompt recognition and treatment of anxiety by the primary care physician would help reduce the total cost associated with this disorder.

TREATING ANXIETY: OPTIONS FOR THE PRIMARY CARE PHYSICIAN

For many years, pharmacologic therapy for anxiety disorders was dominated by the use of BZDs, buspirone, the older tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs).^{26–34} More recently, newer types of antidepressants have emerged as promising alternatives for the treatment of anxiety, as a result of their robust efficacy (particularly in patients with comorbid anxiety and depression), improved safety profiles, and

ease of use.^{33,35–44} The following sections review these agents from a clinical perspective on dose-response potential, drug-drug interaction profiles, and adverse effects.

Traditional Anxiolytic Agents

Benzodiazepines. The BZDs have a rapid onset of action, which becomes clinically apparent within the first week of therapy.²⁸ Many currently available BZDs appear to have equivalent anxiolytic efficacy.²⁷ However, many clinicians favor drugs with relatively short half-lives—such as alprazolam, lorazepam, and oxazepam—over longer-acting agents because of their lower risk of sedation, psychomotor impairment (an effect that is enhanced by the intake of alcohol), and amnesic effects, probably as a result of less drug accumulation.^{26,27} On the other hand, drugs with long half-lives are less likely to produce an intense discontinuation syndrome, a well-characterized reaction in patients who stop therapy with BZDs, which may include symptoms such as rebound anxiety, nervousness, insomnia, restlessness, and depression.^{26,28,29} The duration of therapy and the rate at which the dosage is tapered off appear to contribute to the likelihood or severity of withdrawal symptoms.²⁹ These effects substantially limit the use of BZDs in the primary care setting. Physical dependence and pharmacologic tolerance are additional risks of therapy with BZDs, particularly over the long term. Therefore, continuous treatment with BZDs requires clinical reevaluation for gradual reduction and discontinuation.^{27,29}

Aside from alprazolam, for which higher plasma concentrations correlate with improved clinical response, no clear dose response has been demonstrated for the BZDs. Typical dosage ranges for healthy adults are 0.75 to 4.0 mg/day for alprazolam (dosages of 1.5–10 mg/day are often used in patients with panic disorder), 2 to 6 mg/day for lorazepam, and 30 to 120 mg/day for oxazepam.²⁷ Therapy should be initiated at the lowest possible dosage, to minimize the risk of adverse effects, and should be tailored to patients' clinical and medication history, age, body size, and state of physical health.²⁷

The duration of treatment and the dosing pattern also should be individualized. Once-daily dosing would encourage patients to comply better with treatment. Intermittent therapy may be adequate in patients with intermittent symptoms or symptoms triggered by identifiable anxiety-provoking situations. Patients experiencing persistent symptoms characteristic of an anxiety disorder, such as GAD, may require more sustained courses of therapy²⁷ with an agent carefully selected for its efficacy and safety properties for each individual patient.⁴⁵ Particular care should be exercised when using BZDs in older patients and those with organ dysfunction. Drug clearance of longer-acting agents may be impaired with age, hepatic disease, or the concomitant use of estrogens or cimetidine.²⁶

Bupirone. Since bupirone became available in the late 1980s, it has been used as an alternative to BZDs in certain patients. This agent appears to be somewhat more effective in reducing the psychological symptoms of anxiety than it is in treating somatic complaints, and it appears to have dose-related effects. The average therapeutic dosage is 20 to 30 mg/day.^{28,30} Bupirone has a slow onset of action (as long as 4 weeks for full therapeutic effect), and its anxiolytic efficacy is unclear in patients with panic disorder and reduced in those recently withdrawn from BZD therapy.³⁰

However, bupirone is more suitable than BZDs for the treatment of chronically anxious patients. The starting dosage should be low (5 mg) and given on a 3-times-daily schedule, with incremental increases every few days. Generally, initial aggressive dosing may result in headache, dizziness, and nausea—common reasons why patients stop their medication prematurely.²⁸ Although bupirone has an overall more favorable safety profile than the BZDs, drug discontinuation rates after 6 months are higher with bupirone, suggesting less patient satisfaction.^{28,29} Finally, as with the BZDs, care should be taken to avoid drug-drug interactions with bupirone: levels of diazepam or haloperidol may increase during concomitant therapy, and levels of bupirone may increase in the presence of cimetidine and in patients with renal disease.^{26,46}

Tricyclic antidepressants and monoamine oxidase inhibitors. The TCAs and MAOIs also have been used successfully in patients with anxiety, particularly in panic disorder and in those with coexisting depression. Their overall use in primary care, however, is limited by their associated adverse events, safety issues in terms of lethality in overdose, and, particularly with the MAOIs, significant adverse interactions with foods and drugs.³²⁻³⁴ The TCAs are associated with notable anticholinergic side effects such as dry mouth, blurred vision, and constipation, which generally do not abate during therapy.³⁹ Patients often find these effects intolerable and may discontinue treatment as a result.^{29,39} Because TCAs can cause agitation in anxious patients, initial dosages should be very low. In addition, their use in anxious patients with suicidal tendencies should be avoided because of their potential for lethal overdosing—amounts as small as a 1-week's supply of amitriptyline or imipramine can be lethal.^{39,47}

Newer Antidepressants in the Treatment of Anxiety

The selective serotonin reuptake inhibitors (SSRIs) have been evaluated extensively in the treatment of anxiety disorders, particularly panic disorder^{32,35} and comorbid anxiety and depression,^{33,36,39} although their acceptance by the clinical community preceded the results of formal research to demonstrate their anxiolytic efficacy.³² The more favorable safety and tolerability profiles of the SSRIs are responsible for their preference over the TCAs and MAOIs.³⁹

A growing body of data now suggests that venlafaxine extended release (XR), which acts by blocking the reuptake of both serotonin and norepinephrine, is also efficacious for treating patients with an anxiety disorder^{40-42,48-51} and, possibly, mixed anxiety-depression.^{43,44} Short- and long-term studies in patients meeting DSM-IV criteria for GAD showed venlafaxine XR to be more effective than placebo⁴⁸⁻⁵¹ and, to a statistically significant degree, bupirone.⁴⁸ Venlafaxine XR appears to have one of the most favorable drug-drug interaction profiles relative to those of other antidepressants because it lacks any significant inhibitory effect on the cytochrome P450 isoenzyme system.⁵²

In general, these newer antidepressants are considerably safer than the BZDs in sedative effects, withdrawal liability, and psychomotor impairment, and they lack the anticholinergic effects and risk of overdose of the TCAs. Nausea, headache, insomnia, and somnolence (usually transient) are among the most prominent adverse events noted with these agents.^{39,53,54} In addition to these effects, some sexual dysfunction has been reported with the use of many of the newer antidepressants.^{39,53,55} On the other hand, the use of some SSRIs, such as fluoxetine, has been associated with paradoxical anxiety, jitteriness, and nervousness, which may require a short course of therapy with a BZD³⁹ or starting with a low dosage of the SSRI.

In efficacy, the SSRIs appear to be equivalent to the TCAs in treating anxiety.^{32,33} As is the case with the TCAs and bupirone, the SSRIs are associated with a delay in the onset of activity.^{30,32,34} Evidence also indicates that the SSRIs may reduce the psychological symptoms of anxiety without improving the somatic symptoms.⁵⁶ In contrast, data from studies have shown that venlafaxine XR significantly improves both psychological and somatic symptoms of anxiety in patients with GAD alone and in those with comorbid anxiety and depression, suggesting that this agent may be particularly useful in patients with these types of anxiety disorders.^{44,48-51,57} Both the SSRIs and venlafaxine XR can be taken once daily, which enhances convenience for patients, increasing their compliance and possibly increasing their ability to achieve remission and full resolution of symptoms.

CONCLUSIONS

Primary care physicians have an ever-widening array of pharmacologic therapies to use in treating patients with anxiety or mixed anxiety-depression. Compared with the standard anxiolytic agents, the newer antidepressants offer a number of important advantages in this setting. Agents such as the SSRIs and dual reuptake inhibitors are safer in overdose, more pharmacologically suited to treating anxiety and mixed anxiety-depression, and better tolerated than the older agents. The character-

istics of individual agents that may help guide clinical decisions about which agent to use for a particular patient include the risk of drug-drug interactions, specific side effect profiles, and the presence of coexisting medical or psychiatric disorders.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), buspirone (BuSpar), cimetidine (Tagamet and others), diazepam (Valium and others), fluoxetine (Prozac), haloperidol (Haldol and others), lorazepam (Ativan and others), oxazepam (Serax and others), venlafaxine XR (Effexor XR).

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Real-World Outcomes of Once-Daily Risperidone Dosing

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Background: Recent reports have shown that risperidone, which has established antipsychotic efficacy, is effective and safe in a once-daily dosing regimen.

Method: The efficacy and safety of once-daily risperidone were assessed in a retrospective study of 27 patients with a variety of psychiatric disorders who were attending a community day treatment program. Their DSM-IV diagnoses included schizophrenia, schizoaffective disorder, bipolar disorder, major depression with psychosis, and posttraumatic stress disorder. They had received once-daily risperidone for a mean of more than 18 months.

Results: Disorders of most patients were controlled with once-daily dosages of 1 to 6 mg/day of risperidone. The nighttime once-daily risperidone dosage was well tolerated by patients. In addition, there was no increase in antipsychotic-related side effects, and compliance was enhanced.

Conclusion: Risperidone was well tolerated, and no patient needed antiparkinsonian medications even at high dosages of risperidone once daily.

(*Primary Care Companion J Clin Psychiatry* 2000;2:55-57)

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Presented at the 37th annual meeting of the American College of Neuropsychopharmacology, December 14-18, 1998, Las Croabas, Puerto Rico.

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Risperidone is a safe and effective new antipsychotic that has a high binding affinity for both serotonin and dopamine receptors.¹ Several well-designed controlled clinical trials have been conducted to establish the antipsychotic efficacy of risperidone.^{2,3} In a previously published report,⁴ we had mentioned the rationale for using a once-a-day dosage schedule for risperidone based on the elimination half-life of risperidone and its active

metabolite, 9-hydroxyrisperidone, to enhance compliance. Since that time, the use of risperidone once daily has been studied and recommended. In the setting of a community day treatment program, we had switched patients from a twice-a-day risperidone dosage schedule to a once-daily dosage and found it to be effective. In a retrospective chart review published earlier, we found no increase in side effects such as neuroleptic-induced extrapyramidal symptoms or sedation in patients taking once-daily risperidone.⁵ We found the once-daily dosage to be safe, and patient compliance was enhanced.

We now report a retrospective chart review of patients who had been on once-daily risperidone treatment for an extended period of time. The aim of this study was to assess the efficacy, extrapyramidal side effects, and tolerability of risperidone in these patients over an extended period of time.

METHOD

The medical records of 27 patients who had been on once-daily risperidone treatment for more than 6 months were reviewed. The majority of these patients were registered at a local continuing day treatment program. Rating scales are used in the program as part of the clinical evaluation and follow-up process to monitor efficacy and antipsychotic-induced side effects. All ratings reported in this study were done by the treating psychiatrist (S.G.) to maintain rater reliability.

The data collected from the charts pertained to neuroleptic-induced extrapyramidal symptoms, diagnosis, and substance abuse. The total duration of treatment with risperidone and the duration on once-daily dosage was also obtained. The rating scales used included the Scale for the Assessment of Negative Symptoms (SANS),⁶ the Brief Psychiatric Rating Scale (BPRS),⁷ the Simpson-Angus Scale,⁸ and the Abnormal Involuntary Movement Scale (AIMS).⁹ The ratings presented are from the last psychiatric visit in the chart at the time of medical record review. Because the use of rating scales was instituted recently, no rating scale data were available at the time risperidone treatment was switched to a once-daily dosage. Medication compliance was monitored by the therapists working with the patients and also during medication education groups conducted in the continuing day treatment program.

Table 1. Demographic, Treatment, and Outcome Characteristics of 27 Patients Treated With Once-Daily Risperidone^a

Patient	Age (y)	Substance Abuse	Diagnosis	Rating Scale Score				Risperidone Dose (mg hs)	Duration of Risperidone Treatment (mo)		
				BPRS	Simpson-Angus Scale	SANS	AIMS		Duration	Night-time Dosing	Improvement (patient perception)
1	37	Alcohol	Schizophrenia	33	1	36	8	12	28	24	Moderate
2	23	Drugs	Bipolar affective disorder	22	NA	NA	NA	2	10	8	Mild
3	41	None	Schizoaffective disorder	27	1	20	0	4	38	24	Moderate
4	33	Drugs	Schizophrenia	25	0	15	0	5	28	24	Moderate
5	24	Drugs + alcohol	Bipolar affective disorder	NA	NA	NA	NA	1	16	13	Moderate
6	41	None	Schizophrenia	33	3	36	0	10	40	18	Mild
7	71	None	Bipolar affective disorder	NA	NA	NA	0	2	36	36	Moderate
8	56	None	Schizophrenia	26	NA	25	7	4	44	22	Marked
9	54	Alcohol	Schizoaffective disorder	26	NA	NA	0	6	9	9	Mild
10	77	None	Schizophrenia	20	2	27	2	3	33	24	Moderate
11	45	None	Schizophrenia	28	1	47	0	12	22	22	Mild
12	66	None	Major depressive disorder with psychosis	21	NA	NA	5	3	46	25	Moderate
13	50	None	Schizoaffective disorder	27	0	24	6	8	47	11	Mild
14	42	Alcohol + drugs	Schizophrenia	24	0	23	0	7.5	30	9	Moderate
15	38	None	Schizophrenia	27	0	NA	NA	2	9	9	Mild
16	45	None	Posttraumatic stress disorder	NA	NA	NA	NA	1.5	21	21	None
17	61	None	Bipolar affective disorder	NA	NA	NA	NA	2	14	14	Moderate
18	41	Alcohol	Schizophrenia	32	1	35	0	10	28	28	Moderate
19	29	None	Schizophrenia	33	2	38	0	14	43	12	Mild
20	60	None	Bipolar affective disorder	NA	NA	NA	0	2	16	16	Moderate
21	51	None	Schizophrenia	23	0	NA	1	10	41	19	Moderate
22	71	None	Major depressive disorder with psychosis	NA	0	NA	1	1	22	22	Moderate
23	42	None	Major depressive disorder with psychosis	NA	0	NA	0	10	28	28	Moderate
24	41	None	Schizophrenia	19	0	13	0	6	12	12	Marked
25	30	None	Schizophrenia	NA	NA	NA	0	8	34	20	Moderate
26	38	None	Schizoaffective disorder	36	2	23	0	16	28	12	Moderate
27	40	Alcohol + drugs	Schizophrenia	38	NA	NA	0	4	22	18	Mild

^aAbbreviations: AIMS = Abnormal Involuntary Movement Scale, BPRS = Brief Psychiatric Rating Scale, NA = not available, SANS = Scale for the Assessment of Negative Symptoms.

RESULTS

The sample consisted of 27 patients with varying DSM-IV diagnoses who had been switched in an uncontrolled fashion to once-daily dosage of risperidone and had periodic follow-up over several months. The sample consisted of 15 women and 12 men. The age range was 23 to 77 years (mean = 47.7 years). The diagnoses included schizophrenia (N = 14), bipolar affective disorder (N = 5), schizoaffective disorder (N = 4), major depressive disorder with psychotic features (N = 3), and posttraumatic stress disorder (N = 1) (Table 1). Three patients

had alcohol abuse, 2 had drug abuse, and 3 had a combination of alcohol and drug abuse.

The mean duration of treatment with risperidone was 27.6 months (range, 9–47 months) and the mean duration of once-daily (nighttime) treatment was 18.5 months (range, 8–36 months). The mean bedtime dosage of risperidone was 6.1 mg (range, 1–16 mg) (see Table 1). Patient report of treatment outcome at the time of chart review indicated marked improvement in 2 patients, moderate improvement in 16, mild improvement in 8, and no improvement in 1 (see Table 1) based on Clinical Global Impressions Scale rating.¹⁰ BPRS data were available for 19

patients, with a mean score of 27.4. SANS scores were available for 13 patients, with a mean score of 27.8. The rating scale scores reflect a low level of symptomatology and minimal medication-related side effects. None of the patients had neuroleptic-induced parkinsonism on the basis of review of the psychiatrist's progress notes and Simpson-Angus Scale scores, available for 16 patients (mean = .08; see Table 1). One patient had good symptomatic relief on 16 mg of risperidone at bedtime and did not manifest any side effects. The patients had improved compliance with the medication being given once daily, as noted by the individual therapists and the medication education groups.

DISCUSSION

In a fixed-dose study (N = 211), Nair et al.¹¹ randomly assigned subjects to receive 8 mg of risperidone once daily or 4 mg twice daily for 6 weeks.¹¹ They report both dosage schedules to be similar in clinical efficacy and latency of response to risperidone. No differences were found in side effects between the 2 groups.

Our study has limitations, which include the retrospective design and lack of prechange and postchange data so that a comparison cannot be made of the various measures with regard to twice-daily versus once-daily dosage schedule. Rating scale data were partially or completely missing for some of the patients. Another limiting factor is the lack of availability of rating scale information at the time of the switch to once-daily risperidone.

A strength of this study is the use of standardized rating scales in the clinic on a regular basis, which provided us with objective measures for assessing symptoms and side effects. These rating scales are used in most clinical trials for assessing medication efficacy and side effects. The BPRS is an 18-item scale that is the gold standard for assessing the level of psychosis in clinical trials and is accepted worldwide. It measures symptoms such as auditory hallucinations, delusions, disturbance of thought, agitation, hostility, and affect. The Simpson-Angus Scale assesses the motor side effects of antipsychotics, which include drug-induced parkinsonism. The SANS quantifies negative symptoms of schizophrenia such as anhedonia, avolition, poverty of speech, affective flattening, and disturbance of attention. The AIMS is used to monitor neurologic side effects of antipsychotic agents, such as tardive dyskinesia, a disorder characterized by abnormal involuntary choreiform movements.

Primary care physicians treat more complex patients today, including those with major mental illnesses such as schizophrenia or depression with psychotic symptoms,

especially after stabilization. In other instances, they may treat such patients jointly with a psychiatrist. This study provides information for primary care physicians on safety, tolerability, and efficacy when risperidone is used over an extended period of time (mean = 27.6 months; range, 9–47 months). Information at this time about the long-term use of risperidone is limited. Most patients who need antipsychotics require maintenance on them over their lifetime as is done for diabetes or hypertension. The new-generation antidepressants and antipsychotics have a much improved side effect profile and are more patient friendly. It is important for primary care physicians to be familiar with them with regard to dosage schedules and side effects.

Our study found risperidone to be safe, effective, and well tolerated even at high dosages in a once-daily dosing schedule over a prolonged period of treatment. The once-daily risperidone dosing was found to enhance treatment compliance in this community setting as noted by the therapists and the medication education groups. In this community, we are currently using risperidone in a once-daily dosage schedule. Future controlled studies are recommended to replicate these findings in different populations of patients.

Drug name: risperidone (Risperdal).

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Irritable Bowel . . . or Simply Irritable?

Christian G. Wolff, M.D.

Monday

TG is a 42-year-old fellow whom I have been treating with venlafaxine XR for his first bout with depression. He had been significantly symptomatic for about a year before treatment and responded to a 150-mg dose and counseling. Well, it has been about a year, and spring has been beautiful, so we have decided to wean him from his medication. In spite of a slow taper, twice he developed significant dysphoria that persisted for several days and completely resolved by resuming a 37.5-mg dose. A literature review was unhelpful, and I was a bit annoyed that we were having this difficulty. On our third try, after staying on the lowest dose for 3 weeks, he was able to discontinue medication without difficulty. Whew! I wonder if any colleagues have anecdotal tips for dealing with this problem.

Tuesday

SB is a 40-year-old divorced woman who was severely depressed until last year when she began treatment with paroxetine. Since then, she has repaired a tattered relationship, is engaged to be married, and has received a significant job promotion. We have made great strides with her general health—she has lost 30 pounds through diet and exercise and is now able to discontinue her acetylcholinesterase inhibitor. On her last visit, she broke the news that she was being transferred to a city 70 miles away. Jokingly, I told her that I would require her to hang around as a model for my other patients. You hate to see the success stories leave, don't you?

Wednesday

HG is a 30-year-old woman whom I have been treating for irritable bowel syndrome and generalized anxiety disorder. I began treatment for both simultaneously, and both are significantly improved. This leads me to ask the question that many of you ask many times as well: chicken or egg? I suppose that as long as she is better, it doesn't matter much to her. I think everyone benefits from more fiber anyway.

Thursday

An update on a prior diary entry¹: this gentleman had a meningioma found after CT scan for presumed sinus headaches and has since had concomitant sinus and neurosurgery. Three months after tumor removal and sinus reaming, his breathing was excellent, but his headaches—well, his headaches were unchanged. You will recall that I had used every headache strategy I knew before his CT, and he has seen a neurologist in association with his meningioma. I made an appointment for him with an anesthesiologist for pain control.

Today I received a letter that states: “Mr. so and so’s headaches have completely resolved on 12.5 mg of rofecoxib daily. I now discharge him to return to your care.”

Go figure.

Friday

TP is a 53-year-old man who presented today for an initial visit, my first patient after a difficult flexible sigmoidoscopy. The woman undergoing sigmoidoscopy was incredibly intolerant of discomfort, as she began to howl after the scope was inserted only 15 cm. Finding TP sitting in a chair drowning in tears after finishing the flex had me questioning my choice of vocation. This, clearly, was not in the “Life as a Family Physician” brochure. But then, I digress.

TP was referred to me by his ex-wife, another patient of mine. She, actually, was his third wife. He had just asked his fifth (and current) wife to pack up and leave the house. Through the tears, he began to recount to me severe depression punctuated by “good times” of high living, travel, gambling, and risky business ventures. He had a course of citalopram prescribed by his previous physician in New York a few months ago, which, he says, helped him immensely with his depression. Unfortunately, besides lifting his depression, it helped him slide into a season of spending and womanizing—he lost his sales job and has moved here to be close to his son. During the last 2 weeks, he has restarted the citalopram on his own, and his depression is beginning to improve.

As he left his appointment with a prescription for lithium in hand, I reflected: this sort of thing *should* be in “the brochure.”

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Editor’s note: Dr. Wolff is a board-certified family physician in private practice in Huntersville/Davidson, North Carolina. He finished his family practice residency in 1997. He has graciously consented to share stories from the trenches of primary care. While his practice diary is taken from actual patient encounters, the reader should be aware that some medication references may represent off-label uses. We at the *Companion* are certain that these vignettes will inform, entertain, challenge, and stimulate our readers in their effort to address behavioral issues in the everyday practice of medicine.

Letters to the Editor

Possible Manic Phase Precipitated by Antidepressant Treatment

Sir: I read with interest the December 1999 "Diary From the Front Lines" column by Christian G. Wolff, M.D.¹ I wonder if Dr. Wolff considered that his Wednesday patient, BT, might have cyclothymia or bipolar illness. The patient's excessively loud speech might not be from hearing problems but rather be similar to the typical pressured speech associated with the aforementioned disorders. I believe I have seen this several times in the past. In addition, since the patient's buddies now refer to BT as "Mr. Sunshine," I was suspicious that the unopposed treatment with the antidepressant sertraline without a mood stabilizer might have precipitated a mild manic phase of bipolar illness, uncovering the true diagnosis serendipitously. Perhaps not, but the vignette raised both my suspicion and my curiosity.

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Dr. Wolff Replies

Sir: Dr. Smith raises an interesting and excellent point. As part of BT's annual physical, I obtained audiometry data that supported bilateral sensorineural hearing loss (again, he is a lifelong road construction worker exposed to jackhammers, bulldozers, etc.). As far as hypomania is concerned, I have seen him in follow-up for other incidental items during the interim (sniffles), and he appears to be quite even-keeled. I appreciate Dr. Smith's comments, for they raise an excellent point to consider when evaluating such patients.

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Gabapentin in the Treatment of Aggression Associated With Conduct Disorder

Sir: In this case report, we describe a patient with a DSM-IV diagnosis of conduct disorder resulting in aggression and violent behavior whose symptoms were controlled with gabapentin

after he had failed a trial of divalproex sodium. There is one previously published report¹ of gabapentin in the treatment of mania, but we found no cases describing its use in aggression related to conduct disorder.

Case report. Mr. A, a 17-year-old adolescent boy, was admitted to a children's home in September 1997 owing to multiple offenses including endangering the welfare of a minor, resisting arrest, petty larceny, and criminal mischief. He was first seen in psychiatric consultation because of aggressive behavior and physical assault; the last episode involved a police officer. Mr. A gave a history indicative of poor impulse control, indicating "I act first and think later." He reported getting into altercations that he realized he should have refrained from and that his response to situations was out of proportion to the provocation and was at times even unprovoked. He also gave a history of easy irritability and explosivity. His past psychiatric history revealed one previous psychiatric hospitalization after a fight with the police. Past medical history revealed a closed head injury with loss of consciousness for 4 hours following a fight with the police. There was no history of seizure disorder. He had drunk alcohol twice in his life and had never used drugs. Mr. A had no contact for many years with his biological father. School records from testing done in 1993 indicated a verbal IQ of 95, performance IQ of 108, and a full-scale IQ of 94. His mathematics and English skills were at the seventh- and ninth-grade level, respectively. Legal history was significant for 12 felonies, including armed robbery and drug trafficking, and he had been incarcerated approximately 5 times. Mr. A also admitted to stabbing a sixth grader multiple times. The initial diagnosis was intermittent explosive disorder, with bipolar disorder NOS in the differential diagnosis. Owing to the history of head injury, temporal lobe syndrome cannot be ruled out, despite one normal sleep-deprived electroencephalogram (EEG).

Mr. A underwent a complete medical workup that included laboratory studies, a computed tomographic scan of the brain, and sleep-deprived EEG. All test results were unremarkable. He was started with divalproex, 500 mg twice daily, which was then titrated to a total dosage of 2000 mg in divided dosages (serum level = 91.2 µg/mL), in an effort to address target symptoms such as unprovoked aggression, impulsivity, and explosivity. Because of continuing sleep disturbance, trazodone was added in a dosage of 50 mg at bedtime and was increased to 75 mg. He continued community service at this time and continued to be assaultive to peers and others in an unpredictable fashion. He continued to report racing thoughts and sleep disturbance. He took divalproex for a total duration of 7 months and took the 2000-mg/day dosage for the last 3 months prior to hospitalization. Mr. A developed increasing depressive symptoms and was prescribed fluoxetine, 10 mg daily, but subsequently was hospitalized owing to suicidal ideation stemming from his concern that he was going to spend the rest of his life in prison.

Mr. A returned from the hospital on treatment with a combination of multiple medications, which included gabapentin, 400

mg q.i.d.; risperidone, 2 mg h.s.; bupropion sustained release, 150 mg t.i.d.; and amantadine, 100 mg b.i.d. He was switched to gabapentin owing to lack of response to divalproex. He reported that he was "doing really well," without any racing thoughts, and his sleep pattern had improved. The discharge diagnosis was major depression without psychotic features and conduct disorder, childhood onset. No further aggressive episodes were reported. Mr. A was tapered off the amantadine and risperidone without any increase in aggression. He had been taking gabapentin for a total of 3 months prior to discharge from the children's home and had been free of aggressive episodes for that time frame.

This case describes a teenager with a DSM-IV diagnosis of conduct disorder who had comorbid diagnoses of bipolar disorder, major depression, and intermittent explosive disorder. Gabapentin was found to be effective when used to treat target symptoms such as unprovoked aggression, impulsivity, and explosivity. His symptomatology was complex, which made the case a diagnostic challenge. In addition to conduct disorder, symptoms included depression, manic-type symptoms, and explosive symptoms. Gabapentin was clearly efficacious in controlling the irritability, mood swings, impulsivity, and aggression. Limitations of this case study are the use of adjunctive medications such as bupropion with gabapentin and fluoxetine with divalproex and the initial use of risperidone with gabapentin.

There is one previous report¹ of gabapentin used successfully in an adolescent manic patient who failed a trial of divalproex. That patient had comorbid attention-deficit/hyperactivity disorder, unlike our patient, who had conduct disorder and a complex comorbid symptomatology. Several reports describe the use of gabapentin in mania in adults.²⁻⁵ We found no reports describing the use of gabapentin in patients with severe conduct disorder. Lithium carbonate, divalproex, and antipsychotics have been used extensively in patients with conduct disorder who have severe aggression.

This case suggests that gabapentin is a valuable option because of good tolerability, safety in overdose, and good symptom control. The pharmacokinetic profile of gabapentin offers several advantages over other antiepileptic agents such as absence of serum protein binding and the absence of hepatic metabolism. It is eliminated unchanged by the kidneys. Drug-drug interactions with other antiepileptic drugs and other medications, such as oral contraceptives, appear nonexistent. In the primary care setting, gabapentin is a relatively safe drug to use because of its safety in overdose and lack of need of frequent blood levels for monitoring (unlike divalproex). In adults, the dosage range of gabapentin is 600 to 4800 mg/day, whereas in children, the suggested dosing is 10 to 30 mg/kg/day given in 3 divided dosages. Controlled studies are needed to further establish these findings.

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Citalopram and Hair Loss

Sir: Selective serotonin reuptake inhibitors (SSRIs) are the mainstay of treatment for a wide variety of psychiatric disorders including mood and anxiety disorders. Hair loss with the SSRIs, tricyclic antidepressants (TCAs), and other classes of antidepressants has been anecdotally reported.¹⁻⁶ We report a case of a 50-year-old white woman with bipolar disorder who developed hair loss while taking the SSRI citalopram. Significant hair loss can be a distressing side effect of antidepressants and should be monitored in treatment because it may lead to noncompliance and relapse.

Case report. Ms. A, a 50-year-old divorced white woman with a DSM-IV diagnosis of bipolar disorder, is presently in outpatient treatment at a community mental health clinic. Her past psychiatric history was significant for multiple hospitalizations for both manic and depressive episodes. There was no prior history of suicide attempts, nor was there any comorbid alcohol or substance abuse. She had no significant ongoing medical problems. Her last psychiatric hospitalization was in August 1997, for depressive symptoms and suicidal ideation. At that time, she had lithium-related side effects and had poor tolerance to divalproex and carbamazepine. Results of her laboratory tests, including a complete blood count, electrolyte concentrations, liver and kidney tests, and thyroid hormone studies, were unremarkable. During her last hospitalization, she was started successfully on lamotrigine therapy and titrated to a dosage of 50 mg twice daily. In addition, she was treated with paroxetine, 20 mg daily, and clonazepam, 0.5 mg in the morning and 1 mg at night. Following discharge from the hospital, her compliance with the medication and outpatient visits was good.

Treatment with clonazepam was subsequently successfully discontinued. One year later, owing to worsening depression, the paroxetine dosage was gradually increased to 40 mg daily on an outpatient basis. She then reported nightmares and continuing depressive symptoms. The patient was gradually switched to citalopram, which was started at 20 mg and then titrated to 40 mg with good symptom control. At her next visit a couple of months

later, the patient reported losing clumps of hair while shampooing. She became increasingly anxious at this time and was placed on hydroxyzine, 25 mg 3 times daily. A dermatology consultation was obtained to rule out other causes of hair loss, but none were detected. As the hair loss appeared temporally related to the increase in citalopram dosage, the possibility of dosage reduction was considered, but the patient was reluctant because of good symptom control. A multivitamin formulated for adults aged 50 and over (Centrum Silver) was added in a dosage of 1 tablet daily with the provision that the antidepressant be switched if the hair loss persisted at the next visit 4 weeks later. The hair loss stopped with Centrum Silver use, and there have been no complaints about it for the past 5 months as the patient continues to monitor the condition. The patient remains compliant with all medications. There have been no side effects, such as the rash that has been reported with lamotrigine, nor has there been any recurrence of manic symptoms.

To our knowledge, this is the first case report of hair loss associated with citalopram therapy. Citalopram selectively inhibits the reuptake of serotonin (5-hydroxytryptamine), which potentiates serotonergic neurotransmission and is associated with clinical antidepressant effects.⁷ In some cases, it appears that hair loss accelerates when the dose of the antidepressant is increased.^{2,6} Hair loss with citalopram therapy may be reversible with adjunctive Centrum Silver. An alternative explanation

could be spontaneous resolution of the hair loss independent of the use of Centrum Silver. Significant hair loss is a distressing side effect that should be monitored and treated since it can lead to noncompliance, worsening of symptoms, and relapse.

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Book Review

W. Clay Jackson, M.D., Dip.Th., Editor

Seasonal Affective Disorder and Beyond: Light Treatment for SAD and Non-SAD Conditions

*edited by Raymond W. Lam, M.D. Washington, D.C.,
American Psychiatric Press, 1998, 320 pages, \$47.00.*

Seasonal affective disorder (SAD) is a mood disorder characterized by atypical symptoms of depression (depressed mood, hypersomnia, hyperphagia, and weight gain). It usually begins in the fall or winter and remits during the spring. Five percent to 6% of the U.S. population suffer from full-blown SAD with an additional 15% afflicted with subsyndromal SAD. The prevalence of SAD increases with increasing distance from the equator.

The first published report on the use of bright light to treat SAD appeared in 1982. Subsequent controlled studies have, for the most part, confirmed the efficacy of bright light treatment for SAD. Fifty percent to 60% of patients show a robust response within 4 or 5 days of beginning treatment.

The editor solicited contributions from experts in the field of bright light therapy and had each of them summarize and report their findings in separate chapters. The book is comprehensive. Some chapters, such as the one on biological and physical properties of light, may not be of immediate concern to the primary care physician, but the editor has done such a superb job of organizing the book that the reader will be able to quickly pick out the chapters and sections of greatest relevance. The physician will probably find the information on bright light treatment of SAD, nonseasonal major depression, premenstrual dysphoria, and bulimia to be of most interest. Some physicians may also want to scan the chapters on the use of light to treat sleep phase disorders, jet lag, problems associated with shift work, and insomnia in older patients. The contributors provide convincing evidence that bright light is a viable first-line treatment for all of these conditions.

A few quibbles: Several studies on the use of bright light therapy in the treatment of bipolar depression are mentioned in the chapter on nonseasonal major depression, but are not referenced in the index. The omission is surprising since the first published report on the efficacy of light therapy was with a bipolar patient.¹ In addition, many patients with winter SAD are mildly bipolar. It would also have been helpful if the editor and publisher had included in the index a reference to the use of bright light to extend the antidepressant effects of partial sleep deprivation.

This is an excellent resource for the primary care physician interested in learning about or using bright light therapy.

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Psychiatric Briefs

Racial Variation in Antidepressant Treatment in a Medicaid Population

Melfi CA, Croghan TW, Hanna MP, et al.

Background: Many studies have found racial and socioeconomic variation in medical care for a variety of conditions. Undertreatment of depression for individuals of all races is a concern, but especially may affect vulnerable populations such as Medicaid recipients and minorities. With this study, we examine racial differences in the antidepressant usage in a Medicaid population. **Method:** Treatment of 13,065 depressed patients (ICD-9-CM criteria) was examined in a state Medicaid database covering the years 1989 through 1994. Treatment differences were assessed in terms of whether an antidepressant was received at the time of the initial depression diagnosis and the type of antidepressant prescribed (tricyclic antidepressants [TCAs] vs. selective serotonin reuptake inhibitors [SSRIs]), using logistic regression techniques. **Results:** African Americans were less likely than whites to receive an antidepressant at the time of their initial depression diagnosis (27.2% vs. 44.0%, $p < .001$). Of those receiving an antidepressant, whites were more likely than African Americans to receive SSRIs versus TCAs. These findings remained even after adjusting for other covariates. **Conclusion:** Despite the easy availability of effective treatments, we found that only a small portion of depressed Medicaid recipients receive adequate usage of antidepressants. Within this Medicaid population, limited access to treatment was especially pronounced among African Americans. Racial differences existed in terms of whether an antidepressant was received and the type of medication used.

(*J Clin Psychiatry* 2000;61:16–21)

Alcoholism in the Elderly

Rigler SK

Although underrecognized, alcoholism and alcohol abuse are common problems among the elderly. Late-onset drinking occurs in one third of elderly persons who abuse alcohol, while the other two thirds of elderly alcoholic patients started drinking at a young age. The medical and psychosocial sequelae of early-onset alcoholism in the latter group are compounded by changes associated with aging. Changes in physiology related to aging alter the effects of alcohol at the cellular and organ levels. Also, the interactions of alcohol with numerous drugs prescribed in the elderly may be more serious in this population. The criteria for alcohol abuse and dependence are often more difficult to apply to older persons who are retired or have infrequent social in-

teraction. Screening tools, such as the CAGE questionnaire and the Michigan Alcoholism Screening Test, when supplemented by information about current quantity, frequency, and pattern of alcohol use, can be used by family physicians to identify the older patient with alcohol problems. Older persons should be closely supervised by health care professionals while undergoing detoxification. Age-specific alcohol treatment programs may improve outcomes in some elderly patients.

(*Am Fam Physician* 2000;61:1710–1716)

Zolpidem for Persistent Insomnia in SSRI-Treated Depressed Patients

Asnis GM, Chakraburty A, DuBoff EA, et al.

Background: Depressed individuals effectively treated with selective serotonin reuptake inhibitors (SSRIs) often report persistent insomnia and require adjunctive sleep-promoting therapy. **Method:** Men ($N = 40$) and women ($N = 150$) with a mean age of 41.6 years who had persistent insomnia in the presence of effective and stable treatment (at least 2 weeks) with fluoxetine (≤ 40 mg/day), sertraline (≤ 100 mg/day), or paroxetine (≤ 40 mg/day) for DSM-IV major depressive disorder, dysthymic disorder, or minor depressive disorder of mild-to-moderate severity (and score of ≤ 2 on item 3 of the Hamilton Rating Scale for Depression [HAM-D]) participated in this randomized, double-blind, parallel-group study. At study entry, patients were required to score ≤ 12 on the HAM-D. During a 1-week single-blind placebo period, patients had to report on at least 3 nights a latency of ≥ 30 minutes or a sleep time of < 6.5 hours and clinically significant daytime impairment. Patients received either placebo ($N = 96$) or zolpidem, 10 mg ($N = 94$) nightly, for 4 weeks and single-blind placebo for 1 week thereafter. Sleep was measured with daily questionnaires and during weekly physician visits. **Results:** Compared with placebo, zolpidem was associated with improved sleep: longer sleep times (weeks 1 through 4, $p < .05$), greater sleep quality (weeks 1 through 4, $p < .01$), and reduced number of awakenings (weeks 1, 2, and 4; $p < .05$), together with feeling significantly more refreshed, less sleepy, and more able to concentrate. After placebo substitution, the zolpidem group showed significant worsening relative to pretreatment sleep on the first posttreatment night in total sleep time and sleep quality, reverted to pretreatment insomnia levels on the other hypnotic efficacy measures, or maintained improvement (fewer number of awakenings). There was no evidence of dependence or withdrawal from zolpidem (DSM-IV criteria). Incidence rates of adverse events were similar in both treatment groups (74% and 83% for placebo and zol-

pidem, respectively), but 7 zolpidem patients discontinued compared with 2 placebo patients. **Conclusion:** In this defined patient population, zolpidem, 10 mg, was effectively and safely coadministered with an SSRI, resulting in improved self-rated sleep, daytime functioning, and well-being.

(*J Clin Psychiatry* 1999;60:668–676)

Somatizing Patients, Part 1: Practical Diagnosis

Servan-Schreiber D, Kolb NR, and Tabas G

Somatization is common in primary care settings, but is often unrecognized, leading to inordinately high use of health care resources. Patients with somatoform disorders experience emotional distress or stressful life situations as persistent physical symptoms, ranging from mild stress-related complaints to severe debilitation, for which no physiologic explanation can be found. Because traditional medical training focuses on the identification and treatment of organic disorders, most physicians are ill prepared to manage somatoform complaints. Simple reassurance often leads to response in patients whose symptoms are on the low end of the somatization spectrum, but interventions designed to avoid the unnecessary use of costly and potentially dangerous procedures that fail to reduce suffering are necessary in patients who are highly impaired. The authors' approach to a positive diagnosis of somatization requires 2 criteria: several nonspecific symptoms in different organ systems and a chronic course. They cite empathy as essential to the effective relationship between the physician and the somatizing patient.

(*Am Fam Physician* 2000;61:1073–1078)

Somatizing Patients, Part 2: Practical Management

Servan-Schreiber D, Tabas G, and Kolb NR

Symptoms in patients with somatization are caused by emotional distress rather than physiologic dysfunction. The foundation of effective management of the condition begins with the acknowledgment of the patient's suffering and the development of a concerned attitude. Continuity of care with a single primary care physician is beneficial in addressing the management problems that are typical for the somatizing patient. The successful approach to treatment relies on giving an acceptable explanation of the symptoms to the patient, avoiding unwarranted procedures, establishing reasonable treatment goals, and arranging for brief but regular and frequent office visits to provide the patient with regular medical attention that is independent of symptom development. Antidepressant treatment may be of benefit as well as cognitive psychotherapy for willing participants.

(*Am Fam Physician* 2000;61:1423–1428)

Depression in Women: Diagnostic and Treatment Considerations

Bhatia SC and Bhatia SK

Twice as many women experience depression as men. Family physicians should take gender-related biopsychosocial differ-

ences and phases of the reproductive cycle into consideration when evaluating and treating depression in women. Although the same diagnostic criteria are used for both genders, the presentation and course may differ in women. Women may more often experience hypersomnia, hyperphagia, guilt, anxiety, weight gain, and comorbid eating disorders. Women may require lower dosages of antidepressants than men because plasma antidepressant concentrations may be higher due to biological differences such as hormone levels and body fat to muscle ratio. The potential effects of antidepressants on a fetus or neonate are a consideration for many depressed women. No increased teratogenic risk from in utero exposure to selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants has been shown by research studies. SSRIs have been shown effective in treating premenstrual dysphoric disorder and other comorbid conditions associated with depression. In women with mild-to-moderate depression, psychotherapy may be the sole treatment, or psychotherapy may be used adjunctively with antidepressant drug therapy. Every patient with depression should be screened for suicidal thoughts, intent, and plan during the initial visit. According to the authors, severely depressed women who have active suicidal thoughts or plans should usually be managed in conjunction with a psychiatrist.

(*Am Fam Physician* 1999;60:225–240)

Psychosocial Functioning in Women With Premenstrual Dysphoric Disorder Before and After Treatment With Sertraline or Placebo

Pearlstein TB, Halbreich U, Batar ED, et al.

Background: The objective of this study was to evaluate the pretreatment psychosocial functioning of women with premenstrual dysphoric disorder (PMDD) and the effect of sertraline treatment on psychosocial functioning in these patients. **Method:** 243 women recruited from 12 university-affiliated sites and meeting DSM-IV criteria for PMDD completed 1 cycle of single-blind placebo and were randomly assigned to flexible-dose sertraline or placebo for 3 cycles. Psychosocial functioning was assessed by the Daily Record of Severity of Problems (DRSP), the Social Adjustment Scale (SAS), and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). **Results:** SAS scores during the follicular phase were similar to SAS scores of community norms, whereas the pretreatment SAS and Q-LES-Q scores during the luteal phase were similar to scores of women with depressive disorders. Sertraline was significantly more effective than placebo in improving psychosocial functioning as measured by the SAS, the Q-LES-Q, and the 3 DRSP items of impaired productivity, interference with social activities, and interference with relationships with others. Improvement in psychosocial functioning assessed by SAS and Q-LES-Q correlated with improvement in symptomatology assessed by the Clinical Global Impressions-Improvement (CGI-I) scale and the Hamilton Rating Scale for Depression (HAM-D). Remitters (CGI-I score of 1) were more likely to function better at baseline and showed larger improvements in functioning and quality of life with treatment compared with nonremitters. **Conclusion:** Sertraline was superior to

placebo in improving psychosocial functioning in women with PMDD as reflected by SAS, Q-LES-Q, and DRSP measures. Functional improvement correlated with improvement in premenstrual symptomatology and was apparent by the second cycle of treatment. Comparison of pretreatment SAS scores in women with PMDD with the scores of other populations of women documents the degree of luteal phase functional impairment in women with PMDD and a relative absence of follicular phase impairment.

(*J Clin Psychiatry* 2000;61:101–109)

Mood Stabilizers During Breastfeeding: A Review

Chaudron LH and Jefferson JW

Background: The postpartum period is an exceptionally high-risk time for recurrence of depression, mania, or psychosis for women with bipolar disorder. Puerperal prophylaxis with mood stabilizers decreases this risk. To allow patients and clinicians to make informed decisions about mood-stabilizer use during breastfeeding, there is a need for a critical review and analysis of the data. **Data Sources:** A search of MEDLINE (1966–1998) and the Lithium Database, Madison Institute of Medicine, was conducted to obtain articles about lithium, valproate, carbamazepine, gabapentin, or lamotrigine use during lactation. Search terms used were *pregnancy, teratogenesis, breastfeeding, lactation, breast milk levels* and *lithium, anticonvulsants, mood stabilizers*. No other search restrictions were used. Unpublished data on gabapentin and lamotrigine were provided by the manufacturers. **Results:** The search revealed 11 cases of lithium use during breastfeeding, 8 of which reported infant serum levels. Two cases reported symptoms consistent with lithium toxicity in the infants. Thirty-nine cases of valproate use during breastfeeding were found, 8 of which reported infant serum levels. There was 1 report of thrombocytopenia and anemia in an infant. Fifty cases of carbamazepine use during breastfeeding were found, 10 of which reported infant serum levels. Two infants experienced hepatic dysfunction. One unpublished study of gabapentin in breast milk was found. Three reports of lamotrigine use during breastfeeding were found. **Discussion:** Available information remains limited to uncontrolled studies and case reports. Carbamazepine and valproate, but not lithium, have generally been considered compatible with breastfeeding. The overall paucity of data, data confounded by polypharmacy and infant age differences, and adverse reactions reported with all established mood stabilizers dictate a reassessment of these recommendations. We propose that a woman's historical response to medica-

tion and the clinical circumstances be the primary considerations when choosing a mood stabilizer during breastfeeding, rather than strict adherence to categorical assignments.

(*J Clin Psychiatry* 2000;61:79–90)

Compliance With Antidepressant Medication in the Treatment of Major Depressive Disorder in Primary Care: A Randomized Comparison of Fluoxetine and a Tricyclic Antidepressant

Thompson C, Peveler RC, Stephenson D, et al.

Objective: Using a randomized study design, the authors evaluated differential compliance with antidepressant medications in a primary care setting. Claims have been made for superior compliance with selective serotonin reuptake inhibitors (SSRIs) over tricyclic antidepressants (TCAs), although no meta-analyses have confirmed this claim in randomized controlled trials.

Method: 152 patients (aged 18–70 years) with DSM-III-R major depressive disorder treated in 10 primary care practices in the United Kingdom were randomly assigned to receive the SSRI fluoxetine or the TCA dothiepin at therapeutic doses in a parallel-group, open-label comparison study of 12 weeks. Compliance measures were pill count, patient-completed questionnaire, and the Medication Event Monitoring System. **Results:** Although the differences were not significant, the level of compliance with fluoxetine was numerically higher than the level of compliance with dothiepin on all 3 primary outcome measures. Two measures derived from the Medication Event Monitoring System—survival analysis and the compliance index—showed a significant advantage for fluoxetine. Fluoxetine-treated patients showed superior response on the health transition scale of the 36-item Short-Form Health Survey Questionnaire and numerically greater improvement on the Hamilton Rating Scale for Depression (HAM-D). Those patients in both treatment groups with a superior compliance index were more likely to have improved HAM-D scores by the last study visit. **Conclusion:** The authors state that “this study supports recent meta-analyses of SSRIs versus TCAs in finding no significant differences in crude indices of compliance between fluoxetine and dothiepin, despite marked differences in side effect profile and dose regimen.” They did find, however, that 2 measures used in a secondary analysis—survival analysis for length of time without a gap in medicine taking and a measure that takes account of prolonged periods of noncompliance—distinguished between the treatments and were associated with improvement in both groups.

(*Am J Psychiatry* 2000;157:338–343)

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3. Mah L. Mania in HIV illness. In: *New Research Program and Abstracts of the 151st Annual Meeting of the American Psychiatric Association*; June 1, 1998; Toronto, Ontario, Canada. Abstract NR111:98
4. Huth EJ. *How to Write and Publish Papers in the Medical Sciences*. 2nd ed. Baltimore, Md: Williams & Wilkins; 1990
5. Simon GE. Can depression be managed appropriately in primary care? *J Clin Psychiatry* 1998;59(suppl 2):3-8
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