Refractory Depressed and Anxious States in Hyperthymic Women: A Case Series Generated by a Speaking Engagement

J. Sloan Manning, M.D.

The author discusses 4 referrals that were the direct result of a case description from his own practice that he presented during a lecture on the treatment of mixed anxious and depressive illness in primary care. The cases depict energetic, productive women who suffer fatigue and episodic depressions. These cases suggest that hyperthymic temperaments complicated by depressive episodes represent a form of mood disorder presentation that is highly recognizable and responsive to pharmacologic intervention. Such premorbid temperamental hypomanic tendencies may represent a soft form of bipolar illness that requires somatic strategies in line with those of classic manic depressive illness. The cases underscore the challenge of treating mood disorders and the need for treatment research to reach primary care practitioners, who see the majority of depressed and anxious patients.

(Primary Care Companion J Clin Psychiatry 2000;2:16–19)

Received Jan. 31, 2000; accepted Feb. 7, 2000. From the Department of Family Medicine, University of Tennessee, Memphis, and the UT/Baptist Memorial Hospital Family Medicine Residency Program, Memphis, Tenn.

Reprint requests to: J. Sloan Manning, M.D., 1111 Union Ave., Memphis, TN 38104.

Most of us have participated in local get-togethers sponsored by pharmaceutical companies. New drugs, new indications, and market share grabs are all good reasons for representatives to invite us to hear a speaker, eat a meal, and enjoy a concert, play, or golf game. Is more than goodwill created? Are speakers merely hired guns? Sometimes it may be hard to say; on occasion, however, everyone may benefit.

Sometime ago, a local pharmaceutical representative contacted me in something of a panic. A weekend lunch followed by a theater musical was threatened by the illness of the scheduled speaker. Could I fill in on short notice? I agreed, not burdened by other responsibilities. After all, my wife might enjoy a chance to get away. The honorarium was not bad, either.

The topic was mixed anxious and depressive illness in primary care. This is the usual way that patients present in our offices. At times, the symptoms can be difficult to tease apart. It can be hard to know which symptoms need the most attention, since the patient is often more aware of the anxiety than the comorbid depression. Case examples from our practice followed the lecture material. I like to throw in a ringer to stimulate thinking. The conundrum that caught the eye of several that attended was a case of panic attacks in a woman several months postpartum. "All that wheezes is not asthma" is a common adage in medicine. My twist here was "All that panics is not panic disorder."

The fictitious name that I used for this patient with panic attacks was Ginger. After the presentation, the woman catering the meal rushed up to me and said, "I'm Ginger. Can I come see you?" A physician who had 2 "Gingers" in his practice, about whom he wanted my comments, followed the caterer. Would I see them in consultation? The husband of the caterer worked with a "Ginger" at his office. Could I see her, too? What follows are case descriptions for the original Ginger and the 4 women referred to me as a result of the pinch-hit presentation.

THE ORIGINAL GINGER

"Ginger" was a 32-year-old woman referred by a friend. Since the birth of her second child 9 months before, she found life increasingly difficult to manage. Her usual boundless energy was gone—or at least unavailable when she needed it. She was also uncharacteristically irritable. Periods of sadness lasting a day or 2 punctuated the "funk," but she did not feel depressed, just angry and frustrated. She had attacks of paniclike anxiety. These attacks of breathlessness, palpitation, chest pain, and dizziness escalated to the point that she was unable to go to church, fearing the embarrassment that rushing out of a service might bring. It was her inability to attend church that prompted her to seek help.

Migraines, episodic in the past, now occurred several times a week and lasted 1 to 3 days at a time. Visits to 2 neurologists, laboratory work, and a magnetic resonance imaging (MRI) of her head revealed no abnormalities. A trial of propranolol only worsened her fatigue. Insomnia, particularly difficulty falling asleep, almost certainly made the migraines more frequent, but her mind would not let her fall asleep. Thoughts raced from one subject to

another. Her energy increased in the evening, and she did not feel sleepy at her usual bedtime. She did her housework well past midnight into the early morning hours, knowing sleep would not come even if she tried.

As noted, this was a very different state of affairs for Ginger. She was used to having great energy. She was naturally talkative, outgoing, and social, never needing more than 5 or 6 hours of sleep a night. After the birth of her first child, she purchased a papoose to carry him in and went right along with her usual activities. She was heavily involved in her church and community, cooking for the sick and grieving, taxiing children to and from school. Ginger was very much like her mother. Her mother had been plagued with anxiety from time to time, using lorazepam periodically, but without persistent symptoms or dysfunction. A maternal aunt had been diagnosed with bipolar disorder. Her maternal grandfather was alcoholic and committed suicide. There were no new stressors in Ginger's life except the new baby. Her marriage to a commercial pilot was secure and stable, as were their finances.

Ginger expected a prescription for her anxiety (a la her mother), perhaps with an antidepressant for her panic attacks. She had a friend who took an antidepressant for panic disorder. It came as something of a surprise to hear me connect her family history, premorbid hyperthymic temperament,[1] panic attacks, and migraine. Ginger's aunt had been hospitalized for manic episodes in the past, but Ginger's illness did not resemble that of her aunt, except in the excessive nighttime activity. I explained that the close relatives of those with classic manic depressive illness (bipolar I disorder) often were high functioning and less recognizable as bipolar, but when ill, needed treatment strategies that resembled those with more classic symptoms. Her diagnosis would be termed *bipolar not otherwise specified* in the DSM-IV.[2] In a more recently proposed diagnostic schema, the condition is more nearly bipolar IV,[3] a designation for depressive intrusions into long-standing premorbid temperamental (nonimpairing) hypomanic symptoms. These individuals have a high predilection for bipolar family histories, antidepressant resistance, and treatment-emergent hypomania, mania, rapid cycling, and mixed states. About one third of patients with bipolar illness have comorbid panic disorder,[4–6] thus the admonition about treating panic attacks with antidepressants without inquiries into bipolar symptomatology.

Ginger was placed on divalproex sodium, and the dose was titrated to 750 mg/day. She improved quickly and was asymptomatic within 6 weeks, experiencing mild weight gain managed with diet and exercise. She weaned off the medication after 6 months and has remained asymptomatic.

GINGER #2—THE CATERER

Patti was a 32-year-old who, like the original Ginger, had experienced life as an enjoyable feast until the birth of her only child 9 years earlier. It was then that she began to experience periodic depressions of 1 to 2 months' duration that were debilitating. During the depressions, she found herself extremely fatigued with a tendency to sleep 11 or 12 hours daily. Her appetite and weight increased, leading her into a series of experiences with over-the-counter and prescription diet pills. These helped alleviate the depressed mood, increased her energy, and promoted weight loss, but had adverse effects on her marriage due to irritability and periods of rage. This experimentation culminated in an extramarital affair driven ostensibly by the diet pill combination of fenfluramine and phentermine (Fen/Phen). Her marriage survived the affair, but with lingering scars.

Patti sought help for the depressions and had been treated with 3 different antidepressants. Fluoxetine had helped briefly, but the initial robust response lasted only several weeks. Paroxetine improved her irritability, but with little mood benefits. Both caused troublesome sexual dysfunction. At the time of her initial visit with me, Patti was taking bupropion sustained-release tablets, 150 mg twice per day. This had given her the most consistent benefits with mood improvement, but she still noticed abrupt and unpredictable shifts from lethargy and depressed mood to liveliness and a more normal "driven" mood several times a month. These shifts interfered with planning her home and job activities. She might take on a catering job during a period of energy, only to find herself having to complete the task during a later depression.

Patti's 9-year-old daughter had a diagnosis of attention-deficit/hyperactivity disorder. She was taking paroxetine and dextroamphetamine with inconsistent results. Patti knew relatively little about her family history except that nearly all of her father's siblings and both of his parents were alcoholic.

Patti's bupropion was augmented with divalproex, 250 mg twice daily. Her depressions ended. She also noted that her energy level was somewhat less than that of the periods of liveliness that preceded and followed the depressions. This necessitated a readjustment of expectations for her work capacity. She learned to take on fewer work obligations.

GINGER #3—THE COWORKER OF PATTI'S SPOUSE

Sallie was 28 years old, married without children, and a real estate agent whose tendency to have "ups and downs" was lifelong. Still, she was generally a very productive individual who used her more quiet and contemplative moods to catch up on her reading and rest in anticipation of her next burst of energy. Each phase of the cycle lasted about 2 weeks. She ascribed the periodicity as part of her "romantic tendencies." Several years after she married, Sallie began to notice that her quiet, romantic

phases were becoming more morose and gloomy, with an irritable pessimism that was new to her. She noticed a growing fatigue that affected her work productivity and a sensitivity to the remarks and comments of others. Always a sensitive individual, her feelings were more easily hurt than usual.

Sallie sought help through her gynecologist, who recognized a pattern of premenstrual symptomatic worsening and prescribed sertraline, 50 mg/day. Sertraline did lessen the tendency toward premenstrual worsening of her mood, but the episodic depressions did not cease, and an increase in the sertraline dose to 100 mg/day caused jitteriness and feelings of anxiety.

Sallie's family history contained diagnosed bipolar illness in 3 of her mother's sisters. She suspected that her mother was similarly affected, having suffered through several periods of severe depression during Sallie's teenage years. Her maternal grandfather was alcoholic.

Sallie was begun on divalproex treatment in addition to sertraline, 50 mg/day, but was advised to wean off of the sertraline by reducing her dose to 25 mg/day for 2 weeks. At her 3-week follow-up visit on divalproex, 750 mg daily, she reported substantial improvement in mood stability and work quality. This persisted for several weeks before giving way to a more persistent low-grade depression that was not as severe as that on sertraline alone, but which was not present at the initial response to divalproex. The sertraline was then reinstituted at a dose of 50 mg daily with a prompt return of robust response that has been sustained on the combination of medications.

GINGER #4—REFERRED BY THE FAMILY PHYSICIAN

Mary, 40 years old, was the wife of a physician and had both worked and kept house while her husband finished his education. She was the mother of 3, heavily involved in church and school, and gladly assisted in any and every activity that came her way. She described herself as a "problem magnet," but insisted this had never bothered her until lately. The oldest child of 2 alcoholics, Mary knew her time in Al-Anon had not been unfruitful. She was very aware of her "family baggage." Like the original Ginger, she was a habitual short sleeper—6 hours or less—even on weekends, and was talkative, creative, and people-seeking with a tendency toward impulsive decisions.

For the last 3 years, she had become progressively fatigued, dropping some of her usual activities. This had begun after a hysterectomy and bilateral oophorectomy for endometriosis and dysfunctional uterine bleeding. Her mood was consistently sad, and she worried constantly about trivial matters. This anxiety worsened with a feeling of irritability and tenseness. To unwind, she began to drink wine at night. The amount she needed to relax was escalating. Although the amounts were small compared to what she drank during her college days, she recognized the danger in challenging her family history.

Her physician prescribed fluoxetine, 20 mg/day. Mary remembers that within a week she felt back to her old self. This improvement lasted for 3 or 4 months after which she began to experience periods of depressed mood. At first these lasted only a day or 2, but after another 3 months, she was back where she started symptomatically. A dose increase to 40 mg/day made no improvement. Several attempts at adjusting her hormone replacement therapy, including a combination estrogen and testosterone, were not helpful.

A discussion of treatment options centered on changing antidepressant classes or augmenting with a mood stabilizer—lithium or divalproex. At times, family histories of alcoholism can represent pedigrees loaded for mood disorders. Mary's temperament was classically hyperthymic, but she tied most of her tendencies to her status as an adult child of an alcoholic. I recommended caffeine reduction and suggested counseling. She was concerned about weight gain with divalproex. On a return visit after considering her options, she began lithium carbonate titrated to 600 mg/day over 1 week. She began noticing improvement at the end of week 2 on lithium treatment, and over 8 weeks experienced a gradual, but steady symptom reduction. She noted that her tendency toward dramatics had faded. This, plus her lack of impulsivity while taking the lithium, required some getting used to, but her family and friends encouraged her in that regard with comments about stability and predictability. Mild polyuria and a slight metallic taste were the only side effects lithium caused and were well tolerated.

GINGER #5—ALSO REFERRED BY THE FAMILY PHYSICIAN

Alice was a 58-year-old woman who had never experienced a significant depression until 5 years before when she lost her mother, father, and husband to death all within a 6-month period. This had devastated her. She sank into a period of grief that continued up to the time of her presentation in my office. She, like the others in this case series, was accustomed to the role of superwoman with the typical trappings of the hyperthymic temperament, except that her sleep was not shortened. She had been capable, gregarious, and a good match for her entrepreneurial husband in their 35-year marriage. Four children were successfully launched from the nest and were independent and successful in their own right.

Alice's family history was free of significant mental illness with the exception of an alcoholic paternal uncle. Her father had been an attorney and served on the state legislature.

Her depressed mood had been constant for most of the last 5 years and was accompanied by insomnia, fatigue,

poor concentration, and generalized worry. She, like Sallie, had become uncharacteristically pessimistic in her outlook. Also, Alice's somatic health seemed to be on the decline with a diagnosis of type 2 diabetes mellitus arising from her being overweight. Her medications included an angiotensin-converting enzyme inhibitor, glucophage, levothyroxine, and diltiazem. She felt guilty about her lack of attention to diet and failure to exercise, but lacked motivation for either. Three different antidepressants, 2 selective serotonin reuptake inhibitors (SSRIs) and venlafaxine, had been tried without much improvement, although the maximum dose of venlafaxine had been only 75 mg/day. She arrived for her initial visit with a close friend, who came "for moral support and to make sure I remember what happens."

We discussed the difficulties posed by her multifaceted illness—grief, her physical condition and its possible role in creating a resistant depression, and the potential benefit from a period of structured psychotherapy like interpersonal therapy. Her last hemoglobin A_{1c} was 10.1%, indicating poor glucose control. Her thyroid replacement was adequate as indicated by a TSH well within the normal limit.

She felt more comfortable in continuing to see her primary care physician, so I discussed with him a plan of action that addressed diabetic control, an evaluation for other complicating somatic conditions such as stroke and connective tissue disease, adding psychotherapy, and retitrating venlafaxine to a therapeutic dose with the option of switching to another antidepressant class if this proved ineffective. To date, I have not seen her in follow-up.

CONCLUSION

One should be careful not to overinterpret a small case series such as this. However, the experience described is real, as are the documented illnesses. The cases are thematic and recognizable. The diagnostic impressions and interventions are founded on solid clinical research. What can be concluded?

First, clinical gestalts can be communicated between clinicians. This is dependent, of course, on one's motivation to learn, but is possible in a variety of settings as long as the communication is case- and evidence-based. I bemoan elsewhere in this issue that I often find that the greatest interest in this advanced level of diagnosis and treatment exists among physicians and others who practice in great isolation from centers of research. Frustrated physicians and suffering patients need to know there is hope for refractory mood disorders.

Second, this series suggests that hyperthymic temperaments complicated by depressive episodes represent a form of mood disorder presentation that is highly recognizable and responsive to pharmacologic intervention. The therapeutic hypothesis here is that the premorbid temperamental hypomanic tendencies represent a less penetrant form of bipolar illness and may require somatic strategies that are more in line with those of classic manic depressive illness. There is a growing body of world literature that supports this hypothesis.[7] These "soft" (nonmanic) bipolar patients may also display some of the treatment resistance seen in manic bipolarity—antidepressant refractoriness and erratic, premature, or exaggerated antidepressant responses (so-called flash-in-the-pan) that can take the form of treatment-emergent hypomania or mania and, possibly, rapid cycling.[7,8]

Lastly, the treatment of mood disorders is often not straightforward. Only one half of patients treated with an adequate trial of a single antidepressant will have a full response. This leaves a considerable number of depressed and anxious patients with partial or no response to a single agent.[9] For many, complete symptomatic relief is a prolonged process heavily dependent on the expertise of the treating clinician; the motivation, health, beliefs, and level of social support of the patient; and the quality of the therapeutic alliance. What seems to be needed is research that clarifies the biological underpinnings of this biologically heterogeneous illness "depression" and new ways that the clinical ramifications of this research can be transmitted to those who see the majority of affected patients. That means communication with practitioners in primary care, the "de facto mental health system."[10]

Drug names: bupropion (Wellbutrin), dextroamphetamine (Dexedrine and others), diltiazem (Cardizem and others), divalproex sodium (Depakote), fluoxetine (Prozac), levothyroxine (Synthroid and others), lorazepam (Ativan and others), paroxetine (Paxil), phentermine (Fastin and others), propranolol (Inderal and others), sertraline (Zoloft), venlafaxine (Effexor).

REFERENCES

1. Manning JS, Connor PD, Sahai A. The bipolar spectrum: a review of current concepts and implications for depression management in primary care. Arch Fam Med 1998;7:63–71
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
3. Akiskal HS, Pinto O. The evolving bipolar spectrum: prototypes I, II, III, and IV. Psychiatr Clin North Am 1999;22:517–534
4. Savino M, Perugi G, Simonini E, et al. Affective comorbidity in panic disorder: is there a bipolar connection? J Affect Disord 1993;28:155–163
5. Woodman CL, Noyes R Jr. Panic disorder: treatment with valproate. J Clin Psychiatry 1994;55:134–136
6. Shoaib AM, Dilsaver SC. Panic disorder in subjects with pure mania and depressive mania. Anxiety 1995;1:302–304
7. Akiskal HS, Mallya G. Criteria for the "soft" bipolar spectrum: treatment implications. Psychopharmacol Bull 1987;23:68–73
8. Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 1995;152:1130–1138
9. American Guideline for Major Depressive Disorder in Adults. Am J Psychiatry 1993;150(4, suppl):1–26
10. Regier DA, Narrow WE, Rai DS, et al. The de facto US Mental and Addictive Disorders Service System: Epidemiologic Catchment Area prospective 1-year prevalence rates of disorders and services. Arch Gen Psychiatry 1993;50:85–94