The Implications of Medical and Psychiatric Comorbidity With Panic Disorder

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The frequent presentation of patients with panic disorder in medical settings may, in part, be explained by the physical symptoms inherent in panic disorder. However, a number of medical disorders have symptoms that overlap with panic disorder symptoms, and elevated panic disorder prevalence is comorbid with a number of medical illnesses, including respiratory disorders, vestibular dysfunction, and hyperthyroidism and hypothyroidism. The presence of medical comorbidity complicates the identification, presentation, and treatment of panic disorder. In addition, comorbid mood disorders occur commonly and result in greater severity, poorer quality of life, and greater impairment. Recent work suggests that panic disorder occurs more commonly with bipolar disorder than major depressive disorder, resulting in substantial impairment, as well as poorer response to treatment. The implications of mood disorder and its medical comorbidity for the identification and treatment of panic disorder are discussed. *(J Clin Psychiatry 2005;66[suppl 4]:8–15)*

THE PRESENTATION OF PANIC DISORDER IN PRIMARY CARE

Patients with panic disorder commonly present to their primary care doctors, or in other medical settings, reflecting the high utilization of medical services by patients with panic disorder—even when compared to those with other psychiatric disorders.[1,2] In one study, men and women with 6 or more medical visits in the past 6 months were, respectively, 5 and 8 times more likely to have a diagnosis of panic disorder, while the odds of depression or substance use disorders were substantially lower for those with this level of medical services.[3] Such high utilization of services appears particularly prominent for patients with panic comorbid with other psychiatric disorders.[2]

Furthermore, some patients ultimately diagnosed with panic disorder initially present with somatic complaints and not a primary complaint of anxiety or fear. There is a wide variability in the ability of patients to describe the sensation of anxiety, or what the focus of their anxiety is. Some patients will simply express a general feeling that something is not "right" in their body, responding to somatic symptoms with an explanatory model that there is something physically, not psychiatrically, wrong with them. However, symptoms of panic attacks, such as shortness of breath, chest pain, and dizziness, are among the most common presenting complaints in medical settings, and a small minority of patients receive any specific diagnosis for these presenting somatic complaints,[4] complicating the detection of panic disorder.

Reflecting this, data from the community sample of the National Institute of Mental Health (NIMH) Epidemiologic Catchment Area (ECA) study[5] suggest that patients who present with multiple unexplained symptoms have a 200 times increased likelihood, or odds, of having panic disorder, compared with an odds ratio of 24 for mania and 17 for major depression. Some work also suggests that patients who are referred for psychiatric care by their primary care doctors are more likely to have prominent physical symptoms without significant medical illness than self-referred patients with panic.[6] Thus, while there has been improvement in the detection and treatment of panic in primary care settings, many challenges still remain.

RISK FACTORS FOR PANIC DISORDER

In addition to unexplained physical symptoms, negative or stressful life events may occur as an antecedent of panic disorder.[7] In retrospective studies, as many as 80% of patients with panic disorder report life stressors in the year prior to diagnosis, and a vast majority believe that this event contributed to the onset of the panic disorder.[7–9] Severe life events are more common in patients who develop panic disorder than healthy controls. Faravelli[10] found a high proportion of patients experienced a major

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life event (death or severe illness, either personally or of a relative, within 2 months) prior to the onset of the panic.[10] Further, symptom severity has been correlated with negative life events, including interpersonal conflicts, physical or health-related problems, and trouble at work.[11,12] The presence of chronic life stressors may also worsen the course of panic disorder,[13] while a recent loss or separation appears to elevate the risk of depression comorbid with panic disorder.[8,9]

Life stressors may serve as a trigger for those with a preexisting or underlying diathesis toward anxiety. The way that individuals experience life events and the impact of those life events are influenced by the underlying phenotype of the individual. For example, patients with high levels of anxiety sensitivity, including a fear of physical sensations, have been shown to be at increased risk for panic disorder.[14] An example in keeping with this hypothesis is the greater likelihood for a person with high anxiety sensitivity to have stress-induced somatic symptoms of anxiety or fear resulting in persistent, full-blown panic disorder compared with individuals with low anxiety sensitivity who might only develop transient panic symptoms.

Similarly, the occurrence of a medical disorder may serve as a risk factor, or trigger, for the onset or worsening of panic disorder. In some cases, the medical disorder may onset prior to panic. Alternately, the medical disorder may onset later and may serve to exacerbate the preexisting panic disorder. There are a number of different mechanisms by which medical disorders may theoretically increase the risk of panic disorder. For example, there may be shared pathophysiology between the medical disorder and panic disorder, as may be the case for patients with respiratory diseases. Alternately, the experience of the physical symptoms of a medical disorder may result in a higher level of anxiety and fear for patients with anxiety, which may then amplify their experience of these symptoms.

PANIC DISORDER AND MEDICAL COMORBIDITY

Respiratory Disease

One example of symptoms of a medical disorder overlapping with symptoms of panic attacks is shortness of breath due to a respiratory disease, such as asthma or chronic obstructive pulmonary disease (COPD). There have been numerous studies examining anxiety disorders, specifically panic disorder, in patients with pulmonary disease.[15,16] More than a third of patients with COPD have an anxiety disorder, while up to one fourth meet criteria for panic disorder.[17–20]

Many studies have also reported an overlap between panic disorder and asthma. One study of 51 patients with asthma found a 20% prevalence of panic disorder and a 26% prevalence of unexpected panic attacks, which are significantly higher than reported rates for the general population.[21] Goodwin et al.,[22] in a study of 4181 patients with current severe asthma, found that over a quarter (28.8%) of patients with severe asthma also had an anxiety disorder. Twenty percent of patients with severe asthma experienced panic attacks, and 10% had panic disorder.[22] In a second study by Goodwin and Eaton[23] using epidemiologic data (N = 2768), self-reported asthma was significantly associated with elevated panic attack prevalence at both baseline and follow-up compared with those without asthma. This association of asthma with panic attacks also appears to be present for children between the ages of 9 and 17 years.[24] Overall, the lifetime prevalence of respiratory disease has been reported as high as 47% in patients with panic disorder.[25] Further, high sensitivity to experimentally elevated carbon dioxide levels is a risk factor for panic disorder.[26,27]

Anxiety disorder comorbidity also worsens subjective symptom reporting of symptoms such as shortness of breath (dyspnea), wheezing, and coughing associated with respiratory disorders.[28] The presence of anxiety comorbidity in patients with pulmonary disease is associated with poor quality of life and greater use of treatments, including higher levels of steroid and bronchodilator use and higher rates of hospitalization.[15,29] Some patients with panic disorder but normal pulmonary function nonetheless experience respiratory symptoms as severe as those of patients with asthma.[30] Respiratory irregularity and variability have also been observed in patients with panic disorder.[31–33]

A recent case series of patients with COPD both with and without major mood and anxiety disorders treated with sertraline (25–100 mg/day) reported improvement in both mood and anxiety symptoms, as well as moderate to marked improvement in dyspnea and exercise tolerance, without change in objective measures of pulmonary function.[17] COPD with comorbid panic disorder provides an example of a case in which the medical disorder is chronic, yet intervention for panic disorder may provide symptomatic relief for both disorders.

Vestibular Dysfunction

Another often chronic disorder possibly exacerbated by anxiety is dizziness due to vestibular dysfunction.[34] Patients with vertigo often have episodes that may occur predictably as a result of specific triggers, such as movement, but may also occur at times unpredictably, without a clear trigger; similarly, panic attacks can be brought on by triggers or occur spontaneously. There is also some evidence clinically that patients presenting with dizziness experience anxiety symptoms that are impairing, but that do not meet DSM-IV criteria for diagnosis.

One study[35] of healthy controls found that high anxiety led to a lessened ability of the vestibular system to maintain balance. A second study,[36] also with healthy controls, found that elevated levels of anxiety were associated with increased postural sway. Recent work describing potential neurobiological pathways may help to explain the high co-

morbidity between anxiety and dizziness due to vestibular dysfunction.[37,38] For patients who develop chronic treatment refractory vertigo, the goal is to reduce the intensity of their symptoms and enable them to function regardless of their dizziness. One recent case series[39] of 60 patients with significant dizziness (although not all vestibular in etiology) demonstrated that treatment with a selective serotonin reuptake inhibitor (SSRI) led to improvement in symptoms, although it is unknown whether SSRIs actually alter the primary underlying pathology responsible for the dizziness. More research is needed to understand the interaction of vestibular dysfunction and anxiety and the role of antidepressants in the treatment of these comorbid disorders.

Hyperthyroidism and Hypothyroidism

Another area in which the overlap of medical disorders and anxiety has been well documented is thyroid disorders, particularly hyperthyroidism and hypothyroidism.[40,41] However, data supporting elevated rates of thyroid disease in patients with anxiety disorders have been fairly inconsistent.

Recently, data from thyroid histories and serum testing in 169 patients from 10 clinical trials were compared with the expected combined rate of hyperthyroidism and hypothyroidism in the general population (2.7%).[41] While few patients in this tertiary care population had current thyroid abnormalities detected by serum testing, 1% with panic disorder, 2% with social phobia, and 10% with generalized anxiety disorder (GAD) reported a lifetime history of thyroid disease. These rates were significantly elevated above population rates only for GAD. However, prior panic studies that together examined panic and both thyroid history and test results also suggested significantly elevated rates of thyroid dysfunction (6.5%). Thus, available data suggest all patients with panic disorder should be queried about thyroid histories, and serum thyroid screening of GAD and panic disorder patients who have not received prior testing is warranted.[41]

Cardiac Disease

Another area of medical overlap with panic disorder is cardiac symptoms. There are multiple somatic symptoms such as heart palpitations or chest pain occurring during panic attacks that may not be easily differentiated from those of a primary cardiac disorder.[42] Epidemiologic data suggest that there is a 4 times increased likelihood of panic disorder in patients with chest pain compared with patients without chest pain.[43] Further, many of these patients seek treatment first in the emergency room or in other medical settings.[42]

In one study,[44] one third of ambulatory cardiology patients with negative workups had panic disorder. Another study[45] reported that as many as 43% of emergency room patients with atypical chest pain had either panic attacks or panic disorder. Unfortunately, a recent Canadian emergency room study[46] found that 98% of patients with panic disorder remain undiagnosed when admitted to the emergency room with chest pain. Furthermore, one study[47] found that up to a third of patients admitted to the coronary care unit had panic disorder, with 21% of those with panic also having cardiac findings, including myocardial infarction; however, of those without cardiac findings, fully 55.5% had panic disorder.

A recent meta-analysis also found that patients with panic disorder have elevated risk factors for coronary artery disease and recommended clinical assessment and screening, if indicated, for coronary artery disease in patients with panic disorder.[48] Thus, the presence of panic disorder does not preclude the presence of cardiac disease, but the likelihood of panic disorder in patients with cardiac symptoms who have received negative workups is very high, and all such patients should receive screening and be offered treatment should panic be present. To aid in the detection of panic disorder in emergency rooms and cardiology settings, a recent meta-analysis[42] of predictors identified 5 variables that correlate the presence of panic disorder in patients with chest pain: absence of coronary artery disease, atypical quality of chest pain, female sex, younger age, and a high level of self-reported anxiety.

There has been growing interest in the potential connection between anxiety, particularly panic and phobic anxiety, and increased mortality due to fatal coronary heart disease, including sudden cardiac death. Longitudinal studies have found that men with anxiety symptoms, and specifically phobic anxiety, have a 3-fold increase in the risk of coronary heart disease, with a 4- to 6-fold increased risk of sudden cardiac death.[49,50] One potential etiologic link may be autonomic abnormalities, specifically reduced heart rate variability, a risk factor for arrhythmias and sudden cardiac death.[51,52] A number of studies utilizing different measures of heart rate or rhythm variability have demonstrated abnormalities in patients with panic disorder.[53–56] Of significant interest, treatment of panic disorder with SSRIs such as paroxetine has been associated with a significant improvement in these measures, which theoretically may decrease risk for mortality due to sudden cardiac death; these changes with treatment may be due to alterations in autonomic activity.[57,58] In contrast, 2 different studies[56,59] of tricyclic antidepressants noted a negative impact on these cardiac measures, with no change in the presence of SSRIs.

PANIC AND MOOD DISORDER COMORBIDITY

Major Depressive Disorder

Patients with anxiety disorders, including panic disorder, are also at elevated risk for comorbid mood disorders, which should be assessed and taken into account when selecting a treatment for a patient with panic disorder. Epidemiologic data from the ECA study[60] suggest that comor-

bid panic is also quite common in patients with primary mood disorders, with lifetime panic present in 10% of patients with major depression and 21% of those with bipolar disorder, compared with a panic prevalence of 0.8% for those with no mood disorder. The elevated rate of lifetime major depressive disorder associated with panic disorder has been well established, and should almost be considered the rule rather than the exception in clinical settings, particularly when more than one anxiety disorder is present.

For example, Stein and Uhde[61] reported a 47% risk of depression in patients with panic disorder alone and a 94% risk for depression when both panic and social phobia were present.[61] In a prospective longitudinal study conducted with 3021 14- to 24-year-old participants assessed over a 4-year period, Wittchen and colleagues[62] found that the presence of panic attacks, persistent avoidance, or severe impairment related to anxiety each doubled the participants' odds of having a new episode of major depressive disorder. The presence of 2 or more anxiety disorders again led to a nearly tripling of the risk for developing major depressive disorder.[62]

The order of onset of comorbid disorders with anxiety and depression has been examined as one way to explore the etiology of this comorbidity. Kaufman and Charney[63] illustrated that while GAD, social anxiety disorder, and posttraumatic stress disorder (PTSD) occur more commonly prior to the first episode of depression (63%, 65%, and 53%–78%, respectively), panic disorder has only a 29% rate of onset preceding the development of major depressive disorder.[63] Approximately one third of the time, the onset of panic and depression occurs simultaneously,[63] suggesting potentially overlapping triggers of disorder onset. However, to date, the order of onset has not been demonstrated to alter treatment outcome in the presence of both panic and major depressive disorder.[64]

The precise etiologic connection between depression and anxiety disorders has yet to be elucidated. One potential overlapping trigger is life stress, as demonstrated by the elevated risk for comorbid depression within one year of panic onset for those with a major life stressor of a loss or separation, compared with those without such a stressor (82% compared with only 32% developing a depressive episode, respectively).[8,9] A second study, retrospectively examining those with panic and depression compared with those with panic alone, similarly found higher rates of life stress within the first year of panic onset for those with depression compared with those without (41% vs. 25%).[65] In addition, the anxiety disorder may serve as a stressor, particularly in cases where the onset of anxiety disorder occurred first, although research is needed to understand the precise triggers of depression. Some possibilities include demoralization as a result of work and social dysfunction, as well as overlapping neurobiological vulnerabilities.[66]

Another area of active research is the potential for an overlapping genetic risk for the development of major depressive disorder and panic disorder. For example, a recent multicenter study[67] of siblings with early onset, recurrent major depressive disorder found an elevated risk for comorbid panic disorder in women, but not in men. However, evidence for co-segregation in families with panic disorder and major depression is not all positive,[68] and likely the sharing of familial risk factors, if present, is modest.[69]

Regardless of etiology, the effect of comorbid depression in patients with primary anxiety disorders has been well demonstrated to increase the severity and chronicity of the anxiety disorder, worsen functional impairment for the patient, and increase the risk of other comorbidities such as alcohol and substance abuse.[63,70–72]

An elevated risk of suicidality is also associated with depression comorbidity. For example, the lifetime risk of suicide attempts in patients with panic and major depression comorbid with each other is 19.5 suicide attempts per 100 patients, which is more than double that of the 2 disorders independently (7.0 and 7.9 per 100 patients for panic disorder alone and major depression alone, respectively).[73] Similarly, the likelihood of having suicidal ideation over a 2-week period among primary care patients with panic disorder comorbid with depression was 3 times the odds of suicidal ideation for each disorder alone when compared with a control group with neither disorder, even after statistically controlling for the influence of sociodemographics and substance abuse.[74]

Research examining the impact of comorbid major depressive disorder on treatment selection and outcome for patients with panic disorder is limited. Generally, antidepressants are the first line of pharmacotherapy, since they have proven efficacy for both disorders independently. One 14-week study[75] examined the differential effects of sertraline compared with imipramine for the treatment of comorbid panic and major depressive disorder and found no significant difference between the 2 treatments for improvement in measures of depression or panic severity, although the SSRI, sertraline, was better tolerated.

However, as with panic disorder alone, patients with comorbid panic and depression may have a high level of fear of the physical sensations that often accompany the initiation of antidepressants, and these fears may result in an inability to tolerate or a lack of willingness to continue pharmacotherapy. Therefore, dosing of antidepressants should "start low" and "go slow," initiating at half the recommended initial doses for depression (e.g., initiate sertraline at 25 mg/day or fluoxetine or paroxetine at 10 mg/day). However, the dose should continue to be titrated up to clinically effective doses.

Benzodiazepines may acutely aid in antidepressant initiation.[76,77] However, monotherapy with benzodiazepines for panic should be avoided in the presence of depression comorbidity, since benzodiazepines are not efficacious as monotherapy for depression.

Cognitive-behavioral therapy (CBT) is also an effective treatment for panic disorder with comorbid depression.[78–80] In a study conducted by Tsao and colleagues,[80] 63.6% of patients had at least 1 comorbid condition prior to receiving CBT for panic disorder, and only 27.3% had a comorbid condition posttreatment. However, severe depression may impair outcome,[78] and some type of additional intervention may be needed to treat the depression.[71] When utilizing either CBT or psychopharmacologic treatment, adjunctive or alternative strategies may be needed to optimize outcome in patients with depression comorbidity, who tend to have more severe symptoms. However, data to guide the treatment of comorbid disorders are needed.

Bipolar Disorder

While the field has recognized depression comorbid with panic disorder for some time, the presence of anxiety disorders, and specifically panic disorder, comorbid with bipolar disorder has recently become an area of active interest and research. Population data from the ECA demonstrated that the lifetime prevalence of panic disorder is 26 times greater in patients with bipolar disorder (20.8%) than in control subjects (0.8%) and significantly more common than for those with major depression (10%).[61] The high rate of comorbid anxiety disorders with bipolar disorder has also been identified in clinical samples. For example, a study of 230 patients with either bipolar disorder or major depressive disorder who participated in clinical research trials found that the rate of lifetime panic disorder was much higher in patients with bipolar disorder (37.8%) than the similarly derived sample with unipolar major depression (14.4%).[81] Baseline data from the first 500 patients in a multicenter longitudinal study funded through the NIMH and the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) further demonstrated that over 50% of patients with bipolar disorder had a lifetime DSM-IV anxiety disorder, and 30% had a current anxiety disorder. Furthermore, panic disorder was currently present for 8%, while 17% reported a lifetime history of panic.[82] Higher rates of panic disorder with and without agoraphobia were also present for patients with the bipolar I subtype (9% current, 18% lifetime) than for bipolar II (4% current, 14% lifetime).[82] These findings are contrary to some theories about a specific bipolar II and anxiety connection.[83]

Although the genetics of mood and anxiety disorders appear to be complex, recent family studies[84–87] have provided initial evidence of shared genetics for patients with bipolar disorder and panic disorder to a greater extent than published to date for major depressive disorder and panic. In families with a high prevalence of bipolar disorder, panic disorder occurs commonly comorbid with bipolar disorder; further, it is believed that it is inherited.[84,85] Specifically, a linkage analysis of chromosome 18 data identified 5 consecutive chromosome 18q marker loci that were associated with families specifically with bipolar disorder plus panic disorder.[84] This overlapping, inherited risk, as further demonstrated in a study of 203 families participating in the NIMH Bipolar Genetics Initiative, may signify a common genetic etiology for a subset of patients with panic and bipolar comorbidity.[85] In support of the hypothesis that comorbid panic and bipolar disorder may represent a genetic subtype, a recent Italian study found differential association with polymorphisms of catechol *O*-methyltransferase, serotonin transporter, and tryptophan hydroxylase genes dependent on the presence or absence of comorbid panic disorder.[86] Further supporting a potential bipolar subtype for genetic research, rapid mood switching and panic disorder appear to aggregate in families with bipolar disorder.[87]

Understanding anxiety comorbidity with bipolar disorder is critical because of the negative impact anxiety disorders appear to have on bipolar course and outcome. For example, anxiety disorders including panic have been associated with a younger age of bipolar onset, a poorer course of bipolar disorder, poorer quality of life and function, and substantially elevated levels of suicidality.[82]

A study of 66 patients with bipolar I disorder demonstrated that the presence of lifetime panic spectrum symptoms, in patients with either subsyndromal or full panic disorder, are associated with poor or delayed response to treatment of bipolar disorder.[88] Treatment response was delayed by 27 weeks for patients with panic spectrum comorbidity compared with those without (with acute response in 44 compared with 17 weeks). A history of anxiety symptoms, including panic attacks, has also been demonstrated in a study[89] of maintenance therapies for bipolar I disorder to be significantly associated with longer time to remission, a greater number of medications required to achieve remission, as well as more severe side effects with medications.

Very limited data are available to guide pharmacotherapy selection for the treatment of anxiety disorders comorbid with bipolar disorder. Two studies[90,91] utilized billing or diagnostic codes used in a clinical setting to examine the impact of "any" comorbidity on prescription patterns for patients with bipolar disorder. While this method is limited by the potential for a lack of inclusion of some comorbid diagnoses, one study reported greater antipsychotic and antidepressant use in the setting of comorbidity[90] and the other reported a lack of impact of comorbidity on prescribing practices.[91] Another study[92] utilizing recorded pharmacotherapy data from baseline entry into a clinical study of bipolar disorder (STEP-BD) examined the impact of comorbid anxiety disorders on prescribed medication. In addition, definitions of "minimally adequate" treatment for anxiety disorders and for mood stabilization were developed based on available data and expert consensus. In this patient cohort in clinical treatment prior to entry into a clinical study, the presence of anxiety

disorders was minimally associated with pharmacotherapy selection.[92] Further, 60% of patients, regardless of comorbidity, were receiving inadequate mood stabilization, and only 42% of patients with a current anxiety disorder were receiving "minimally adequate" pharmacotherapy for the anxiety disorder.[92] However, these findings likely reflect the many problems associated with treatment selection for panic or other anxiety disorders comorbid with bipolar disorder.

Primarily, there is a lack of study of the area of comorbid panic and bipolar disorders, and clinicians may be utilizing treatments without proven efficacy that may nonetheless be clinically useful. Pharmacotherapy selection for patients with bipolar disorder and anxiety comorbidity is also complicated by the high rates of comorbid substance abuse, limiting prescribing of benzodiazepines by physicians, and the risk of increased cycling with antidepressants, now the first line of treatment for panic disorder without bipolar comorbidity. Finally, the complexity of managing the primary symptoms of bipolar disorder may interfere with the detection and treatment of comorbid anxiety disorders. While controlled studies of the pharmacotherapy of anxiety disorders comorbid with bipolar disorder are needed, it is clear that mood stabilization should be optimized and prioritized for these patients, and monotherapy with antidepressants should be avoided. Emerging data support the efficacy of anticonvulsants for anxiety disorders,[93–97] and further study of their safety and efficacy for panic and bipolar comorbidity is indicated. In addition, psychosocial therapies such as CBT may be helpful. While panic disorder in the setting of bipolar disorder is clearly a marker of poor outcome, suggesting clinical attention should be given to both disorders, there are no data available to understand the impact of treating comorbid anxiety on bipolar outcomes, and much research is needed.[98]

Drug names: fluoxetine (Prozac and others), imipramine (Tofranil and others), paroxetine (Paxil and others), sertraline (Zoloft).

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REFERENCES

1. Katon W, Von Korff M, Lin E. Panic disorder: relationship to high medical utilization. Am J Med 1992;92:7S–11S
2. Roy-Byrne PP, Stein MB, Russo J, et al. Panic disorder in the primary care setting: comorbidity, disability, service utilization, and treatment. J Clin Psychiatry 1999;60:492–499
3. Simon GE. Psychiatric disorder and functional somatic symptoms as predictors of health care use. Psychiatr Med 1992;10:49–59
4. Kroenke K, Mangelsdorff AD. Common symptoms in ambulatory care: incidence, evaluation, therapy, and outcome. Am J Med 1989;86:262–266
5. Simon G, Von Korff M. Somatization and psychiatric disorder in the NIMH Epidemiologic Catchment Area study. Am J Psychiatry 1991;148:1494–1500
6. Roy-Byrne P, Katon W, Cowley D, et al. Panic disorder in primary care: biopsychosocial differences between recognized and unrecognized patients. Gen Hosp Psychiatry 2000;22:405–411
7. Manfro GG, Otto MW, McArdle ET, et al. Relationship of antecedent stressful life events to childhood and family history of anxiety and the course of panic disorder. J Affect Disord 1996;41:135–139
8. Roy-Byrne PP, Geraci M, Uhde TW. Life events and course of illness in patients with panic disorder. Am J Psychiatry 1986;143:1033–1035
9. Roy-Byrne PP, Geraci M, Uhde TW. Life events and the onset of panic disorder. Am J Psychiatry 1986;143:1424–1427
10. Faravelli C. Life events preceding the onset of panic disorder. J Affect Disord 1985;9:103–105
11. Lteif G, Mavissakalian M. Life events and panic disorder/agoraphobia: a comparison at two time periods. Compr Psychiatry 1996;37:241–244
12. Lteif G, Mavissakalian M. Life events and panic disorder/agoraphobia. Compr Psychiatry 1995;36:118–122
13. Wade SL, Monroe SM, Michelson LK. Chronic life stress and treatment outcome in agoraphobia with panic attacks. Am J Psychiatry 1993;150: 1491–1495
14. Gardenswartz C, Craske M. Prevention of panic disorder. Behav Ther 2001;32:725–737
15. Smoller JW, Pollack MH, Otto MW, et al. Panic anxiety, dyspnea, and respiratory disease: theoretical and clinical considerations. Am J Respir Crit Care Med 1996;154:6–17
16. Goodwin RD, Pine DS. Respiratory disease and panic attacks among adults in the United States. Chest 2002;122:645–650
17. Smoller JW, Otto MW. Panic, dyspnea, and asthma. Curr Opin Pulm Med 1998;4:40–45
18. Yellowlees PM, Alpers JH, Bowden JJ, et al. Psychiatric morbidity in patients with chronic airflow obstruction. Med J Aust 1987;146:305–307
19. Karajgi B, Rifkin A, Doddi S, et al. The prevalence of anxiety disorders in patients with chronic obstructive pulmonary disease. Am J Psychiatry 1990;147:200–201
20. Porzelius J, Vest M, Nochomovitz M. Respiratory function, cognitions, and panic in chronic obstructive pulmonary patients. Behav Res Ther 1992;30:75–77
21. Perna G, Bertani A, Politi E, et al. Asthma and panic attacks. Biol Psychiatry 1997;42:625–630
22. Goodwin RD, Jacobi F, Thefeld W. Mental disorders and asthma in the community. Arch Gen Psychiatry 2003;60:1125–1130
23. Goodwin RD, Eaton WW. Asthma and the risk of panic attacks among adults in the community. Psychol Med 2003;33:879–885
24. Goodwin RD, Pine DS, Hoven CW. Asthma and panic attacks among youth in the community. J Asthma 2003;40:139–145
25. Zandbergen J, Bright M, Pols H, et al. Higher lifetime prevalence of respiratory diseases in panic disorder? Am J Psychiatry 1991;148:1583–1585
26. Klein D. False suffocation alarms, spontaneous panics, and related conditions: an integrative hypothesis. Arch Gen Psychiatry 1993;50:306–317
27. Gorman J, Fyer M, Goetz R, et al. Ventilatory physiology of patients with panic disorder. Arch Gen Psychiatry 1988;45:31–39
28. Dales RE, Spitzer WO, Schechter MT, et al. The influence of psychological status on respiratory symptom reporting. Am Rev Respir Dis 1989; 139:1459–1463
29. Carr R. Panic disorder and asthma. J Asthma 1999;36:143–152
30. Carr R, Lehrer P, Hochron S. Panic symptoms in asthma and panic disorder: a preliminary test of the dyspnea-fear theory. Behav Res Ther 1992;30:251–261
31. Yeragani V, Radhakrishna R, Tancer M, et al. Nonlinear measures of respiration: respiratory irregularity and increased chaos of respiration in patients with panic disorder. Neuropsychobiology 2002;46:111–120
32. Martinez J, Coplan J, Browne S, et al. Respiratory variability in panic disorder. Depress Anxiety 2001;14:232–237
33. Abelson JL, Weg JG, Nesse RM, et al. Persistent respiratory irregularity in patients with panic disorder. Biol Psychiatry 2001;49:588–595
34. Yardley L, Redfern MS. Psychological factors influencing recovery from balance disorders. J Anxiety Disord 2001;15:107–119
35. Bolmont B, Gangloff P, Vouriot A, et al. Mood states and anxiety influence abilities to maintain balance control in healthy human subjects. Neurosci Lett 2002;329:96–100
36. Wada M, Sunaga N, Nagai M. Anxiety affects the postural sway of the antero-posterior axis in college students. Neurosci Lett 2001;302:157–159
37. Balaban CD. Neural substrates linking balance control and anxiety. Physiol Behav 2002;77:469–475

38. Balaban CD, Thayer JF. Neurological bases for balance-anxiety links. J Anxiety Disord 2001;15:53–79
39. Staab JP, Ruckenstein MJ, Solomon D, et al. Serotonin reuptake inhibitors for dizziness with psychiatric symptoms. Arch Otolaryngol Head Neck Surg 2002;128:554–560
40. Demet MM, Ozmen B, Deveci A, et al. Depression and anxiety in hyperthyroidism. Arch Med Res 2002;33:552–556
41. Simon NM, Blacker D, Korbly NB, et al. Hypothyroidism and hyperthyroidism in anxiety disorders revisited: new data and literature review. J Affect Disord 2002;69:209–217
42. Huffman JC, Pollack MH. Predicting panic disorder among patients with chest pain: an analysis of the literature. Psychosomatics 2003;44:222–236
43. Ford D. The relationship of psychiatric illness to medically unexplained chest pain. Presented at Mental Disorders in General Health Care Settings: A Research Conference; 1987; Seattle, Wash
44. Beitman BD, Mukerji V, Lamberti JW, et al. Panic disorder in patients with chest pain and angiographically normal coronary arteries. Am J Cardiol 1989;63:1399–1403
45. Wulsin LR, Hillard JR, Geier P, et al. Screening emergency room patients with atypical chest pain for depression and panic disorder. Int J Psychiatry Med 1988;18:315–323
46. Lynch P, Galbraith KM. Panic in the emergency room. Can J Psychiatry 2003;48:361–366
47. Carter C, Maddock R, Amsterdam E, et al. Panic disorder and chest pain in the coronary care unit. Psychosomatics 1992;33:302–309
48. Katerndahl D. Panic plaques: panic disorder & coronary artery disease in patients with chest pain. J Am Board Fam Pract 2004;17:114–126
49. Kawachi I, Colditz GA, Ascherio A, et al. Prospective study of phobic anxiety and risk of coronary heart disease in men. Circulation 1994;89:1992–1997
50. Kawachi I, Sparrow D, Vokonas PS, et al. Symptoms of anxiety and risk of coronary heart disease: the Normative Aging Study. Circulation 1994; 90:2225–2229
51. Gorman JM, Sloan RP. Heart rate variability in depressive and anxiety disorders. Am Heart J 2000;140(suppl 4):77–83
52. Friedman BH, Thayer JF. Autonomic balance revisited: panic anxiety and heart rate variability. J Psychosom Res 1998;44:133–151
53. Yeragani VK, Pohl R, Berger R, et al. Decreased heart rate variability in panic disorder patients: a study of power-spectral analysis of heart rate. Psychiatry Res 1993;46:89–103
54. Yeragani VK, Pohl R, Jampala VC, et al. Increased QT variability in patients with panic disorder and depression. Psychiatry Res 2000;93: 225–235
55. McCraty R, Atkinson M, Tomasino D, et al. Analysis of twenty-four hour heart rate variability in patients with panic disorder. Biol Psychol 2001;56:131–150
56. Yeragani VK, Jampala VC, Sobelewski E, et al. Effects of paroxetine on heart period variability in patients with panic disorder: a study of holter ECG records. Neuropsychobiology 1999;40:124–128
57. Yeragani VK, Pohl R, Jampala VC, et al. Effects of nortriptyline and paroxetine on QT variability in patients with panic disorder. Depress Anxiety 2000;11:126–130
58. Tucker P, Adamson P, Miranda R Jr, et al. Paroxetine increases heart rate variability in panic disorder. J Clin Psychopharmacol 1997;17:370–376
59. Rechlin T. The effect of amitriptyline, doxepin, fluvoxamine, and paroxetine treatment on heart rate variability. J Clin Psychopharmacol 1994;14: 392–395
60. Chen Y, Dilsaver S. Comorbidity of panic disorder in bipolar illness: evidence from the Epidemiologic Catchment Area survey. Am J Psychiatry 1995;152:280–282
61. Stein MB, Uhde TW. Panic disorder and major depression: a tale of two syndromes. Psychiatr Clin North Am 1988;11:441–461
62. Wittchen H, Kessler R, Pfister H, et al. Why do people with anxiety disorders become depressed? a prospective-longitudinal community study. Acta Psychiatr Scand Suppl 2000;102(suppl 406):14–23
63. Kaufman J, Charney D. Comorbidity of mood and anxiety disorders. Depress Anxiety 2000;12(suppl 1):69–76
64. Rogers MP, Warshaw MG, Goisman RM, et al. Comparing primary and secondary generalized anxiety disorder in a long-term naturalistic study of anxiety disorders. Depress Anxiety 1999;10:1–7
65. Servant D, Bailly D, Allard C, et al. Major depression in panic disorder: role of recent life events. J Affect Disord 1991;22:79–82
66. Ninan PT, Dunlop BW. Neurobiology and Etiology of Panic Disorder. J Clin Psychiatry 2005;66(suppl 4):3–7
67. Levinson DF, Zubenko GS, Crowe RR, et al. Genetics of recurrent early-onset depression (GenRED): design and preliminary clinical characteristics of a repository sample for genetic linkage studies. Am J Med Genet 2003;119B:118–130
68. Goldstein RB, Weissman MM, Adams PB, et al. Psychiatric disorders in relatives of probands with panic disorder and/or major depression. Arch Gen Psychiatry 1994;51:383–394
69. Maier W, Minges J, Lichtermann D. The familial relationship between panic disorder and unipolar depression. J Psychiatr Res 1995;29:375–388
70. Leckman JF, Weissman MM, Merikangas KR, et al. Panic disorder and major depression: increased risk of depression, alcoholism, panic, and phobic disorders in families of depressed probands with panic disorder. Arch Gen Psychiatry 1983;40:1055–1060
71. Woody S, McLean P, Taylor S, et al. Treatment of major depression in the context of panic disorder. J Affect Disord 1999;53:163–174
72. Ball SG, Otto MW, Pollack MH, et al. Predicting prospective episodes of depression in patients with panic disorder: a longitudinal study. J Consult Clin Psychol 1994;62:359–365
73. Johnson J, Weissman MM, Klerman GL. Panic disorder, comorbidity, and suicide attempts. Arch Gen Psychiatry 1990;47:805–808
74. Goodwin R, Olfson M, Feder A, et al. Panic and suicidal ideation in primary care. Depress Anxiety 2001;14:244–246
75. Lepola U, Arato M, Zhu Y, et al. Sertraline versus imipramine treatment of comorbid panic disorder and major depressive disorder. J Clin Psychiatry 2003;64:654–662
76. Pollack MH, Simon NM, Worthington JJ, et al. Combined paroxetine and clonazepam treatment strategies compared to paroxetine monotherapy for panic disorder. J Psychopharmacol 2003;17:276–282
77. Goddard AW, Brouette T, Almai A, et al. Early coadministration of clonazepam with sertraline for panic disorder. Arch Gen Psychiatry 2001;58:681–686
78. Martinsen EW, Olsen T, Tonset E, et al. Cognitive-behavioral group therapy for panic disorder in the general clinical setting: a naturalistic study with 1-year follow-up. J Clin Psychiatry 1998;59:437–442
79. McLean PD, Woody S, Taylor S, et al. Comorbid panic disorder and major depression implications for cognitive-behavioral therapy. J Consult Clin Psychol 1998;66:240–247
80. Tsao JC, Lewin MR, Craske MG. The effects of cognitive-behavior therapy for panic disorder on comorbid conditions. J Anxiety Disord 1998;12:357–371
81. Simon NM, Smoller JW, Fava M, et al. Comparing anxiety disorders and anxiety-related traits in bipolar disorder and unipolar depression. J Psychiatr Res 2003;37:187–192
82. Simon NM, Otto MW, Wisniewski SR, et al. Anxiety disorder comorbidity in bipolar disorder: data from the first 500 participants of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2004;161:2222–2229
83. Perugi G, Akiskal HS, Ramacciotti S, et al. Depressive comorbidity of panic, social phobic, and obsessive-compulsive disorders re-examined: is there a bipolar II connection? J Psychiatr Res 1999;33:53–61
84. MacKinnon DF, Xu J, McMahon FJ, et al. Bipolar disorder and panic disorder in families: an analysis of chromosome 18 data. Am J Psychiatry 1998;155:829–831
85. MacKinnon DF, Zandi PP, Cooper J, et al. Comorbid bipolar disorder and panic disorder in families with a high prevalence of bipolar disorder. Am J Psychiatry 2002;159:30–35
86. Rotondo A, Mazzanti C, Dell'Osso L, et al. Catechol O-methyltransferase, serotonin transporter, and tryptophan hydroxylase gene polymorphisms in bipolar disorder patients with and without comorbid panic disorder. Am J Psychiatry 2002;159:23–29
87. MacKinnon DF, Zandi PP, Gershon ES, et al. Association of rapid mood switching with panic disorder and familial panic risk in familial bipolar disorder. Am J Psychiatry 2003;160:1696–1698
88. Frank E, Cyranowski J, Rucci P, et al. Clinical significance of lifetime panic spectrum symptoms in the treatment of patients with bipolar I disorder. Arch Gen Psychiatry 2002;59:905–911
89. Feske U, Frank E, Mallinger A, et al. Anxiety as a correlate of response to the acute treatment of bipolar I disorder. Am J Psychiatry 2000;157: 956–962
90. Russo P, Smith M, Dirani R, et al. Pharmacotherapy patterns in the treatment of bipolar disorder. Bipolar Disord 2002;4:366–377

91. Blanco C, Lage G, Olfson M, et al. Trends in the treatment of bipolar disorder by outpatient psychiatrists. Am J Psychiatry 2002;159:1005–1010
92. Simon NM, Otto MW, Weiss RD, et al. Pharmacotherapy for bipolar disorder and comorbid conditions: baseline data from STEP-BD. J Clin Psychopharmacol 2004;24:512–520
93. Pande A, Davidson J, Jefferson J, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. J Clin Psychopharmacol 1999; 19:341–348
94. Pande A, Pollack M, Crockatt J, et al. Placebo-controlled study of gabapentin treatment of panic disorder. J Clin Psychopharmacol 2000;20: 467–471
95. Pande A, Crockatt J, Feltner D, et al. Pregabalin in generalized anxiety disorder: a placebo-controlled trial. Am J Psychiatry 2003;160:533–540
96. Kinrys G, Pollack M, Simon N, et al. Valproic acid for the treatment of social anxiety disorder. Int Clin Psychopharmacol 2003;18:169–172
97. Feltner DE, Crockatt JG, Dubovsky SJ, et al. A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. J Clin Psychopharmacol 2003;23: 240–249
98. Freeman MP, Freeman SA, McElroy SL. The comorbidity of bipolar and anxiety disorders: prevalence, psychobiology, and treatment issues. J Affect Disord 2002;68:1–23