Anxiety in Medically Ill Patients

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Anxiety disorders and anxiety symptoms are highly prevalent in the general population and more so in the medically ill. They have a number of negative consequences for these patients and may worsen the outcome of the medical illness and increase health care utilization. In the evaluation of these patients, it is of paramount importance to identify the etiology of the anxiety and, in particular, to differentiate primary from secondary anxiety. Management includes medications (especially benzodiazepines and selective serotonin reuptake inhibitors) and psychotherapy (particularly cognitive-behavioral therapy).

Introduction

Patients commonly present to primary care physicians with anxiety. The lifetime prevalence of having any anxiety disorder has been estimated to be approximately 25% [1] and is thought to be higher in the medically ill. It is important to recognize and treat anxiety in medically ill patients for a number of reasons. Anxiety disorders are associated with higher rates of suicidal ideation and suicide attempts [2•], depression, and substance abuse [3]. They reduce quality of life by amplifying the sensation of pain and by interfering with sleep and appetite [4]. They may worsen the outcomes of various illnesses, including cardiovascular diseases, irritable bowel syndrome, and chronic obstructive pulmonary disease. An increased likelihood of disability in individuals with physical disorders and comorbid anxiety disorders has been found, even when controlling for severity of pain, comorbid substance use, and mood disorders [5]. In addition to negatively affecting the treatment of physical illnesses, anxiety disorders are also associated with higher health care utilization [6] and reduced work productivity [7].

Patients who are medically ill face many challenges to their normal coping strategies, including interruption of their normal routine, invasive and painful medical procedures, emotional responses to illness, prognostic worries, financial concerns, occupational repercussions, effects on family members, and need for assistance with activities of daily living. Anxiety in this population can be a primary disorder, but it also can be a secondary phenomenon, such as when it is a psychological reaction to a medical illness, a physiologic consequence of an illness such as hyperthyroidism, a pharmacologic side effect of a medication or a drug interaction, or a manifestation of another psychiatric disorder.

Although anxiety disorders are common in the medically ill, they continue to be under-recognized and inadequately treated. Patients may contribute to the lack of appropriate care; they often are reluctant to talk about their mental health, resist taking psychiatric medications, or refuse referrals to psychiatrists. Thus, it should not be surprising to know that the majority of individuals with anxiety disorders receive their care from their primary care physicians [8]. Primary care patients with anxiety disorders generally receive low rates of appropriate pharmacotherapy (25%), however, and even lower rates of appropriate psychotherapy than have been reported for patients who are treated for depression by primary care physicians [9].

This article reviews the literature on anxiety disorders presenting with comorbid medical conditions in order to address the impact that anxiety can have on the eventual outcome of various medical conditions and to discuss the available treatment options.

Approach to Evaluating a Patient for Anxiety in the Medical Setting

In evaluating a patient for anxiety, the clinical history and examination are crucial to an accurate diagnosis. Primary anxiety disorders can usually be diagnosed with a careful history. Does the patient have a personal history or a family history of anxiety? If the anxiety is a recent development, has there been a recent stressor? What is the patient's biggest concern? A secondary cause of anxiety is especially likely in the absence of a prior personal or family history of anxiety or identifiable, recent psychological stressors.

For medical inpatients, thoroughly reviewing the chart and interviewing the staff often provide clues to

Table 1. Medications that commonly cause anxiety symptoms

Antineoplastic agents (vinblastine, ifosfamide)
Baclofen
Bupropion
Captopril
Corticosteroids
Estrogens
HMG-CoA reductase inhibitors
Interferon alfa and beta
Levodopa
Mefloquine
Metoclopramide
Methylxanthines (caffeine, theophylline)
Narcotic analgesics
Procaine derivatives
Stimulants (methylphenidate, dextroamphetamine)
Sumatriptan
Thiabendazole

the patient's behavior. Observations by nurses are often helpful in noting distress and may assist in constructing a timeline of the symptom development. It is imperative to rule out medical causes of anxiety symptoms, withdrawal states, and medication-induced side effects. Delirium should be ruled out in all medically ill patients who are evaluated for anxiety. Is the patient oriented in all spheres? Does the "anxiety" wax and wane in intensity? Is the behavior correlated with hypoxia, metabolic abnormalities, or the recent addition or discontinuation of medication? Is the patient in pain? It is important to review vital signs, as trends may suggest infectious etiologies or withdrawal states. A complete medication history is needed, including outpatient medications, inpatient medications, and "PRN" medications. Many medications can cause anxiety; some of the more common ones are listed in Table 1. A more comprehensive list can be found in Abramowicz [10].

A review of laboratory and other diagnostic tests may also provide important information about the chief complaint. Routine evaluation should include an electrocardiogram and chemistries, including calcium and magnesium, complete blood count, thyroid studies, vitamin B12, folate, rapid plasma reagin, liver function tests, urine drug screen, and serum levels of medications for which therapeutic ranges are available (eg, lithium, valproic acid, carbamazepine, phenytoin, and digoxin). A CT scan of the brain, chest x-ray, ventilation/perfusion scan, lumbar puncture, or an electroencephalogram may be indicated, depending on the history and findings in the physical examination.

Secondary versus Primary Anxiety Symptoms

Panic disorder, acute stress disorder, post-traumatic stress disorder, agoraphobia, simple phobias, obsessive-compulsive disorder, generalized anxiety disorder, and social phobia are considered the primary anxiety disorders. Of these disorders, post-traumatic stress disorder, panic attacks, and agoraphobia are more likely to be associated with specific physical disorders than are generalized anxiety disorder, social phobia, or simple phobias [5].

Anxiety in a patient with comorbid medical illness can result from a psychological reaction to that particular condition, an example of secondary anxiety. Levenson et al. [11] have summarized the causes that can lead to excessive anxiety in patients with medical illnesses. These include uncertainty of medical diagnoses and prognosis, fear of loss of body parts (amputations), fear of dependency on other people or on machines such as ventilators, fear of adverse effects of cancer chemotherapy, fear of costs of treatment, separation anxiety in cases of isolation precautions, fear of disability, and fear of pain or death.

Effect of Anxiety on Medical Illnesses

Anxiety disorders are very common in medically ill populations and can have a tremendous impact on the patients' course and prognosis. Approximately one half of the health-related visits in the United States that result from anxiety disorders involve primary care physicians [12]. A wide variety of anxiety disorders, such as adjustment disorders, panic disorder, and generalized anxiety disorder, are common in patients with comorbid medical illnesses. Anxiety heightens the perception of symptoms like pain, itching, dyspnea, nausea, and dizziness. It can also be a risk factor for exacerbation or development of some medical conditions such as arrhythmia, angina, hypertension, movement disorders, asthma, common pruritic skin conditions, and irritable bowel syndrome [11]. Anxiety is one of the main reasons some patients avoid seeking medical care. Medical inpatients with high anxiety levels also have higher health care costs when compared with patients who have similar medical conditions but lower levels of anxiety [11].

We will now review some of the literature assessing the adverse effects of anxiety on specific types of comorbid medical illnesses.

Cardiovascular disease

Compared with studies of depression and heart disease, relatively few studies link the anxiety disorders with an increased risk of coronary artery disease and higher mortality rates, but the available literature does support this association. Frasure-Smith [13] conducted a prospective study of 222 patients who were followed for 1 year after having a myocardial infarction. Patients with major depression or a history of depression and anxiety symptoms were at risk of further cardiac complications.

Further evidence of a link between anxiety and increased cardiac morbidity was provided by another study, which examined the relationship between a reduction in psychological distress and long-term cardiac and psychological results in patients participating in a psychosocial intervention program [14]. The results showed that a person who recently suffered a myocardial infarction and had comorbid anxiety was 3.3 times more likely to have further cardiac complications (eg, acute coronary syndrome) than a similar patient without anxiety [14]. Another study followed 3682 patients for 10 years and found mental tension to be an independent risk factor for new-onset atrial fibrillation, incident coronary heart disease, and mortality in men. Anxiety also increased the risk for total mortality in men and women [15].

Higher rates of sudden cardiac death have been associated with higher anxiety states. Men with high phobic anxiety showed a threefold increase in RR of fatal cardiac events when compared with men with low anxiety [16].

Additionally, many studies link the placement of an implantable cardioverter-defibrillator (ICD) with the development of anxiety reactions. Despite its life-saving function, ICD firing is often unpredictable and has been likened by many to "being kicked in the chest by a mule"! Many patients have experienced ICD maladjustment (anticipatory anxiety, attempts to control the firings, and negative attributions) after repeated ICD firing. Sola and Bostwick [17] wrote an excellent review on this topic and stated that up to 38% of patients with ICDs developed diagnosable anxiety disorders. They went on to summarize various studies that have identified factors associated with the development of anxiety disorders, including the frequency of firing, younger age, gender, family response, patient attributions, and the perception of control over the firing.

Respiratory diseases

Many investigators have examined the association of respiratory illness and anxiety disorders. Multiple studies have found the prevalence of anxiety in patients with lung disease to be significantly higher than in the general population. Brenes [18] reviewed the literature on chronic obstructive pulmonary disease (COPD) in patients with anxiety disorders and found that the prevalence of generalized anxiety disorder was 10% to 15.8% and the prevalence of panic disorder was 8% to 32% in these patients. Anxiety also had a major negative impact on quality of life of patients with COPD. Patients with COPD who have low health status and anxiety also are noted to have higher rates of rehospitalization [19].

Lowe et al. [20] investigated the prevalence and management of anxiety, depression, and other mental ailments in patients with pulmonary hypertension. They concluded that anxiety and depression are frequently found in patients with pulmonary hypertension and that these symptoms become more severe as the disease progresses.

Katon et al. [21] reviewed the literature on the relationship between asthma and anxiety disorders. They reported on 12 studies of adults with asthma, which estimated that the prevalence of panic disorder in these patients ranges from 6.5% to 24%. These are important findings when one considers that the prevalence of panic disorder in the general community has been estimated to be 1% to 3 % [1].

Gastrointestinal (GI) illnesses

There has long been a relationship between GI dysfunction and psychiatric symptoms. GI disorders are categorized into "functional" (involving psychological factors) and "organic" (structural). The functional disorders include functional esophageal disorders (noncardiac chest pain and functional dyspepsia); globus; cyclic vomiting; functional diarrhea, constipation, and abdominal pain; and the most common functional GI disorder, irritable bowel syndrome [22]. The organic disorders include Crohn's disease and ulcerative colitis, the inflammatory bowel disorders. In general, treatment of the comorbid psychiatric condition is more likely to greatly improve the patient's overall well-being in functional disorders than in organic conditions. This distinction is not intended to equate functional with psychiatric conditions, however, but rather to call attention to psychological concerns in addition to physiologic factors involved in the disorders.

In a population of patients attending a gastroenterology clinic, the prevalence of anxiety and mood disorders in patients with functional disorders was found to be approximately double the prevalence in patients with inflammatory bowel disease [23]. Stress has been shown to precede the onset of GI symptoms of the functional bowel syndromes. Proper identification of psychosocial stressors has been shown to be the most important factor in predicting outcome of patients with irritable bowel syndrome [24]. Another important association is the relationship between a history of childhood sexual abuse and irritable bowel syndrome. Various studies have examined this association, and many have failed to support the link between childhood sexual abuse and functional bowel syndromes. One study found that a history of abuse predicts the chronicity and severity of functional GI syndromes [25].

Cancer

Anxiety is a very common symptom in patients with cancer. The cancer diagnosis is often traumatic, as patients are concerned about upcoming treatments, pain, body image changes, prognosis, and death. All patients should be screened for depression and post-traumatic stress disorder, as the diagnosis and treatment of cancer may evoke earlier traumatic memories and may lead to an increased risk of anxiety and depressive symptoms [26]. Anxiety is common during routine follow-up vis-

its and during critical points of treatment such as the beginning or end of treatment and the treatment of recurrence or cancer progression [27]. Chan et al. [28] studied the prevalence of breathlessness, fatigue, and anxiety in patients with advanced lung cancer who were undergoing palliative radiation therapy and advocated the treatment of these anxiety symptoms during the radiation therapy because of their high prevalence and moderate intensity. Needle phobia, MRI scanner–related claustrophobia, and anticipatory nausea and vomiting are other anxiety-related problems that often disrupt the course of cancer treatment.

Almost one half of cancer patients have significant anxiety symptoms, but the rates of specific anxiety disorders are similar to baseline rates in the general population [29]. Patients with advanced cancer have a low rate of utilizing mental health services. The clinical outcomes of these patients can be improved if oncology professionals increase utilization of mental health services by discussing mental health concerns with their patients [30].

Neurologic disorders

Anxiety symptoms are common following a stroke; they have been estimated to occur in 25% to 30% of these patients [31]. The reported prevalence of generalized anxiety disorder has ranged from 4% to 28% [32]. This variability has been attributed to difficulty in separating anxiety and depressive symptoms from neurobehavioral consequences of stroke (aphasia, denial, emotional lability, and affective dysprosodia). Anxiety has a significant detrimental effect on the severity and course of poststroke depression and difficulties with social functioning and activities of daily living [33].

A comparison of the prevalence of anxiety and depressive disorders in patients with Parkinson's disease and in matched medical controls found that 29% of those with Parkinson's disease had a formal anxiety disorder, compared with 4.8% of the controls. Among patients with Parkinson's disease and an anxiety disorder, 92% had a comorbid depressive disorder. Similarly, of patients with Parkinson's disease and a depressive disorder, 67% had a comorbid anxiety disorder [34].

Depressive and anxiety disorders are found in one third of patients with epilepsy [35]. Prodromal symptoms of nervousness and irritability are common with complex partial seizures. It is important to suspect complex partial seizures as an etiology with this presentation. Treatment should focus on using an anticonvulsant instead of an antidepressant to manage anxiety symptoms in this context.

Treating Anxiety in Patients with Comorbid Medical Illness

Pharmacologic treatment

Patients with anxiety symptoms or anxiety disorders who suffer from comorbid medical illnesses can be treated successfully with most classes of anxiolytic drugs. Most patients with acute anxiety symptoms can be treated effectively with benzodiazepines. Of these, lorazepam is often preferred because it can be given either by mouth, intravenously, or by the intramuscular route; it has no active metabolite; and its metabolism does not change with increased age of the patient. Among this class of drugs, pharmacokinetic issues like the half-lives of the medications and the nature of their metabolites are important to the selection of a particular drug in clinical use [36]. The duration of effect following a single dose or an occasional dose is largely determined by the distribution half-life rather than the elimination half-life [37]. Thus, with occasional dosing, choosing lorazepam instead of diazepam is likely to produce a longer duration of effect because the distribution half-life for lorazepam is longer than for diazepam. With chronic dosing, the duration of effect will depend on the elimination half-life of the medication and any active metabolites. In patients with impaired liver function, benzodiazepines that require only conjugation with glucuronide for their metabolism—namely, lorazepam, oxazepam, and temazepam (which can be remembered by the mnemonic LOT)—are preferred, as their elimination half-lives are not significantly affected by age and liver function.

Benzodiazepines should be used with caution in patients with a history of substance abuse, in the elderly (because of an increased risk of falls and amnestic or disinhibition effects), and in children (because of risk of paradoxic reaction). Benzodiazepines are not recommended as the treatment of choice in patients with COPD because they can decrease respiratory drive, worsen lung function, and reduce exercise tolerance [38].

Unlike the benzodiazepines, buspirone is an anxiolytic drug that does not have the side effect of sedation. The effects of buspirone on breathlessness and exercise tolerance in patients with chronic airway obstruction were assessed in a very small, double-blind, randomized clinical trial in which 16 patients were randomized for 14 days to either buspirone (20 mg/d) or placebo [39]. Buspirone significantly reduced anxiety and dyspnea and also improved exercise tolerance [39]. However, although buspirone may be safer in patients with respiratory compromise, we have not found buspirone to be adequately efficacious for clinically significant anxiety in our patients. The utility of buspirone is also limited by the 2-week delay in its effect.

Nortriptyline and other tricyclic antidepressants have been shown to be effective in the treatment of functional bowel syndromes, poststroke anxiety, and anxiety with COPD. Borson et al. [40] conducted a randomized, placebo-controlled trial with nortriptyline versus placebo in 30 patients with COPD and comorbid depression, 83% of whom also reported symptoms of anxiety during the study. Nortriptyline was successful in reducing both depression and anxiety in these patients.

Selective serotonin reuptake inhibitors (SSRIs) are efficacious in the treatment of anxiety disorders such as obsessive-compulsive disorder, generalized anxiety disorder, social anxiety disorder, panic disorder, and post-traumatic stress disorder. Some SSRIs (especially fluoxetine, paroxetine, and fluvoxamine) cause clinically significant inhibition of some P450 drug-metabolizing liver enzymes, thereby creating a risk of drug-drug interactions in the medically comorbid patient who is taking multiple medications [41]. Sertraline, citalopram, and escitalopram seem less likely to affect P450 isozymes and therefore may be more beneficial in anxious patients using multiple medications. Unlike tricyclic antidepressants and monoamine oxidase (MAO) inhibitors, SSRIs do not directly affect cardiac function in routine doses or even in overdose, so they are generally safe for use by anxious patients with comorbid cardiac disease.

For more information regarding drug-drug interactions with psychotropic drugs, please refer to the recent excellent article by Sanderson et al. [42••].

Psychotherapy

Psychotherapy is a widely used treatment modality for the medically ill, anxious patient. It may include individual, group, or family therapy. Psychotherapeutic approaches based on understanding the patient's developmental history, interpersonal dynamics, and defense mechanisms may help the patient to use a more adaptive strategy for coping with the medical illness.

Cognitive-behavioral treatments have been shown to be effective for treatment of anxiety disorders. In this treatment strategy, anxiety is seen as an emotional signal or an "alarm reaction" to suggest the person's perception that something negative is happening either internally (within his or her body) or externally [43]. In a randomized controlled trial, cognitive-behavioral therapy was found to decrease anxiety and depression symptoms in patients with COPD [44]. In patients with COPD, progressive muscle relaxation has been shown to reduce dyspnea, anxiety, and also airway obstruction [45]. Patients with COPD can master the technique of progressive muscle relaxation using a taped message [46].

Certain cognitive techniques can prove very beneficial in uncovering and correcting various anxiety-provoking misinterpretations and thoughts. Behavioral techniques like systematic desensitization can be helpful in overcoming both rational fears, such as fear of chemotherapy-induced nausea and vomiting, and irrational fears like needle phobia [4].

Vila et al. [47] studied the usefulness of relaxation techniques for patients with ischemic cardiomyopathy, evaluating anxiety levels and measures of quality of life. A relaxation-technique workshop in primary care reduced anxiety and led to improved quality of life.

Home-based psychological nursing interventions in a post-myocardial infarction population showed that reducing psychological distress improved long-term prognosis as well as psychological status in both men and women [14].

Group therapy for cancer patients has been a widely used modality. It may decrease the sense of social isolation and help the patient to learn practical and adaptive coping strategies to assist with adjusting to the illness. Spiegel et al. [48] developed a supportive-expressive group psychotherapy for women with breast cancer. Although the initial reports of prolonged longevity were replicated only in some of the subsequent studies, group therapy remains an important intervention for helping patients cope with medical illness.

Conclusions

Anxiety symptoms are common in the medically ill and have a significant impact on the prognoses of these illnesses. Recognition and treatment of anxiety disorders can lead to improved quality of life and may improve the medical status of patients with comorbid medical conditions.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Kessler RC, McGonagle KA, Zhao S, et al.: **Lifetime and 12-month prevalence of the DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey.** *Arch Gen Psychiatry* 1994, **51:**8–19.
2.• Sareen J, Cox BJ, Afifi TO, et al.: **Anxiety disorders and risk for suicidal ideation and suicide attempts: a population-based longitudinal study of adults.** *Arch Gen Psychiatry* 2005, **62:**1249–1257.

This is the first study to show that having a pre-existing anxiety disorder is an independent risk factor for the development of suicidal ideation and suicide attempts. It also showed that the combination of an anxiety disorder and a mood disorder was associated with a higher risk of suicide attempts.

3. Kessler RC, Nelson CB, McGonagle KA, et al.: **The epidemiology of co-occurring addictive and mental disorders: implications for prevention and service utilization.** *Am J Orthopsychiatry* 1996, **66:**17–31.
4. Levenson JL: **Anxiety in the medically ill.** *Primary Psychiatry* 2005, **12:**24–26.
5. Sareen J, Cox BJ, Clara I, et al.: **The relationship between anxiety disorders and physical disorders in the US National Comorbidity Survey.** *Depress Anxiety* 2005, **21:**193–202.
6. Regier DA, Boyd JH, Burke J, et al.: **One-month prevalence of mental disorders in the United States.** *Arch Gen Psychiatry* 1988, **45:**977–986.
7. Dupont RL, Rice DP, Miller LS, et al.: **Economic costs of anxiety disorders.** *Anxiety* 1996, **2:**167–172.
8. Young AS, Klap R, Sherbourne CD, Wells KB: **The quality of care for depressive and anxiety disorders in the United States.** *Arch Gen Psychiatry* 2001, **58:**55–61.
9. Stein MB, Sherbourne CD, Craske MG: **Quality of care for primary care patients with anxiety disorders.** *Am J Psychiatry* 2004, **161:**2230–2237.

10. Abramowicz M: **Some drugs that cause psychiatric symptoms.** *Med Lett Drugs Ther* 1998, **40:**21–24.
11. Levenson JL, Hamer RM, Rossiter LF: **Relation of psychopathology in general medical inpatients to use and cost of services.** *Am J Psychiatry* 1990, **147:**1498–1503.
12. Harman JS, Rollman BL, Hanusa BH, et al.: **Physician office visits of adults for anxiety disorders in the United States, 1985-1998.** *J Gen Intern Med* 2002, **17:**165–172.
13. Frasure-Smith N: **In-hospital symptoms of psychological stress as predictors of long-term outcome after acute myocardial infarction in men.** *Am J Cardiol* 1991, **67:**121–127.
14. Cossette S, Frasure-Smith N, Lesperance F: **Clinical implications of a reduction in psychological distress on cardiac prognosis in patients participating in a psychosocial intervention program.** *Psychosom Med* 2001, **63:**257–266.
15. Eaker ED, Sullivan LM, Kelly-Hayes M, et al.: **Tension and anxiety and the prediction of the 10-year incidence of coronary heart disease, atrial fibrillation, and total mortality: the Framingham Offspring Study.** *Psychosom Med* 2005, **67:**692–696.
16. 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.
17. Sola CL, Bostwick JM: **Implantable cardioverter-defibrillators, induced anxiety, and quality of life [review].** *Mayo Clin Proc* 2005, **80:**232–237.
18. Brenes GA: **Anxiety and chronic obstructive pulmonary disease: prevalence, impact, and treatment.** *Psychosom Med* 2003, **65:**963–970.
19. Gudmundsson G, Gislason T, Janson C, et al.: **Risk factors for rehospitalisation in COPD: role of health status, anxiety and depression.** *Eur Respir J* 2005, **26:**414–419.
20. Lowe B, Grafe K, Ufer C, et al.: **Anxiety and depression in patients with pulmonary hypertension.** *Psychosom Med* 2004, **66:**831–836.
21. Katon WJ, Richardson L, Lozano P, McCauley E: **The relationship of asthma and anxiety disorders.** *Psychosom Med* 2004, **66:**349–355.
22. Creed F, Olden KW: **Gastrointestinal disorders.** In *The American Psychiatric Publishing Textbook of Psychosomatic Medicine.* Edited by Levenson JL. Washington, DC: American Psychiatric Publishing; 2005:465–481.
23. Drossman DA, Creed FH, Olden KW, et al.: **Psychosocial aspects of the functional gastrointestinal disorders.** In *Rome II: The Functional Gastrointestinal Disorders,* edn 2. Edited by Drossman DA, Corazziari E, Talley NH, et al. McLean, VA: Degnon; 2000:157–245.
24. Bennett EJ, Tennant CC, Piesse C, et al.: **Level of chronic life stress predicts clinical outcome in irritable bowel syndrome.** *Gut* 1998, **43:**256–261.
25. Longstreth GF, Wolde-Tsadik G: **Irritable bowel-type symptoms in HMO examinees. Prevalence, demographics, and clinical correlates.** *Dig Dis Sci* 1993, **38:**1581–1589.
26. Baider L, Peretz R, Hadani PE, et al.: **Transmission of response to trauma? Second-generation Holocaust survivors' reaction to cancer.** *Am J Psychiatry* 2000, **157:**904–910.
27. Massie MJ, Greenberg DB: **Oncology.** In *The American Psychiatric Publishing Textbook of Psychosomatic Medicine.* Edited by Levenson JL. Washington, DC: American Psychiatric Publishing; 2005:517–534.
28. Chan CW, Richardson A, Richardson JA: **Study to assess the existence of the symptom cluster of breathlessness, fatigue and anxiety in patients with advanced lung cancer.** *Eur J Oncol Nurs* 2005, **9:**325–333.
29. Stark D, Kiely M, Smith A, et al.: **Anxiety disorders in cancer patients: their nature, associations, and relation to quality of life.** *J Clin Oncol* 2002, **20:**3137–3148.
30. Kadan-Lottick NS, Venderwerker LC, Block SD, et al.: **Psychiatric disorders and mental health service use in patients with advanced cancer: a report from the coping with cancer study.** *Cancer* 2005, **104:**2872–2881.
31. Burvill PW, Johnson GA, Jamorozik KD, et al.: **Anxiety disorders after stroke: results from the Perth Community Stroke Study.** *Br J Psychiatry* 1995, **166:**328–332.
32. Astrom M: **Generalized anxiety disorder in stroke patients: a three-year longitudinal study.** *Stroke* 1996, **27:**270–275.
33. Shimoda K, Robinson RG: **Effects of anxiety disorder on impairment and recovery from stroke.** *J Neuropsychiatry Clin Neurosci* 1998, **10:**34–40.
34. Menza MA, Robertson-Hoffman DE, Bonapace AS: **Parkinson's disease and anxiety: comorbidity with depression.** *Biol Psychiatry* 1993, **34:**465–470.
35. Jalava M, Sillanpaa M: **Concurrent illness in adults with childhood-onset epilepsy: a population-based 35-year follow-up study.** *Epilepsia* 1996, **37:**1155–1163.
36. Goddard AW, Brouette T, Almai A, et al.: **Early coadministration of clonazepam with sertraline for panic disorder.** *Arch Gen Psychiatry* 2001, **58:**681–686.
37. Reiman, EM: **Anxiety.** In *The Practitioner's Guide to Psychoactive Drugs,* edn 4. Edited by Gelenberg AJ, Bassuk, EL. New York: Plenum; 1998:213–264.
38. Franco-Bronson K: **The management of treatment-resistant depression in the medically ill.** *Psychiatr Clin North Am* 1996, **19:**329–350.
39. Argyropoulou P, Patakas D, Koukou A, et al.: **Buspirone effect on breathlessness and exercise performance in patients with chronic obstructive pulmonary disease.** *Respiration* 1993, **60:**216–220.
40. Borson S, McDonald GJ, Gayle T, et al.: **Improvement in mood, physical symptoms, and function with nortriptyline for depression in patients with chronic obstructive pulmonary disease.** *Psychosomatics* 1992, **33:**190–201.
41. Sheehan DV: **Attaining remission in generalized anxiety disorder: venlafaxine extended release comparative data.** *J Clin Psychiatry* 2001, **62(Suppl 19):**26–31.
42.•• Sanderson NB, Armstrong SC, Cozza KL: **An overview of psychotropic drug-drug interactions.** *Psychosomatics* 2005, **46:**464–494.

This is a wonderful overview of the relevant mechanisms involved in drug-drug interactions. It includes a table that details clinically important facts to assist in the management of patients taking multiple medications.

43. Ball S, Goddard A, Shekhar A: **Evaluating and treating anxiety disorders in medical settings.** *J Postgrad Med* 2002, **48:**317–321.
44. Kunik ME, Braun U, Stanley MA: **One session cognitive behavioural therapy for elderly patients with chronic obstructive pulmonary disease.** *Psychol Med* 2001, **31:**717–723.
45. Renfroe KL: **Effect of progressive relaxation on dyspnea and state anxiety in patients with chronic obstructive pulmonary disease.** *Heart Lung* 1988, **17:**408–413.
46. Gift AG, Moore T, Soeken K: **Relaxation to reduce dyspnea and anxiety in COPD patients.** *Nurs Res* 1992, **41:**242–246.
47. Vila R, Benedicto M, Pujadas C, et al.: **Usefulness of relaxation techniques for patients with ischaemic cardiopathy: intervention in a health district [in Spanish].** *Aten Primaria* 2005, **36:**78–84.
48. Spiegel D, Kiely M, Smith A, et al.: **Effect of psychosocial treatment on survival of patients with metastatic breast cancer.** *Lancet* 1989, **20:**88–89.