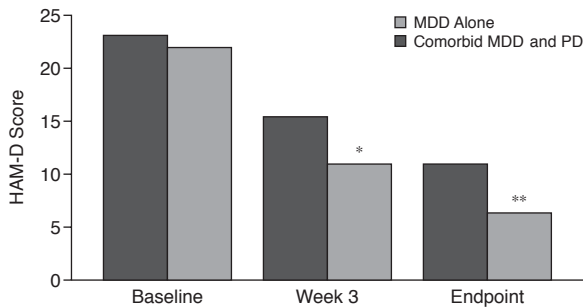




**Figure 1. Effect of Comorbid Major Depressive Disorder (MDD) and Panic Disorder (PD) on Response to Antidepressant Treatment<sup>a</sup>**



<sup>a</sup>Data from Grunhaus et al.<sup>21</sup>

\* $p < .05$  between groups, t test.

\*\* $p < .01$  between groups, t test.

Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

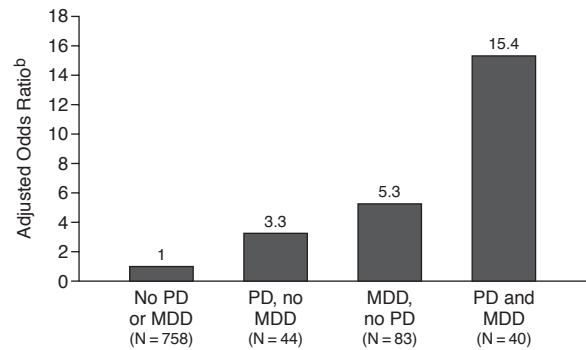
disorder than those with depression had a diagnosis of comorbid panic disorder (37.8% vs. 14.4%, respectively;  $p < .001$ ) or generalized anxiety disorder (27.3% vs. 9.7%, respectively;  $p < .01$ ).<sup>15</sup>

### CLINICAL CONSEQUENCES OF COMORBID ANXIETY AND DEPRESSION

The presence of comorbid depression in patients with anxiety disorders increases the severity and chronicity of the illnesses, associated social and vocational impairment, likelihood of alcohol or substance abuse, and risk of suicide; comorbidity also predicts poor response to treatment.<sup>16</sup> Conversely, patients with depression who have comorbid anxiety symptoms are likely to have an earlier age at onset, more severe depressive symptoms, increased suicidality, longer depressive episodes, more chronic course, worse psychosocial impairment, poorer response to medication, and less recovery from the index episode than those without anxiety.<sup>17-20</sup>

In an early retrospective study comparing response to antidepressant treatment among 41 inpatients with depression and panic disorder ( $N = 19$ ) and those with depression alone ( $N = 22$ ),<sup>21</sup> patients with depression alone had lower Hamilton Rating Scale for Depression (HAM-D)<sup>22</sup> scores at 3 weeks and at discharge than did those with comorbid panic disorder (Figure 1). The association of anxiety with poor outcome in patients with bipolar I disorder was reported in a study of 124 consecutive patients treated with lithium-based pharmacotherapy and adjunctive psychosocial therapy.<sup>23</sup> Patients with current or past anxiety symptoms or a history of panic attacks required a longer time to achieve remission than did patients without anxiety. Patients with anxiety and panic attacks also required more medications and experienced more severe adverse events from medication than those without anxiety symptoms.

**Figure 2. Suicidal Ideation Among Primary Care Patients With Panic Disorder (PD), Major Depressive Disorder (MDD), or Both<sup>a</sup>**



<sup>a</sup>Data from Goodwin et al.<sup>25</sup> Diagnoses defined by Primary Care Evaluation of Mental Disorders (PRIME-MD) criteria.

<sup>b</sup>Two-week prevalence of suicidal ideation, adjusted for sociodemographics and substance abuse.

Comorbidity of panic disorder and major depressive disorder is also associated with increased rates of suicidality compared with either disorder alone. Data from the Epidemiologic Catchment Area study of more than 18,000 adults in the United States<sup>24</sup> indicated that 19.5% of patients with comorbid panic disorder and depression had attempted suicide, compared with 7.0% of those with panic disorder alone and 7.9% of those with major depressive disorder alone. Among a sample of more than 1000 primary care patients in an urban setting,<sup>25</sup> the odds ratio of suicidal ideation within the previous 2 weeks in patients with comorbid panic disorder and depression was approximately thrice that of patients with depression alone (15.4 vs. 5.3; Figure 2).

### RISK FACTORS FOR DEVELOPMENT OF COMORBID ANXIETY AND DEPRESSION

That anxiety disorders predate the onset of major depressive disorder in most patients for whom these disorders co-occur prompted investigation of the clinical and demographic correlates of comorbidity and the environmental and genetic factors that might contribute to the increased risk of concurrence.<sup>1,16</sup> In a prospective 4- to 5-year longitudinal study of approximately 3000 adolescents and young adults with DSM-IV depressive or anxiety disorders, Wittchen et al.<sup>26</sup> found that clinical characteristics that predicted the development of depression were panic-like attacks, persistent avoidance, severe impairment, and the presence of more than 2 anxiety disorders. Another prospective longitudinal study<sup>27</sup> identified degree of agoraphobia, comorbid generalized anxiety disorder, degree of assertiveness, and previous history of major depressive disorder as additional risk factors for the

development of secondary depression. Factors identified as predictive of comorbid anxiety and depressive disorders include female sex, difficulties at school, early separation from a parent, perinatal risk factors, parental history of mental disorders, and financial situation and income.<sup>26</sup>

Comorbid depression and anxiety disorders may represent discrete disorders or different manifestations of a shared underlying neurobiological vulnerability. In addition, given their generally earlier age at onset, anxiety disorders may be a stressor triggering an underlying neurobiological vulnerability to depression, perhaps through serotonergic dysregulation or induction of hypothalamic-pituitary-adrenal axis dysfunction.<sup>28</sup>

Familial and genetic predisposition for depressive and anxiety disorders has also been investigated. In studies by Leckman et al.,<sup>29,30</sup> increased rates of both major depressive disorder and anxiety disorders, including panic disorder, were present in first-degree relatives of patients with both disorders compared with family members of patients without these disorders. However, in first-degree relatives of patients with depression alone, rates of depression were increased, but rates of anxiety disorders were significantly lower than when the proband also had a diagnosis of anxiety. These findings suggest that familial risk factors for these 2 disorders may be unique to each disorder.

Other studies have focused on environmental risk factors for major depressive disorder or anxiety disorders and the interactions between genetic predisposition and life experience.<sup>31,32</sup> Kendler et al.<sup>33</sup> studied generalized anxiety disorder in female twins and concluded that a genetic predisposition is common to both generalized anxiety disorder and depression and that development of either or both is due in part to environmental factors. Fyer<sup>32</sup> concluded that genetic factors are responsible for roughly one third and environmental factors for up to two thirds of the risk of developing social phobia, although the relative contributions of these factors across mood and anxiety disorders remain an area of active investigation.

Interaction between environmental stressors and familial factors was demonstrated in a study of the families of 81 rape survivors with and without posttraumatic stress disorder (PTSD).<sup>34</sup> Family members of the probands with PTSD had an increased incidence of major depressive disorder but not of anxiety disorders. The influence of environmental factors was also demonstrated in a longitudinal study of 404 women for whom experiences of loss or danger were associated with subsequent development of depressive and anxiety disorders, respectively.<sup>35</sup> A longitudinal study by Caspi et al.<sup>36</sup> demonstrated that the presence of 1 or 2 copies of the short allele of the promoter region of the serotonin transporter gene, rather than homozygosity for the long allele, was associated with greater risk of depressive symptoms,

**Table 1. Selective Serotonin and Serotonin-Norepinephrine Reuptake Inhibitors for Anxiety**

Drug	Dosage, mg/d	Initial Dosage, mg/d
Fluoxetine	20–80	5–10
Sertraline	50–200	25–50
Paroxetine	20–60	10
Paroxetine CR	25–75	12.5
Fluvoxamine	50–300	25
Citalopram	20–60	10
Escitalopram	10–40	5–10
Venlafaxine ER	75–225	37.5
Duloxetine	60–120	30

Abbreviations: CR = controlled release, ER = extended release.

diagnosis of depression, and suicidal ideation following stressful life events, lending further support to the model of depression developing in response to environmental stressors and experiences interacting with a genetic vulnerability.

## PHARMACOTHERAPY FOR COMORBID ANXIETY AND DEPRESSION

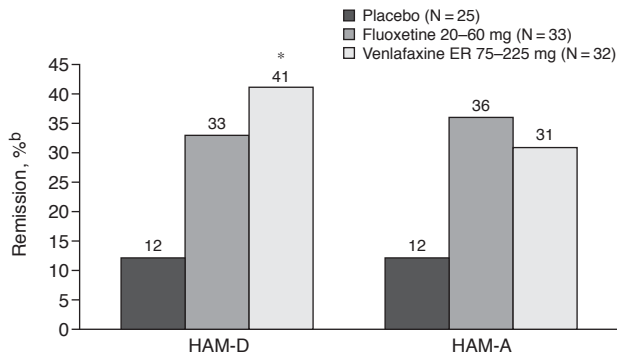
A number of medications from different classes of therapeutic agents are available for treating comorbid anxiety and depressive disorders.

### Selective Serotonin Reuptake Inhibitors

Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (Table 1), are often used as first-line pharmacotherapy for anxiety disorders because, in contrast to benzodiazepines, they provide a broad spectrum of efficacy against common comorbidities, particularly depression, and lack liability for abuse and dependence. SSRIs/SNRIs are also generally better tolerated and safer than the older classes of antidepressants, the tricyclic antidepressants and monoamine oxidase inhibitors. In early comparative studies of fluoxetine and a tricyclic antidepressant for patients with agitated depression, those treated with fluoxetine had greater improvement in anxiety and agitation with less troubling adverse effects than did those treated with a tricyclic antidepressant.<sup>37,38</sup> In addition, the presence of greater anxiety and agitation in patients with depression predicted a greater response of depressive symptoms to treatment with an SSRI.<sup>39</sup>

In a study by Silverstone and Salinas,<sup>40</sup> 92 patients with comorbid depression and generalized anxiety disorder were treated with the SNRI venlafaxine, fluoxetine, or placebo for 12 weeks. Among those treated with venlafaxine, 66% and 59% of patients responded, as defined by a decrease of 50% or more from baseline in scores on the HAM-D and the Hamilton Rating Scale for Anxiety (HAM-A),<sup>41</sup> respectively. Response rates in the fluoxetine group were 52% and 45% for HAM-D and HAM-A, respectively; remission rates are shown in Figure 3.

**Figure 3. Remission Rates in Patients With Comorbid Anxiety and Depression Treated With Venlafaxine Extended Release (ER), Fluoxetine, or Placebo for 12 Weeks<sup>a</sup>**



<sup>a</sup>Data from Silverstone and Salinas.<sup>40</sup>

<sup>b</sup>HAM-D or HAM-A score  $\leq 7$ .

\* $p < .05$ , venlafaxine vs. placebo.

Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression.

### Benzodiazepines

Benzodiazepines are effective anxiolytics and can be used in combination with antidepressants in patients with comorbid anxiety and depression. Benzodiazepines provide rapid anxiolysis during the delay in onset of antidepressant-associated therapeutic effect, decrease early anxiety associated with initiation of the antidepressant, and may hasten antidepressant response. Although benzodiazepines may have a depressive effect, the concomitant therapy with antidepressants can prevent benzodiazepine-related depression. Furukawa et al.<sup>42</sup> performed a meta-analysis of 9 controlled studies of patients with depression treated with an antidepressant plus a benzodiazepine compared with patients treated with an antidepressant alone. Patients treated with combination therapy were 37% less likely to discontinue treatment and were 38% more likely to have a greater than 50% decrease in baseline depressive symptoms at week 4 than those treated with an antidepressant alone.

In a randomized comparative study of augmentation of fluoxetine with clonazepam versus fluoxetine alone in 80 patients with depression,<sup>43</sup> combination therapy led to more rapid antidepressant response; significantly more patients receiving combination therapy had a 50% or greater decrease in HAM-D scores after 3 weeks of treatment (45% vs. 28%;  $p < .001$ ). A study of 126 patients with panic disorder and mild to moderate levels of major depressive episode, dysthymia, or depressive disorder not otherwise specified<sup>44</sup> examined outcomes after treatment for 16 weeks with alprazolam, imipramine, or placebo. Although overall phobic symptoms were more rapidly reduced with alprazolam than with imipramine, by 8 weeks imipramine was as effective as alprazolam in reducing

phobic symptoms. At endpoint, mean HAM-D scores were significantly lower in the alprazolam and imipramine groups (8.95 and 8.78, respectively) than in the placebo group (13.62;  $p = .004$ ), with no significant differences between the 2 active agents. However, this study included relatively few patients with more severe levels of depression, who might be expected to benefit preferentially from antidepressant treatment.

### Other Agents

Bupirone is a nonbenzodiazepine nonsedating anxiolytic<sup>45</sup> that has effects on serotonin and dopamine receptors.<sup>46,47</sup> It is indicated for use in generalized anxiety but may have weak antidepressant effects at higher doses.<sup>48</sup> Although bupirone has demonstrated inconsistent effectiveness in practice, some reports and clinical experience suggest a role for this drug as an adjunct to standard therapies for the treatment of panic disorder,<sup>49</sup> social phobia,<sup>50</sup> depression,<sup>51</sup> and sexual dysfunction.<sup>52</sup>

Beta-blockers, which diminish the autonomic response to stress,<sup>53</sup> may be useful for discrete forms of social phobia, such as performance anxiety,<sup>54</sup> as well as for adjunctive treatment of residual somatic symptoms of anxiety, such as palpitations or tremor, that are incompletely responsive to initial anxiolytic interventions. However, because their use may be associated with the development of depressive syndromes,<sup>55</sup> beta-blockers should be used cautiously for the treatment of anxiety symptoms in the presence of comorbid depression.

### Anticonvulsants

Anticonvulsants have been studied as monotherapy and adjunctive therapy for treating mood and anxiety disorders, although there has been little systematic study of their impact on the comorbid conditions. Valproate, carbamazepine, and lamotrigine have demonstrated efficacy as mood stabilizers in bipolar disorder, with lamotrigine perhaps being particularly useful for bipolar depression.<sup>56</sup> Data regarding the utility of these agents in treating anxiety disorders are also accruing, but few controlled studies have been published. In a 28-day open-label trial,<sup>57</sup> valproate significantly decreased HAM-A scores in 14 patients with panic disorder and was also reported effective, in an open trial,<sup>58</sup> for treatment of social phobia. Carbamazepine was found to be potentially beneficial in the treatment of patients with PTSD<sup>59</sup> but ineffective for panic disorder.<sup>60</sup>

Gabapentin, in placebo-controlled trials, effectively decreased symptoms of social phobia in affected patients<sup>61</sup> and decreased scores on the Panic and Agoraphobia Scale<sup>62</sup> in more severely ill patients with panic disorder.<sup>63</sup> Topiramate, in a small open series,<sup>64</sup> and lamotrigine, in a controlled trial,<sup>65</sup> have been reported to be effective for PTSD. A randomized open-label study of tiagabine compared with paroxetine in 40 patients with generalized

anxiety disorder<sup>66</sup> demonstrated statistically significant decreases in mean HAM-A scores from baseline to week 10 in both groups (−10.6 and −11.8, respectively) as well as statistically significant reductions in HAM-D scores in both treatment groups (−3.9 and −4.1, respectively). In an open-label trial,<sup>67</sup> the novel anticonvulsant levetiracetam was reported effective for the treatment of social anxiety.

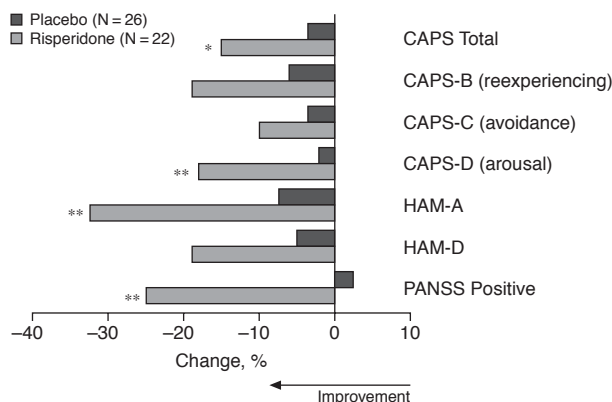
### Atypical Antipsychotics

Although conventional antipsychotics have been used clinically for treating anxiety, their use is limited by concerns regarding extrapyramidal symptoms and tardive dyskinesia. The more favorable adverse effect profile of atypical antipsychotics and emerging evidence of their efficacy for disorders other than psychoses have encouraged their use, typically as augmentation therapy, for refractory mood and anxiety disorders. Clozapine was reported to decrease depressive symptoms in 3 patients with treatment-refractory psychotic depression.<sup>68</sup> In a double-blind, randomized, controlled trial of 833 patients with bipolar I depression,<sup>69</sup> the mean decrease in scores on the Montgomery-Asberg Depression Rating Scale<sup>70</sup> in patients treated with a combination of olanzapine and fluoxetine for 8 weeks was statistically greater than that in patients treated with olanzapine alone (−18.5 and −15.0, respectively;  $p < .01$ ).

Several small studies support the use of atypical antipsychotics as augmentation therapy for various anxiety disorders. In patients with obsessive-compulsive disorder resistant to treatment with SSRIs, decreases in scores on the Yale-Brown Obsessive Compulsive Scale<sup>71</sup> were seen after treatment augmentation with risperidone,<sup>72</sup> quetiapine,<sup>73,74</sup> or olanzapine.<sup>75</sup> In a 5-week, double-blind, placebo-controlled trial of 40 patients with chronic PTSD,<sup>76</sup> the overall decrease in scores on the Clinician-Administered PTSD Scale (CAPS)<sup>77</sup> in patients given adjunctive risperidone (mean dosage, 2.5 mg/day) did not differ from that in patients given placebo; however, improvement in reexperiencing symptoms was greater with risperidone than placebo. In a 4-month double-blind, placebo-controlled study of 48 patients with PTSD,<sup>78</sup> most of whom were persistently symptomatic despite SSRI pharmacotherapy, risperidone in doses up to 3 mg/day significantly decreased overall CAPS and HAM-A scores compared with placebo; percent change in CAPS, HAM-A, Positive and Negative Syndrome Scale, and HAM-D scores are shown in Figure 4.<sup>78</sup>

In an 8-week double-blind study of 19 SSRI-resistant patients with PTSD treated with olanzapine 10 mg/day (N = 10) or placebo (N = 9),<sup>79</sup> olanzapine augmentation significantly decreased total CAPS scores compared with placebo and also improved depressive symptoms, as measured by changes in scores on the self-rated Center for Epidemiologic Studies Depression Scale. A double-blind, placebo-controlled study of olanzapine monotherapy in

Figure 4. Decrease in Scores in Patients With Chronic Posttraumatic Stress Disorder (PTSD) Treated With Risperidone, 3 mg/day, or Placebo<sup>a</sup>



<sup>a</sup>Data from Bartzokis and Freeman.<sup>78</sup>

\* $p < .05$  vs. placebo.

\*\* $p < .01$  vs. placebo.

Abbreviations: CAPS = Clinician-Administered PTSD Scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, PANSS = Positive and Negative Syndrome Scale.

12 patients with social anxiety disorder<sup>80</sup> demonstrated significantly greater response in primary outcome measures of social anxiety at 8 weeks in patients treated with olanzapine compared with those given placebo. In a double-blind, placebo-controlled study of 40 patients with generalized anxiety disorder who were persistently symptomatic despite at least 4 weeks of anxiolytic therapy,<sup>81</sup> low doses of risperidone were significantly more effective than placebo in reducing anxiety symptoms; similar results have been reported with the use of olanzapine augmentation of fluoxetine for refractory generalized anxiety disorder.<sup>82</sup>

### COGNITIVE-BEHAVIORAL THERAPY FOR ANXIETY DISORDERS

Cognitive-behavioral therapy may be useful alone or in combination with medication for refractory symptoms; comorbid conditions; and persistent cognitive symptoms, dysfunctional behavioral patterns, and anxiety sensitivity. It can be provided by a therapist or self-administered. In patients with both anxiety and depression, greater levels of depression are associated with poorer response of anxiety symptoms to cognitive-behavioral therapy,<sup>83,84</sup> as is true for pharmacotherapy. In 83 patients with panic disorder who received 11 weeks of cognitive-behavioral therapy,<sup>83</sup> 89% of those who completed the trial were classified as responders, as defined by a 50% or greater decrease in scores on the Phobic Avoidance Rating Scale. However, higher Beck Depression Inventory scores at the end of treatment predicted higher Phobic Avoidance Rating

Scale scores at 1-year follow-up.<sup>83</sup> In patients with comorbid panic disorder and depression who completed 10 cognitive-behavioral therapy sessions for panic disorder,<sup>84</sup> a diagnosis of depression did not affect outcome after 10 sessions; however, patients with more severe depression had less improvement in several anxiety outcomes than did those with lower Beck Depression Inventory scores.

Comorbid depression or anxiety symptoms may or may not improve with cognitive-behavioral therapy targeted just for the principal disorder, and additional intervention focused on the comorbid condition may be necessary.<sup>85,86</sup> Proposed strategies for improving outcomes in anxiety patients with comorbid depression include the use of motivational interventions and reward, focusing on cognitive distortions regarding negative evaluation of self and progress, and additional cognitive-behavioral therapy aimed specifically at the depression and other comorbidities.

## CONCLUSION

Comorbid depression and anxiety disorders are common. Comorbidity is associated with increased morbidity and may decrease treatment response. Gene-environment interactions are likely relevant in the development and course of these disorders. Many treatment options are available for comorbid depression and anxiety disorders. Antidepressants are generally first-line therapy, but additional pharmacologic and psychosocial interventions are often needed to achieve optimal response.

*Drug names:* alprazolam (Xanax, Niravam, and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), clonazepam (Klonopin and others), clozapine (Clozaril, FazaClo, and others), duloxetine (Cymbalta), escitalopram (Lexapro), fluoxetine (Prozac and others), gabapentin (Neurontin and others), imipramine (Tofranil and others), lamotrigine (Lamictal), levetiracetam (Keppra), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), olanzapine and fluoxetine combination (Symbyax), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), tiagabine (Gabitril), topiramate (Topamax), venlafaxine (Effexor).

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, buspirone is not approved by the U.S. Food and Drug Administration for the treatment of panic, social phobia, and depression-related sexual dysfunction; citalopram, clozapine, gabapentin, imipramine, levetiracetam, lithium, olanzapine, olanzapine and fluoxetine combination, quetiapine, risperidone, tiagabine, and topiramate are not approved for the treatment of any anxiety disorder; escitalopram is not approved for the treatment of any anxiety other than generalized anxiety disorder (GAD); fluoxetine is not approved for the treatment of any anxiety other than panic or GAD; and venlafaxine is not approved for the treatment of any anxiety disorder other than GAD and social phobia.

## REFERENCES

- Kessler RC, Nelson CB, McGonagle KA, et al. Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. *Br J Psychiatry Suppl* 1996;30:17-30
- Judd LL, Kessler RC, Paulus MP, et al. Comorbidity as a fundamental feature of generalized anxiety disorders: results from the National Comorbidity Study (NCS). *Acta Psychiatr Scand Suppl* 1998;393:6-11
- Stein MB, Uhde TW. Panic disorder and major depression: a tale of two syndromes. *Psychiatr Clin North Am* 1988;11:441-461
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*. Washington, DC: American Psychiatric Association; 1987
- Coplan JD, Gorman JM. Treatment of anxiety disorder in patients with mood disorders. *J Clin Psychiatry* 1990;51(10, suppl):9-13
- Keller MB, Hanks DL. Anxiety symptom relief in depression treatment outcomes. *J Clin Psychiatry* 1995;56(suppl 6):22-29
- Clayton PJ, Grove WM, Coryell W, et al. Follow-up and family study of anxious depression. *Am J Psychiatry* 1991;148:1512-1517
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. Washington, DC: American Psychiatric Association; 2000
- Zimbarg RE, Barlow DH, Liebowitz M, et al. The DSM-IV field trial for mixed anxiety-depression. *Am J Psychiatry* 1994;151:1153-1162
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994
- Stein MB, Kirk P, Prabhu V, et al. Mixed anxiety-depression in a primary-care clinic. *J Affect Disord* 1995;34:79-84
- Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561-571
- McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *Am J Psychiatry* 2001;158:420-426
- 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
- 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
- Kaufman J, Charney D. Comorbidity of mood and anxiety disorders. *Depress Anxiety* 2000;12(suppl 1):69-76
- Coryell W, Endicott J, Andreasen NC, et al. Depression and panic attacks: the significance of overlap as reflected in follow-up and family study data. *Am J Psychiatry* 1988;145:293-300
- Joffe RT, Bagby RM, Levitt A. Anxious and nonanxious depression. *Am J Psychiatry* 1993;150:1257-1258
- Andrade L, Eaton WW, Chilcoat HD. Lifetime co-morbidity of panic attacks and major depression in a population-based study: age of onset. *Psychol Med* 1996;26:991-996
- Fawcett J, Scheffner WA, Fogg L, et al. Time-related predictors of suicide in major affective disorder. *Am J Psychiatry* 1990;147:1189-1194
- Grunhaus L, Harel Y, Krugler T, et al. Major depressive disorder and panic disorder: effects of comorbidity on treatment outcome with antidepressant medications. *Clin Neuropharmacol* 1988;11:454-461
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62
- Feske U, Frank E, Mallinger AG, et al. Anxiety as a correlate of response to the acute treatment of bipolar I disorder. *Am J Psychiatry* 2000;157:956-962
- Johnson J, Weissman MM, Klerman GL. Panic disorder, comorbidity, and suicide attempts. *Arch Gen Psychiatry* 1990;47:805-808
- Goodwin R, Olfson M, Feder A, et al. Panic and suicidal ideation in primary care. *Depress Anxiety* 2001;14:244-246
- Wittchen HU, Kessler RC, Pfister H, et al. Why do people with anxiety disorders become depressed? a prospective-longitudinal community study. *Acta Psychiatr Scand Suppl* 2000;406:14-23
- 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
- Coplan JD, Andrews MW, Rosenblum LA, et al. Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: implications for the pathophysiology of mood and anxiety disorders. *Proc Natl Acad Sci U S A* 1996;93:1619-1623
- Leckman JF, Merikangas KR, Pauls DL, et al. Anxiety disorders and depression: contradictions between family study data and DSM-III conventions. *Am J Psychiatry* 1983;140:880-882
- Leckman JF, Weissman MM, Merikangas KR, et al. Major depression

- and panic disorder: a family study perspective. *Psychopharmacol Bull* 1985;21:543-545
31. Kendler KS, Neale MC, Kessler RC, et al. Major depression and phobias: the genetic and environmental sources of comorbidity. *Psychol Med* 1993; 23:361-371
  32. Fyer AJ. Heritability of social anxiety: a brief review. *J Clin Psychiatry* 1993;54(12, suppl):10-12
  33. Kendler KS, Neale MC, Kessler RC, et al. Familial influences on the clinical characteristics of major depression: a twin study. *Acta Psychiatr Scand* 1992;86:371-378
  34. Davidson JR, Tupler LA, Wilson WH, et al. A family study of chronic post-traumatic stress disorder following rape trauma. *J Psychiatr Res* 1998;32:301-309
  35. Brown GW. Life events and affective disorder: replications and limitations. *Psychosom Med* 1993;55:248-259
  36. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 2003;301: 386-389
  37. Tollefson GD, Greist JH, Jefferson JW, et al. Is baseline agitation a relative contraindication for a selective serotonin reuptake inhibitor: a comparative trial of fluoxetine versus imipramine. *J Clin Psychopharmacol* 1994;14: 385-391
  38. Montgomery SA. The efficacy of fluoxetine as an antidepressant in the short and long term. *Int Clin Psychopharmacol* 1989;4(suppl 1):113-119
  39. Filteau MJ, Baruch P, Lapierre YD, et al. SSRIs in anxious-agitated depression: a post-hoc analysis of 279 patients. *Int Clin Psychopharmacol* 1995;10:51-54
  40. Silverstone PH, Salinas E. Efficacy of venlafaxine extended release in patients with major depressive disorder and comorbid generalized anxiety disorder. *J Clin Psychiatry* 2001;62:523-529
  41. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;32:50-55
  42. Furukawa TA, Streiner DL, Young LT. Is antidepressant-benzodiazepine combination therapy clinically more useful? a meta-analytic study. *J Affect Disord* 2001;65:173-177
  43. Smith WT, Londborg PD, Glaudin V, et al. Short-term augmentation of fluoxetine with clonazepam in the treatment of depression: a double-blind study. *Am J Psychiatry* 1998;155:1339-1345
  44. Keller MB, Lavori PW, Goldenberg IM, et al. Influence of depression on the treatment of panic disorder with imipramine, alprazolam and placebo. *J Affect Disord* 1993;28:27-38
  45. Riblet LA, Eison AS, Eison MS, et al. Neuropharmacology of buspirone. *Psychopathology* 1984;17(suppl 3):69-78
  46. Okazawa H, Yamane F, Blier P, et al. Effects of acute and chronic administration of the serotonin 1A agonist buspirone on serotonin synthesis in the rat brain. *J Neurochem* 1999;72:2022-2031
  47. Gobert A, Rivet JM, Cistarelli JM, et al. Buspirone enhances duloxetine- and fluoxetine-induced increases in dialysate levels of dopamine and norepinephrine, but not serotonin, in the frontal cortex of freely moving rats. *J Neurochem* 1997;68:1326-1329
  48. Strand M, Hetta J, Rosen A, et al. A double-blind, controlled trial in primary care patients with generalized anxiety: a comparison between buspirone and oxazepam. *J Clin Psychiatry* 1990;51(9, suppl):40-45
  49. Gastfriend DR, Rosenbaum JF. Adjunctive buspirone in benzodiazepine treatment of four patients with panic disorder. *Am J Psychiatry* 1989;146: 914-916
  50. Van Ameringen M, Mancini C, Wilson C. Buspirone augmentation of selective serotonin reuptake inhibitors (SSRIs) in social phobia. *J Affect Disord* 1996;39:115-121
  51. Appelberg BG, Syvälahti EK, Koskinen TE, et al. Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. *J Clin Psychiatry* 2001;62:448-452
  52. Landen M, Eriksson E, Agren H, et al. Effect of buspirone on sexual dysfunction in depressed patients treated with selective serotonin reuptake inhibitors. *J Clin Psychopharmacol* 1999;19:268-271
  53. Albus M, Zellner A, Bondy B, et al. Influence of CGP 361A, propranolol and diazepam on autonomous reactions to different stressors. *Prog Neuropsychopharmacol Biol Psychiatry* 1989;13:87-97
  54. Liebowitz MR, Schneier F, Campeas R, et al. Phenzelazine and atenolol in social phobia. *Psychopharmacol Bull* 1990;26:123-125
  55. Patten SB, Barbui C. Drug-induced depression: a systematic review to inform clinical practice. *Psychother Psychosom* 2004;73:207-215
  56. Yatham LN, Kusumakar V, Calabrese JR, et al. Third generation anticonvulsants in bipolar disorder: a review of efficacy and summary of clinical recommendations. *J Clin Psychiatry* 2002;63:275-283
  57. Keck PE Jr, Taylor VE, Tugrul KC, et al. Valproate treatment of panic disorder and lactate-induced panic attacks. *Biol Psychiatry* 1993;33:542-546
  58. Kinrys G, Pollack MH, Simon NM, et al. Valproic acid for the treatment of social anxiety disorder. *Int Clin Psychopharmacol* 2003;18:169-172
  59. Brodsky L, Doerman AL, Palmer LS, et al. Post traumatic stress disorder: an eclectic approach. *Int J Psychosom* 1990;37:89-95
  60. Uhde TW, Stein MB, Post RM. Lack of efficacy of carbamazepine in the treatment of panic disorder. *Am J Psychiatry* 1988;145:1104-1109
  61. Pande AC, Davidson JR, Jefferson JW, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. *J Clin Psychopharmacol* 1999;19:341-348
  62. Bandelow B. Assessing the efficacy of treatments for panic disorder and agoraphobia, 2: the Panic and Agoraphobia Scale. *Int Clin Psychopharmacol* 1995;10:73-81
  63. Pande AC, Pollack MH, Crockatt J, et al. Placebo-controlled study of gabapentin treatment of panic disorder. *J Clin Psychopharmacol* 2000;20:467-471
  64. Berlant J, van Kammen DP. Open-label topiramate as primary or adjunctive therapy in chronic civilian posttraumatic stress disorder: a preliminary report. *J Clin Psychiatry* 2002;63:15-20
  65. Hertzberg MA, Butterfield MI, Feldman ME, et al. A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. *Biol Psychiatry* 1999;45:1226-1229
  66. Rosenthal M. Tiagabine for the treatment of generalized anxiety disorder: a randomized, open-label, clinical trial with paroxetine as a positive control. *J Clin Psychiatry* 2003;64:1245-1249
  67. Simon NM, Worthington JJ, Doyle AC, et al. An open-label study of levetiracetam for the treatment of social anxiety disorder. *J Clin Psychiatry* 2004;65:1219-1222
  68. Ranjan R, Meltzer HY. Acute and long-term effectiveness of clozapine in treatment-resistant psychotic depression. *Biol Psychiatry* 1996;40:253-258
  69. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 2003;60:1079-1088
  70. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382-389
  71. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, 1: development, use, and reliability. *Arch Gen Psychiatry* 1989;46:1006-1011
  72. Hollander E, Rossi NB, Sood E, et al. Risperidone augmentation in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Int J Neuropsychopharmacol* 2003;6:397-401
  73. Denys D, van Meegen H, Westenberg H. Quetiapine addition to serotonin reuptake inhibitor treatment in patients with treatment-refractory obsessive-compulsive disorder: an open-label study. *J Clin Psychiatry* 2002;63:700-703
  74. Atmaca M, Kuloglu M, Tezcan E, et al. Quetiapine augmentation in patients with treatment resistant obsessive-compulsive disorder: a single-blind, placebo-controlled study. *Int Clin Psychopharmacol* 2002;17:115-119
  75. D'Amico G, Cedro C, Muscatello MR, et al. Olanzapine augmentation of paroxetine-refractory obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2003;27:619-623
  76. Hamner MB, Faldowski RA, Ulmer HG, et al. Adjunctive risperidone treatment in post-traumatic stress disorder: a preliminary controlled trial of effects on comorbid psychotic symptoms. *Int Clin Psychopharmacol* 2003;18:1-8
  77. Blake DD, Weathers FW, Nagy LM, et al. The development of a Clinician-Administered PTSD Scale. *J Trauma Stress* 1995;8:75-90
  78. Bartzokis G, Freeman T. Risperidone treatment for combat-related PTSD. Presented at the 156th annual meeting of the American Psychiatric Association; May 17-22, 2003; San Francisco, Calif
  79. Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. *Am J Psychiatry* 2002;159:1777-1779
  80. Barnett SD, Kramer ML, Casat CD, et al. Efficacy of olanzapine in social anxiety disorder: a pilot study. *J Psychopharmacol* 2002;16:365-368
  81. Brawman-Mintzer O, Knapp R, Nietert P. Risperidone augmentation in generalized anxiety disorder: a double-blind, placebo-controlled study. Presented at the 16th annual meeting of the European College of Neuro-

- psychopharmacology; September 20–24, 2003; Prague, Czech Republic
82. Pollack MH, Simon NM, Zalton A, et al. Adjunctive olanzapine for SSRI refractory generalized anxiety disorder. Presented at the 24th annual national conference of the Anxiety Disorders Association of America; March 11–14, 2004; Miami, Fla
  83. 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
  84. 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
  85. 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
  86. Woody S, McLean PD, Taylor S, et al. Treatment of major depression in the context of panic disorder. *J Affect Disord* 1999;53:163–174