Comorbid Anxiety and Depression

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Anxiety and depressive disorders often occur as comorbid illnesses and share many common symptoms. Risk factors for these disorders most likely include interactions of environmental and genetic factors. The presence of comorbid anxiety and depression adversely affects clinical and treatment outcomes. Selective serotonin reuptake inhibitors are usually considered first-line treatment for patients with these disorders, although alternative antidepressants or additional therapies are often necessary. Studies suggest that benzodiazepines, anticonvulsants, and atypical antipsychotics may be effective as augmentation therapy to optimize outcome, with buspirone and beta-blockers useful in some patients as well. Cognitive-behavioral therapy is also an effective therapeutic alternative for affected patients. *(J Clin Psychiatry 2005;66[suppl 8]:22–29)*

Although anxiety and depression are considered 2 separate classes of disorders, they often occur comorbidly.[1] In the U.S. National Comorbidity Survey, 58% of patients with major depressive disorder had a comorbid anxiety disorder[1] and 67% of patients with generalized anxiety disorder had a lifetime history of comorbid unipolar depressive disorder.[2] The presence of multiple anxiety disorders increases the risk of depression. Stein and Uhde[3] reported that among patients meeting *Diagnostic and Statistical Manual of Mental Disorders,* Third Edition, Revised *(*DSM-III-R*)*[4] diagnostic criteria for panic disorder alone, 69% had experienced a major depressive episode, whereas among those meeting criteria for both panic disorder and social phobia, 94% had experienced a major depressive episode.

Although depressive and anxiety disorders have unique symptoms, many symptoms are common to both.[5–8] Furthermore, many patients who do not meet the diagnostic criteria for either a depressive or an anxiety disorder have a subsyndromal overlap of anxiety and depression symptoms. In a study of more than 600 outpatients at 5 primary care and 2 mental health clinics,[9] patients with anxiety and affective symptoms not meeting DSM-III-R criteria for either a depressive or an anxiety disorder were at least as common as those who met formal DSM-III-R criteria for 1 or more of these disorders. Such subsyndromal symptoms are associated with considerable distress and impairment.

To identify patients with features of both anxiety and depression who may not meet formal criteria for a disorder from either diagnostic category, research criteria for a diagnosis of mixed anxiety-depressive disorder were published in an appendix to *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV).[10] Criteria for the diagnosis of mixed anxiety-depressive disorder are persistent or recurrent dysphoric mood lasting at least 1 month and accompanied by 4 or more of the following: difficulty concentrating, sleep disturbance, fatigue or low energy, irritability, worry, easily moved to tears, hypervigilance, anticipating the worst, hopelessness, low self-esteem, or feelings of worthlessness. Additionally, patients with mixed anxiety-depressive disorder must not meet criteria for other mood or anxiety disorders.

In a study by Stein et al.[11] of 78 consecutive patients in a primary care setting without previously recognized psychiatric illness, 19.2% had comorbid anxiety and depressive disorders, and 12.8% had mixed anxiety-depressive disorder by the authors' criteria. However, patients were prescreened for mood symptoms using the Beck Depression Inventory,[12] which may have resulted in an overestimate of frequency in this study.

Comorbidity of anxiety disorders and bipolar disorder is also an area of increasing interest.[13,14] In the U.S. National Comorbidity Survey, 17% of patients with generalized anxiety disorder also had lifetime bipolar disorder.[2] Conversely, between 16% and 42% of patients with bipolar disorder have a comorbid anxiety disorder.[13,14] Simon et al.[15] studied patients with a primary lifetime diagnosis of either bipolar disorder (N = 122) or major depressive disorder (N = 114) to determine whether specific types of anxiety disorders are differentially associated with bipolar rather than unipolar depression. In this study, a significantly higher percentage of patients with bipolar

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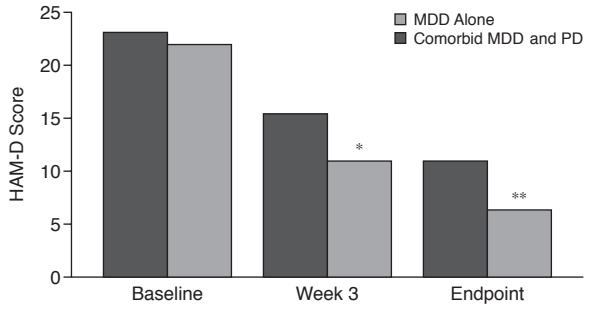
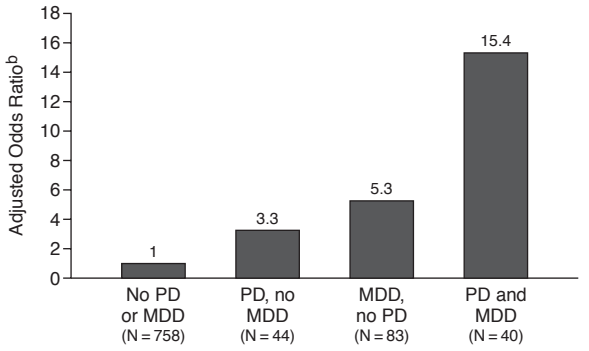
Figure 1. Effect of Comorbid Major Depressive Disorder (MDD) and Panic Disorder (PD) on Response to Antidepressant Treatment[a]



[a]Data from Grunhaus et al.[21]
*p < .05 between groups, t test.
**p < .01 between groups, t test.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Figure 2. Suicidal Ideation Among Primary Care Patients With Panic Disorder (PD), Major Depressive Disorder (MDD), or Both[a]



[a]Data from Goodwin et al.[25] Diagnoses defined by Primary Care Evaluation of Mental Disorders (PRIME-MD) criteria.
[b]Two-week prevalence of suicidal ideation, adjusted for sociodemographics and substance abuse.

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; $p < .01$).[15]

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.[16] 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.[17–20]

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),[21] patients with depression alone had lower Hamilton Rating Scale for Depression (HAM-D)[22] 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.[23] 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.

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[24] 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,[25] 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.[1,16] 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.[26] 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[27] 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.[26]

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.[28]

Familial and genetic predisposition for depressive and anxiety disorders has also been investigated. In studies by Leckman et al.,[29,30] 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.[31,32] Kendler et al.[33] 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[32] 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).[34] 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.[35] A longitudinal study by Caspi et al.[36] 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, 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.

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.

PHARMACOTHERAPY FOR COMORBID ANXIETY AND DEPRESSION

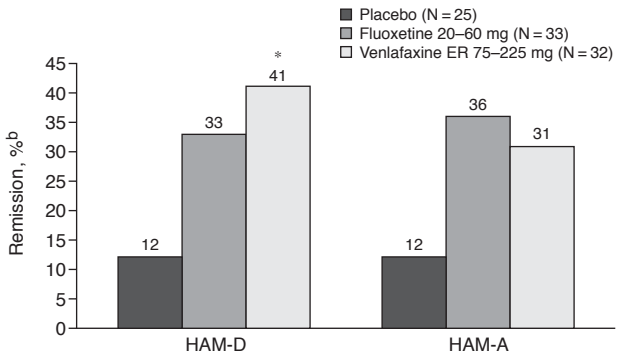
A number of medications from different classes of therapeutic agents are available for treating comorbid anxiety and depressive disorders.

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.[37,38] 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.[39]

In a study by Silverstone and Salinas,[40] 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),[41] 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[a]



[a]Data from Silverstone and Salinas.[40]
[b]HAM-D or HAM-A score ≤ 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.[42] 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,[43] 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[44] 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

Buspirone is a nonbenzodiazepine nonsedating anxiolytic[45] that has effects on serotonin and dopamine receptors.[46,47] It is indicated for use in generalized anxiety but may have weak antidepressant effects at higher doses.[48] Although buspirone 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,[49] social phobia,[50] depression,[51] and sexual dysfunction.[52]

Beta-blockers, which diminish the autonomic response to stress,[53] may be useful for discrete forms of social phobia, such as performance anxiety,[54] 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,[55] 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.[56] 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,[57] valproate significantly decreased HAM-A scores in 14 patients with panic disorder and was also reported effective, in an open trial,[58] for treatment of social phobia. Carbamazepine was found to be potentially beneficial in the treatment of patients with PTSD[59] but ineffective for panic disorder.[60]

Gabapentin, in placebo-controlled trials, effectively decreased symptoms of social phobia in affected patients[61] and decreased scores on the Panic and Agoraphobia Scale[62] in more severely ill patients with panic disorder.[63] Topiramate, in a small open series,[64] and lamotrigine, in a controlled trial,[65] 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[66] 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,[67] the novel anticonvulsant levetiracetam was reported effective for the treatment of social anxiety.

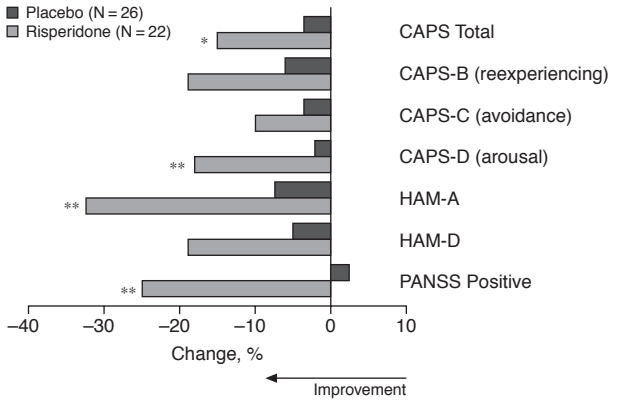
Atypical Antipsychotics

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.[68] In a double-blind, randomized, controlled trial of 833 patients with bipolar I depression,[69] the mean decrease in scores on the Montgomery-Asberg Depression Rating Scale[70] 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[71] were seen after treatment augmentation with risperidone,[72] quetiapine,[73,74] or olanzapine.[75] In a 5-week, double-blind, placebo-controlled trial of 40 patients with chronic PTSD,[76] the overall decrease in scores on the Clinician-Administered PTSD Scale (CAPS)[77] 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,[78] 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.[78]

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),[79] 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[a]



[a]Data from Bartzokis and Freeman.[78]
*$p < .05$ 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[80] 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,[81] 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.[82]

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,[83,84] as is true for pharmacotherapy. In 83 patients with panic disorder who received 11 weeks of cognitive-behavioral therapy,[83] 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.[83] In patients with comorbid panic disorder and depression who completed 10 cognitive-behavioral therapy sessions for panic disorder,[84] 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.[85,86] 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.

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