Combination Treatment With Benzodiazepines and SSRIs for Comorbid Anxiety and Depression: A Review

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Objective: To review the literature on the co-occurrence of anxiety with depressive disorders and the rationale for and use of combination treatment with benzodiazepines and selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs) for treating comorbid anxiety and depression.

Data Sources: PubMed and PsycINFO were searched using terms identified as relevant based on existing practice guidelines. The primary search terms were *anxiety*, *anxiety disorders*, *depression*, *depressive disorders*, *comorbidity*, *epidemiology*, *benzodiazepines*, *antidepressants*, *pharmacology*, *clinical trials*, and *pharmacotherapy*. Reference lists of identified articles were also reviewed to ensure capture of relevant literature.

Study Selection: Publications were selected for inclusion in the review if they applied to adult populations and specifically addressed the comorbidity of anxiety and depression, their epidemiology, or their management. Case reports and case series were not considered for inclusion.

Data Extraction: Each author assessed the publications independently for content related to the review topics. Findings considered relevant to the clinical understanding and management of comorbid anxiety and depression were incorporated into the review.

Data Synthesis: Comorbidity is very common among patients with anxiety and depressive disorders, and, even when full criteria for 2 separate disorders are not met, subsyndromal symptoms are often present. Little controlled research has explored how benzodiazepines and SSRIs/SNRIs may be usefully combined, yet their combination is frequently employed in clinical practice. Patients with comorbidities are likely to have poorer treatment outcomes and have greater utilization of health care resources. Currently SSRIs/SNRIs are considered first-line therapy and are effective in both anxiety and depressive states. Nevertheless, many patients have only a partial response or have difficulty tolerating efficacious doses of antidepressant monotherapy. Benzodiazepines appear to improve treatment outcomes when an anxiety disorder co-occurs with depression or for depression characterized by anxious features. Specifically, they may provide benefits both in terms of speed of response and overall response.

Conclusions: Long-term management plans for anxiety disorder with or without comorbid depression should include strategies for acute or short-term care, long-term maintenance, and episodic or breakthrough symptoms. Combination therapy with benzodiazepines and antidepressants in appropriate clinical settings may improve outcomes over monotherapy in some patients.

(Prim Care Companion J Clin Psychiatry 2008;10:222–228)

Received May 2, 2007; accepted Nov. 13, 2007. From the Department of Psychiatry and Behavioral Sciences, Emory University, School of Medicine, Atlanta, Ga. (Dr. Dunlop); and Medical Communications, Inc., Tequesta, Fla. (Dr. Davis).

Dr. Davis received financial assistance from Schwarz Pharma to provide research and editorial/writing support for this article. The article's content was not reviewed by Schwarz Pharma.

Dr. Dunlop is a consultant to Cephalon, Forest, Schwarz Pharma, Shire, and Wyeth; has received grant/research support from AstraZeneca, Bristol-Myers Squibb, Cephalon, Forest, the National Institute of Mental Health, and Novartis; has received honoraria from Schwarz Pharma; and has participated in speakers/advisory boards for Cephalon. Dr. Davis reports no other significant commercial relationships relevant to the study.

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Anxiety and depressive disorders are highly comorbid and have overlapping symptom presentations. Indeed, comorbidity of the illnesses appears to occur more often than not.[1] Anxiety disorders and depression are debilitating, chronic in nature, and costly to individuals and society. The implications and impact of comorbidities need to be considered routinely in treatment planning. In clinical practice, multimodal and combination therapy, tailored to the individual, can play important roles in improving treatment outcomes. The evidence base for the pharmacologic treatment of anxiety disorders is currently greatest for the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and benzodiazepines. How and when these agents ought to be combined in the treatment of anxiety and related comorbidities is less well established. Recent data suggest that primary care physicians use benzodiazepines less frequently than psychiatrists in the treatment of anxiety disorders.[2] Combination therapy, however, may be of clinical value in many patients who present with symptoms consistent with comorbid anxiety and depression. Although the focus of this article is on these most commonly employed medications for depression and anxiety, other pharmacologic treatment options exist, including the tricyclic antidepressants, buspirone, and atypical antipsychotics.[3] Psychotherapies, particularly those employing cognitive and behavioral techniques, are also often effective for motivated patients.[3] This review aims to examine the evidence base of combination treatment with SSRIs/SNRIs and benzodiazepines for comorbid anxiety and depression, because these are the 2 most widely prescribed classes of medications for these disorders and the co-occurrence of anxiety and depression is a common clinical scenario.

METHOD

To review the literature, we searched PubMed and PsycINFO using relevant terms based on existing practice guidelines. The primary search terms were *anxiety*, a*nxiety disorders*, *depression*, *depressive disorders*, *comorbidity*, *epidemiology*, *benzodiazepines*, *antidepressants*, *pharmacology*, *clinical trials*, and *pharmacotherapy*. We also searched reference lists of identified articles to ensure capture of relevant literature.

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COMORBID ANXIETY AND DEPRESSION: A SPECTRUM OF SYMPTOMS

Clark and Watson[4] developed a tripartite model to differentiate the symptoms of anxiety from those of depression. They found anxiety to be most specifically associated with physiologic arousal and depression with a reduction of positive affect; they also identified a "general distress" factor shared between the conditions.[4] Despite the existence of diagnostic criteria for various anxiety and depressive disorders, presenting symptoms overlap in many circumstances and can present a diagnostic and management challenge, particularly given the frequency of somatic symptoms and the high rates of both medical and psychiatric comorbidities.[5,6] Not surprisingly, significant underdiagnosis and undertreatment have remained relatively common, even in psychiatric specialty clinics.[6–9]

Underdiagnosis often stems from the clinician's exclusive focus on the patient's chief complaint, in which symptoms of depression may overshadow comorbid anxiety, or vice versa. Misdiagnosis can also occur, as anxiety disorders can present with symptoms of depression, and, conversely, depressive disorders can present with prominent anxious features. The concept of an anxious subtype of depression, although not a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) diagnostic subtype, has undergone significant debate, due in part to its frequent clinical presentation.[10,11] In attempting to accommodate this diagnostic overlap, the DSM-IV-TR included the category, mixed anxiety-depressive disorder, in its appendix, indicating the need for additional study, although its clinical utility is controversial.[12,13] Nevertheless, management strategies must account for the individual patient's totality of symptoms regardless of how they are currently categorized, recognizing that anxiety and depression symptoms exist on overlapping spectrums.

Table 1. Clinical Ramifications of Comorbid Anxiety and Depression[a]

Poorer response to treatment
More chronic course of illness
Increased incidence of suicidal ideation and attempts
Greater functional and occupational impairment
Increased societal burden/socioeconomic costs
Increased health care utilization

[a]Based on Stein,[6] Wittchen et al.,[14] and Sareen et al.[21]

Estimates of the prevalence of comorbid anxiety and depression can vary based on the patient population, the clinical setting, and the specific diagnostic criteria used.[14] Well-controlled studies have found that at least half of all patients with panic disorder or generalized anxiety disorder (GAD) have a lifetime diagnosis of major depressive disorder (MDD).[14,15] The results of the U.S. National Comorbidity Survey Replication revealed high degrees of correlation between major depression and every anxiety disorder.[7,16]

CLINICAL IMPACT

Natural History of Depression and Anxiety

Both MDD and anxiety disorders are characterized by high rates of chronicity and recurrence.[17] The majority of patients who recover from an episode of depression will experience a recurrence at some point, as will nearly half of all patients who recover from an anxiety disorder.[17,18] Although many patients with depression return to premorbid functioning between episodes, at least 20% to 35% will have residual symptoms and impairment between episodes.[18] Except for panic disorder, which most often develops concurrently with or after the onset of major depression, anxiety disorders precede the development of major depression about two thirds of the time.[19,20]

The Clinical Consequences of Comorbidity

Comorbidity of anxiety and depression portends a poorer prognosis for the patient, as well as greater personal and socioeconomic costs (Table 1).[6,14,21] In the Harvard/Brown Anxiety Disorders Research Program,[17] which naturalistically followed community-treated patients for up to 12 years, the presence of comorbid MDD predicted a lower likelihood of recovery from panic disorder with agoraphobia than from either illness alone (risk ratio [RR] = 0.54, $p < .01$) and from GAD (RR = 0.57, $p < .01$).[17] The presence of MDD also increased the likelihood of recurrence in patients with panic disorder

Table 2. Risk for Suicidal Ideation and Attempts Among Patients With Mood and Anxiety Disorders[a,b]

	Lifetime Risk (N = 7074)[c]		Incidence of New Onset (N = 4246)[d]	
Disorders Group	Suicidal Ideation, Adjusted OR[e] (95% CI)	Suicidal Attempts, Adjusted OR[e] (95% CI)	Suicidal Ideation, Adjusted OR[e] (95% CI)	Suicidal Attempts, Adjusted OR[e] (95% CI)
Anxiety disorder only	3.26 (2.42 to 4.40)†	3.63 (2.05 to 6.43)†	3.34 (1.75 to 6.40)§	3.24 (1.09 to 9.69)†
Mood disorder only	9.56 (7.45 to 12.28)†	7.62 (4.48 to 12.99)†	3.46 (1.78 to 6.72)§	2.44 (0.79 to 7.55)
Anxiety and mood disorder	17.60 (13.90 to 22.29)†	16.96 (10.84 to 26.54)†	4.64 (2.28 to 9.43)§	10.05 (4.33 to 23.32)§

[a]Adapted with permission from Sareen et al.[21]
[b]Adjusted odds ratio (95% CI) versus those without anxiety or mood disorder.
[c]Lifetime risk of suicidal ideation or suicidal attempts at baseline interview.
[d]Incidence of new-onset suicidal ideation or suicidal attempts after 3-year follow-up.
[e]Adjusted for sociodemographic variables and other mental disorders (alcohol or drug use disorders, eating disorders, schizophrenia) at baseline.
†$p < .001$.
§$p < .05$.

by a factor of 1.85 ($p < .05$).[17] Similarly poor outcomes have been found in primary care settings for patients with comorbid depression and an anxiety disorder.[22,23]

The presence of an anxiety disorder also significantly increases the risk for suicidal ideation and suicide attempts (Table 2).[21,24] In a population-based study of 7076 people in the Netherlands,[21] the presence of any anxiety disorder at the time of first interview was associated with more than double the likelihood of ever having had suicidal ideation or a suicide attempt. Over the 3-year follow-up period, the likelihood of developing first-ever suicidal ideation and attempts was again twice as great or more in people with anxiety disorders than those without. Presence of both a mood and anxiety disorder predicted a 5-fold increased risk for suicidal ideation and a 10-fold increased risk for suicide attempts compared to nonanxious, nondepressed controls during the follow-up period.[21]

Many studies have attempted to examine general and specific risk factors associated with suicide attempts and ideation, and a full discussion is beyond the scope of this article. Nevertheless, results indicate relationships between suicidality and sleep disturbances such as nightmares, irritability, and psychomotor agitation.[25–27] The specific nature of these associations likely depends on the patient population, including diagnosis as well as other demographic factors. Whereas depressive symptoms contribute to the risk of suicide in part through the development of hopelessness and excessive guilt over the long term, the anxiety symptoms of irritability, agitation, and the feeling of a need to escape may contribute to a more immediate suicide risk.

CLINICAL CHALLENGES AND PHARMACOLOGIC TREATMENT OPTIONS

The high rates of comorbidity between anxiety disorders and depression, their overlapping and distinctive symptomatology, and their shared as well as unique neurobiologic mechanisms present considerable clinical challenges.

The Importance of Recognition, Diagnosis, and Treatment

Undertreatment of anxiety disorders and depression is not uncommon, primarily due to lack of recognition or underappreciation of their chronicity.[28,29] Some of the challenges in recognizing these disorders are the variability in symptom presentation, the presence of somatic symptoms, and associations between these disorders and medical illnesses, such as cardiac disease, hypertension, gastrointestinal disorders, and neurologic conditions.[5,9,30]

Multimodal Therapy Options

Approaches to the management of anxiety disorders include nonpharmacologic and pharmacologic options. Psychotherapeutic approaches, such as cognitive-behavioral therapy (CBT), relaxation techniques, and other forms of therapy, can play an important role in management, both as single intervention and as an adjunct to pharmacologic therapy.[31,32] Unfortunately, large segments of the patient population may not have ready access to therapists trained in CBT methods or may not avail themselves of these services for a variety of reasons.[33]

The 2 main categories of medication used in the treatment of anxiety disorders are benzodiazepines and SSRIs and the related SNRIs (Table 3). SSRIs are now considered first-line therapy in the treatment of various anxiety disorders, in part because of their established efficacy, their broad spectrum of activity, their generally good tolerability profile, their efficacy for comorbid depression, and their suitability for long-term use, in keeping with treatment recommendations for these generally chronic conditions.[18] The primary limitations of SSRIs and SNRIs involve the delay to onset of effect,[18,34] the risk of agitation and anxiety at the initiation of treatment,[8,35,36] and high rates of sexual dysfunction.[37] These factors may contribute to reduced adherence to treatment and poorer outcomes.

A recent analysis of a large managed-care database assessed antidepressant adherence and medical resource utilization in over 13,000 patients with diagnosed anxiety disorders.[38] Eligible patients had received at least 1 pre-

Table 3. Strengths and Limitations of SSRIs/SNRIs and Benzodiazepines for Use in Anxiety Disorders[a]

Medication	Strengths	Limitations
SSRIs/SNRIs	Approved for a variety of anxiety disorders, as well as depression Treat comorbid depression Associated with minimal cardiovascular risk (SSRIs only)	Slow onset Breakthrough and/or recurrent anxiety symptoms Induction of agitation/anxiety Sleep disturbance Sexual dysfunction Weight gain Cost
Benzodiazepines	Rapid onset Relatively low cost High patient acceptance Manage acute exacerbations of anxiety symptoms Effective versus somatic symptoms	Generally not recommended for long-term use Minimal impact on depressive symptoms May exacerbate depression Psychomotor/cognitive impairment Abuse potential Ataxia and falls Respiratory depression

[a]Based on American Psychiatric Association,[18] Shader and Greenblatt,[34] Nutt,[35] Susman and Klee,[36] and Clayton et al.[37]
Abbreviations: SNRIs = serotonin-norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors.

scription for any SSRI or SNRI. At 6 months after the initial prescription, 57% of the patients were not adherent to their therapy. Those who received specialty mental health care were more likely to be adherent (48.5%) than those not receiving such care (40.7%; $p < .001$) Interestingly, patients with dual diagnoses of anxiety and depression were more adherent than those with anxiety alone (46.8% vs. 40.2%; $p < .001$), perhaps reflecting the greater level of distress that comorbidity generates.

Recently, concern has arisen about a potential link between SSRI/SNRI use in some populations and increased suicidality. Despite warnings included in prescribing information with regard to increased suicidality among children, adolescents, and young adults, reviews of the literature do not unequivocally demonstrate increased suicide risks overall associated with the use of these agents.[39] In some cases, however, increased anxiety associated with the initiation of antidepressant therapy, whether monotherapy or combination treatment, may increase patients' distress, which may, in rare cases, lead to thoughts of suicide. Patients should always be monitored closely in the weeks after starting an antidepressant to ensure excessive agitation or anxiety is not occurring. If either occurs, dose reductions and use of benzodiazepines may be useful in reducing agitation and anxiety stemming from a new SSRI.

In contrast to SSRIs, benzodiazepines are useful in anxiety disorders because of their rapid onset of effect. Available since the 1960s, benzodiazepines are highly effective anxiolytics (Table 3).[40] In addition to their rapid onset of action, they are associated with high patient acceptance and a good tolerability profile.[41] Adverse effects include sedation, psychomotor impairment, rebound anxiety with discontinuation of medication, the possibility of cognitive impairment, and the risk of fetal birth defects if taken during pregnancy.[42–44]

A leading concern with prescribing benzodiazepines is their potential for abuse and dependence. Substance abuse, in its simplest terms, is continuing use of a psychoactive compound despite the user's knowledge of the harmful consequences engendered. Substance dependence implies an inability to control use, so that the substance is taken more frequently or in greater amounts than intended, and activities are given up to pursue use of the substance. This form of dependence is distinguishable from simple physical dependence on a substance, which does not involve excessive use resulting in life-damaging behaviors. Both forms of dependence can result in withdrawal symptoms if the substance is suddenly discontinued. Substance withdrawal may be distinguished from a substance discontinuation syndrome by the absence of drug craving in the latter.[45] For example, discontinuation symptoms (Table 4) appear to be relatively common when SSRI or benzodiazepine therapy is halted and require patient education and active clinical management, including drug tapering.[46] Similarities between some SSRI and benzodiazepine discontinuation symptoms may derive from the changes in γ-aminobutyric acid (GABA) signaling that result from both forms of therapy.[47,48] Detriments in the quality of patient care can result when these concepts

Table 4. Comparison of SSRI/SNRI and Benzodiazepine Discontinuation Symptoms[a]

Symptom Type	SSRIs/SNRIs	Benzodiazepines
Psychiatric	Increased anxiety Irritability Insomnia Increased depression Lethargy	Increased anxiety Irritability Insomnia
Sensory	Dizziness Headache Paresthesias	Dizziness Heightened sensations
Other	Diaphoresis Tremor Nausea	Diaphoresis Tremor Seizures

[a]Based on Haddad.[46]
Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

are confused and appropriate treatments unnecessarily withheld by clinicians.[49]

Benzodiazepines carry some abuse potential and are associated with physical dependence and withdrawal, sometimes marked by drug craving. However, abuse of benzodiazepines typically occurs in the setting of polysubstance abuse, and benzodiazepines are rarely used as the primary drug of abuse.[50] Prescription of benzodiazepines is best avoided for persons with a history of alcohol or other substance abuse. Clinical data and expert clinical opinion support the unique and important role of benzodiazepines in the management of anxiety disorders and indicate that the risks of abuse are low when these agents are used as directed for legitimate therapeutic indications.[50,51] A long-term population-based study of benzodiazepine use among 2440 patients found dose escalation to be relatively rare—exhibited by only 1.6% of patients during 2 years of continuous use.[52] These results confirmed an earlier community-based study finding that dose escalation occurred infrequently with long-term use of benzodiazepines.[53] In itself, dose escalation does not necessarily imply abuse of the substance or tolerance to the anxiolytic effects. Rather, as patients experience a reduction in anxiety with initial treatment, they may increase their level of exposure to feared stimuli, resulting in greater anxiety and need for a higher dose.

Recently, data on the comorbidity of substance abuse/dependence and mood and anxiety disorders were published.[54] The data were from the National Epidemiologic Survey on Alcohol and Related Conditions and were based on a community sample of 43,093. Not unexpectedly, the lifetime prevalence of mood and anxiety disorders among respondents with drug use disorders was high: 41% had a mood disorder and 30% had an anxiety disorder. Conversely, among those with a lifetime mood or anxiety disorder, the prevalence of lifetime drug use disorders was 22% and 19%, respectively. Of the 8 classes of drugs evaluated, however, the prevalence of tranquilizer abuse was only 1.7% (SD = 0.2) among those with any anxiety disorder and 1.9% (SD = 0.2) among those with any mood disorder. The prevalence of tranquilizer dependence was even lower: 0.8% (SD = 0.1) among those with any anxiety or mood disorder. These data would suggest a low probability (about 1 in 50) that patients with anxiety and depressive disorders treated with benzodiazepines will develop abuse of the medication.

Integrated Therapy of Benzodiazepines in Combination With SSRIs

The most widely accepted use for benzodiazepines in the treatment of anxiety and depression is for short-term use to achieve rapid symptom relief at the beginning of therapy, with subsequent tapering when the SSRI begins to exert an effect.[6,9] The rationale for the combined treatment with antidepressants and benzodiazepines is multidimensional, comprising both neurologic and clinical factors. Both anxiety and depression appear to have distinct as well as shared pathophysiologic mechanisms.[55–59] In principle, combination regimens with agents having different primary mechanisms of action provide an opportunity to address multiple underlying disease mechanisms, take advantage of complementary mechanisms of action, and afford potentially greater flexibility in developing individualized treatment plans.

Given the high rates of discontinuation with initial SSRI therapy, rapid symptom resolution may improve adherence to antidepressant medication, which may ultimately improve overall outcomes.[2] Addition of a benzodiazepine to an SSRI can provide more rapid improvement in depression and more rapid stabilization of panic or social phobia symptoms than the SSRI alone, although findings are not unequivocal.[60–63] For example, in patients with generalized social anxiety disorder, the addition of clonazepam to an SSRI did not lead to more rapid symptom resolution, but did suggest improved global improvement.[63] In a randomized controlled trial in panic disorder, paroxetine and placebo was compared to paroxetine plus clonazepam, which was either tapered or continued.[62] The benefits of combined treatment were apparent at week 1 and were maintained through week 5 of the 12-week study.

A recent open-label study examined the effect of sequential therapy with clonazepam followed by the SNRI milnacipran in patients with panic disorder and comorbid unipolar depression.[64] The sequential regimen comprised 28 days of clonazepam with a gradual taper. Milnacipran treatment began on day 14. At the study endpoint (7 weeks later), 70% of patients were free of full panic attack symptoms and 85% had achieved a good antidepressant response.

Benzodiazepines are not recommended as monotherapy in depression, as they primarily improve the symptoms of insomnia and restlessness, rather than the core depressive symptoms of sadness, anhedonia, and low energy.[65] A systematic review and meta-analysis of 9 randomized studies[66] found that patients receiving the combination of an antidepressant and benzodiazepine for MDD were less likely to discontinue treatment and more likely to show improvement than those receiving antidepressant monotherapy, although only 1 of these studies used an SSRI antidepressant. Overall, the number needed to treat with combination therapy to prevent a premature dropout was 8, and the number needed to treat to improve depression response with combination therapy was 7 at 4 weeks. Only 1 of the studies specifically evaluated depressed patients who also had moderate to severe anxiety, finding superiority for combination treatment at weeks 1 and 2.[67] The study using an SSRI[68] administered fluoxetine 20 mg per day plus clonazepam 0.5 mg per day (or matching placebo) in depressed patients with or without significant anxiety. Over the first 6 weeks of treatment, the active combination

was only superior at day 7 on the total depression score.[68] This finding suggests that combination therapy, at least with a low dose of benzodiazepine, adds little to the treatment of nonanxious depressed patients.

Confounding the issue of adding benzodiazepines to antidepressants is the belief that benzodiazepines can exacerbate or cause depression.[69] It is well established that in some individuals, benzodiazepines can have a paradoxical effect, i.e., causing irritability or agitation (generally referred to as "disinhibition"). The question of whether benzodiazepines actually cause depression, however, has not been well evaluated. A case-control study comparing regular users of high dose benzodiazepines versus a psychiatrically ill control group did not find a difference in risk for suicide attempts.[70] However, long-term use of alcohol, another drug that acts directly on GABA systems, is believed to contribute to depression; by analogy, the same risk may be posited for long-term use of benzodiazepines. Thus, although short-term studies suggest efficacy of combination treatment in patients with co-occurring anxiety and depression, the long-term implications are less clear and warrant cautious evaluation, particularly if higher doses are employed.

A recent development in administration of benzodiazepines is the availability of different formulations, including extended-release alprazolam and orally dissolving tablets of alprazolam and clonazepam. Each of these may have utility in different settings. Extended-release alprazolam produces a more sustained plasma concentration than immediate-release alprazolam. This formulation, however, did not demonstrate a benefit over immediate-release alprazolam in a controlled study of panic disorder.[71] Two recent randomized studies of GAD and panic disorder explored the use of an orally dissolving form of alprazolam plus an SSRI/SNRI versus SSRI/SNRI alone.[72,73] In both studies, the combination treatment did not reduce time to response, the primary efficacy variable. However, the combination did improve secondary outcome measures of insomnia and the clinicians' global impression of improvement.[72,73] Access to a benzodiazepine and the ability to easily take the medication on an as needed basis may be a significant help to patients in managing their anxiety disorders.[35]

SUMMARY AND CONCLUSIONS

Major depression and anxiety disorders, although separable clinical syndromes, often contain significant symptomatology of each other. Patients experience significant distress and poorer outcomes when both forms of disorders co-occur. Effective treatments are available to target these conditions, although monotherapy is frequently inadequate to attain complete remission. In practice, combining a benzodiazepine with an SSRI can offer the patient the following benefits: (1) more rapid control of anxiety, (2) reduction of SSRI-induced anxiety or agitation that can occur early in the course of therapy, (3) improved adherence to antidepressant therapy, and (4) improved control of episodic or situational anxiety that occurs in response to certain stimuli. These benefits need to be weighed against the potential risks of combination therapy, including side effects, abuse of medication, and potential for worsening of depressive symptoms.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar and others), clonazepam (Klonopin and others), fluoxetine (Prozac and others), paroxetine (Paxil and others).

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