Anxiolytic Antidepressant Augmentation

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The administration of anxiolytic drugs often accompanies treatment with antidepressant medications. Although benzodiazepines help alleviate the secondary depressive symptoms of anxiety and sleep disturbance, they do not actually enhance antidepressant response. On the other hand, the anxiolytic agent buspirone does facilitate direct antidepressant response, largely through its ability to activate both presynaptic and postsynaptic 5-HT$_{1A}$ receptors and thus modulate serotonin release. Several case studies and open-label trials have demonstrated the effectiveness of buspirone as an augmentation agent. Because buspirone is also associated with few adverse effects, it appears to be both effective and safe in the augmentation of antidepressant pharmacotherapy.

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The compounds lithium and thyroid hormone are the best-documented and most widely employed among those used for antidepressant augmentation. More recently, buspirone and pindolol, medications active at the 5-HT$_{1A}$ receptor, have been described as successful add-on augmentation treatments. Pindolol is discussed elsewhere in this supplement.[1] This review focuses on buspirone and other anxiolytics as combination treatment to enhance antidepressant response.

Antidepressant and antianxiety drugs are used together about as often as they are used separately. For example, the benzodiazepines lorazepam, diazepam, and alprazolam and the azapirone buspirone represent 73% of all antianxiety medications sold in the United States. They are used alone only about 50% of the time. When coadministered, they are combined primarily with antidepressant agents (Table 1), although diazepam is most often combined with narcotic analgesics (Physician Drug & Diagnosis Audit [PDDA], June 1996–May 1997, Scott-Levin, a division of PMSI Scott-Levin, Inc). One recent survey[2] found that between 33% and 41% of patients taking serotonin selective reuptake inhibitors (SSRIs) were also taking a sedative or hypnotic agent, mainly benzodiazepines. Given the prevalence of this pattern of use, it is of interest whether the coadministration of antianxiety and antidepressant agents improves treatment outcome by enhancing the antidepressant effects of medication, represents efforts to manage anxiety and sleep symptoms that often accompany depressive illness, or reflects prescribing habits.

BENZODIAZEPINES

Benzodiazepine agonists—such as diazepam, chlordiazepoxide, lorazepam, temazepam, alprazolam, and clonazepam—have many approved indications. These include insomnia, generalized anxiety, panic, epilepsy, and conscious sedation. They are not, however, indicated as a treatment for depression. The efficacy of benzodiazepines as antidepressants has been compared with that of antidepressants, most commonly tricyclic agents. In double-blind studies that compared standard benzodiazepines, such as diazepam and chlordiazepoxide, with tricyclics, benzodiazepines were found to be helpful in alleviating symptoms of anxiety and insomnia, but not core symptoms of depression.[3] In treating depressed patients, traditional benzodiazepines appear to complement or act as auxiliary treatment with the more standard tricyclic antidepressants.[4] There are suggestive data that alprazolam may have antidepressant properties. Findings about the effectiveness of alprazolam as an antidepressant, however, are generally considered inconclusive, especially for severely depressed patients.[3]

The most probable reason that benzodiazepines are given with antidepressants is that benzodiazepines reduce anxiety and sleep disturbance, symptoms that are both common and distressing manifestations of depression. They are not used in this manner to enhance the effects of the antidepressant on the core symptoms of depression and in this sense do not represent true augmentation. Rather, they are adjunctive agents used for symptom control. The history of popularity of Limbitrol,[5] a combination of amitriptyline and chlordiazepoxide, may reflect this. Prescription of benzodiazepines in the treatment of depression is

largely limited to helping to manage the symptoms of agitation, anxiety, and insomnia that accompany depression. Augmentation for the purpose of converting nonresponders or partial responders is not mentioned in the literature.

There are few data that support the value of benzodiazepines for the purpose of enhancing antidepressant response at the outset of treatment. Smith et al.[28] have reported the results of a double-blind study of clonazepam augmentation of fluoxetine. The combined treatment group exhibited significantly more improvement than those taking fluoxetine but only during the first 3 weeks of treatment. The mean Hamilton Rating Scale for Depression (HAM-D) scores for both groups converged later during the study, and by Day 42 the scores were similar. The investigators concluded that clonazepam augmentation of fluoxetine was superior to fluoxetine alone in the first 3 weeks of treatment and that such faster response to treatment reduced the suffering associated with the delay in onset of antidepressant efficacy. They also speculated that additional potential benefits include the reduced risk of early suicide, suppression of antidepressant side effects, and increased compliance with treatment.

One possible conclusion is that augmentation with a benzodiazepine during the first weeks of treatment may in fact facilitate tolerability, but not long-term response. Drawbacks include sedation, psychomotor impairment, risk of withdrawal phenomena, and long-term dependence. These concerns tend to limit the use of benzodiazepines in the treatment of anxiety disorders, and the same concerns are even more applicable for its use in antidepressant augmentation. A triazolobenzodiazepine, adinazolam, was extensively studied in the 1980s and 1990s and found to have antidepressant properties. The drug was not approved for that indication, in large measure because of concerns about dependence and withdrawal. Similarly, alprazolam has also been found to have possible antidepressant activity, but has not been given that indication for the same reason.

BUSPIRONE

Buspirone was introduced as an anxiolytic agent in 1986. It has become a well-established alternative to the benzodiazepines,[6] primarily because of its safety and tolerability. It is not sedating, does not impair cognition, spares psychomotor functions, has no abuse potential, has no withdrawal symptoms, and does not interact with central nervous system depressants.

The contrast in side effect profiles between buspirone and the benzodiazepines reflects their differences in underlying synaptic pharmacology. Unlike the benzodiazepines, buspirone does not interact with GABA receptors. It acts as a partial 5-HT_{1A} receptor agonist at both autoreceptors and postsynaptic receptors. Interest in the use of this agent for antidepressant augmentation derives directly

Table 1. Concomitant Usage of Antianxiety Drugs*

Drug	Total Occurrences ($\times 1000$)[a]	Percent Used Alone	Percent Used Concomitantly	Percent of Concomitant Usage With Antidepressant
Alprazolam	6170	56.8	43.2	84.2
Lorazepam	4682	44.6	55.4	66.8
Diazepam	3512	45.1	54.9	28.6
Buspirone	2218	50.2	49.8	82.8

*Marketing data are from Scott-Levin Physician Drug & Diagnosis Audit, Scott-Levin, a division of PMSI Scott-Levin, Inc., with permission.
[a]The number of "occurrences" indicates estimated prescribing in the United States from June 1996 to May 1997.

from this synaptic pharmacology as well as empirical evidence that it can facilitate antidepressant responses.

Data suggest, for example, that these receptors, particularly the postsynaptic receptors, exhibit impaired sensitivity in patients with melancholic depression.[7,8] Acutely, buspirone decreases dorsal raphe and hippocampal extracellular concentrations of serotonin through activation of 5-HT_{1A} receptors on the cell body and dendrites of dorsal raphe serotonergic neurons. These receptors are termed *presynaptic heteroreceptors*, and their function is to modulate serotonin release. This decrease in serotonin release would be the opposite of what is generally expected of drugs with antidepressant effects. However, after several days, these receptors become sensitized to the buspirone. Possibly more important to its antidepressant properties is the activation by buspirone of postsynaptic 5-HT_{1A} receptors. This activation of receptors, which is independent of extracellular serotonin, mimics the effects of serotonin.[9]

There is also evidence that buspirone may potentiate the clinical effects of SSRIs by markedly facilitating elevation of both dopamine and norepinephrine in the frontal cortex.[10] Reinforcement of catecholamine activity represents one strategy to enhance SSRI efficacy, as reflected in the combined use of SSRIs with amphetamine, bupropion, and tricyclic antidepressants. A buspirone metabolite may also contribute to its mood effects. The major metabolite of buspirone, 1-pyrimidinylpiperazine (1-PP) acts as an α_2-adrenergic agonist. Concentrations of 1-PP in the central nervous system are higher than those of buspirone.[10] It acts exclusively on the noradrenergic system, not binding to dopamine or serotonin receptors. Additional evidence that 1-PP may contribute to the therapeutic effects of buspirone comes from clinical experience with the antidepressant mirtazapine. Like buspirone, mirtazapine is believed to produce its clinical effects, in part, through α_2-adrenergic blockade and 5-HT_{1A} receptor activation.

Preclinical Findings

There are several lines of evidence that buspirone possesses intrinsic antidepressant properties. These include animal models of antidepressant activity, clinical observation, and findings of clinical studies.

Animal studies have found that buspirone produces behavioral effects that are presumed measures of antidepressant activity. These include reversal of learned helplessness and behavioral despair, and reduced immobility time in the forced swim test.[11] A related biochemical finding that buspirone may augment cortisol escape from suppression by dexamethasone in depression also indicates primary antidepressant activity.[12]

An additional finding that predicts antidepressant activity is the ability of a drug to induce manic symptoms. Buspirone has been reported to produce hypomania.[13–15]

Buspirone Monotherapy: Antidepressant Effects

Open-label clinical trials have found evidence that buspirone monotherapy is associated with antidepressant activity. Schweizer and colleagues,[16] for example, determined that buspirone at dosages up to 30 mg/day for 4 weeks in 30 patients with major depression resulted in significant antidepressant effects. The subjects were nonmelancholic depressed outpatients with major depression who also had moderate associated anxiety. Rickels and associates[17] conducted a double-blind, placebo-controlled trial in 155 depressed patients with significant anxiety symptoms. Patients were treated with buspirone dosages of up to 90 mg/day. Antidepressant effects of buspirone were noted in all outcome measures, whether patients were highly anxious or not. The largest statistically significant differences between buspirone and placebo were found in their effects on core symptoms of depression.

This study was a part of a series of trials that compared treatment with buspirone with placebo in approximately 400 patients with major depression.[18] The trials were multicenter, double-blind, and placebo-controlled with parallel-group design and random assignment to an 8-week treatment. Patients included in the trials were diagnosed with major depression (DSM-III-R) and had a minimum Hamilton Rating Scale for Depression (HAM-D) score of greater than 18. One hundred eighty-three patients were treated with buspirone (15 mg/day, up to 90 mg/day); 199 patients were treated with placebo. The study found marked improvement with buspirone compared with placebo. The most impressive changes were noted for two core symptoms: depressed mood, and work and interest. Also highly significant were drug-placebo differences for middle insomnia, agitation, psychic anxiety, anergia, and diurnal variation. More severely depressed melancholic patients did better than nonmelancholic patients (Figure 1).

Buspirone Augmentation of Antidepressants

It was awareness of the above findings that prompted the use of buspirone as an augmentation agent. Several case reports appeared, followed by open-label studies. One double-blind study has been completed and is in press.[29] Preliminary results have been presented.

Figure 1. Antidepressant Effects of Buspirone*
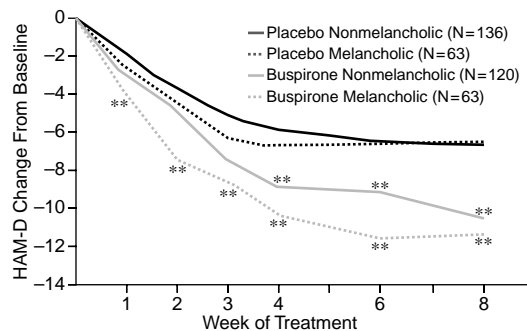
*From reference 18. Figure shows improvement in 25-item HAM-D scores of patients with melancholic and nonmelancholic major depression.
**Improvement was significantly (p ≤ .05) greater with buspirone compared with placebo treatment by diagnostic subtype.

Case histories. Case reports have appeared that note positive responses to buspirone augmentation. One of these reports[19] describes three patients who had obsessional traits, symptoms of depressive illness, marked anxiety, and a history of eating disorder and who had prior partial responses to fluoxetine. They each showed dramatic improvement after buspirone addition (30 mg/day). The combination of fluoxetine and buspirone produced very few side effects. In the other report,[20] two elderly patients diagnosed with depression who were taking trazodone (100–250 mg q h.s.) experienced a complete remission of depressive symptoms following the addition of buspirone (20–30 mg/day). Mania was induced in a third patient. This side effect, mania, is associated with all drugs that have antidepressant activity.

Open-label studies. Jacobsen[21] was the first to report a case series of patients treated with buspirone for the purpose of antidepressant augmentation. Two outpatient groups were described: one group consisted of patients with typical major depression; the other, patients with winter-relapsing depression. The first group, consisting of patients who had failed to respond to at least one trial of an antidepressant, was given 30 mg/day of buspirone. The dosage was reduced if side effects were intolerable. Seven patients were treated with fluoxetine, and one was treated with imipramine. Patients were evaluated within 3 weeks of the start of treatment. A good response was defined as a remission of depressive symptoms, as reflected by a reduction in Clinical Global Impressions (CGI) scores (which measure severity of depression) by three or more points. Partial response was reflected by a two-point reduction in CGI score. Seven of the eight antidepressant nonresponders exhibited a partial or full antidepressant response after the addition of buspirone (Table 2). The posttrial group mean (± SD) CGI score was 1.9 (1.4, p < .001). Reported side effects were negligible.

Another group of patients reported by Jacobsen included nine antidepressant refractory patients refractory

Table 2. Characteristics of Antidepressant Nonresponders Completing Trial of Buspirone Potentiation*

Age (y)	Sex	Axis I Diagnosis	Antidepressant	Other Medications	Days of Antidepressant Treatment Before Trial	Dose	Effect[a]	Months Monitored on Buspirone	CGI Ratings[b] Pretrial	CGI Ratings[b] Posttrial
37	F	Major depression	Imipramine 300 mg (serum level >150 ng/mL)	…	60	30 mg	++	12	4	1
39	F	Major depression	Fluoxetine 20 mg	Lithium 1200 mg	45	15 mg	+	1[c]	4	2
41	F	Major depression	Fluoxetine 20 mg	…	60	30 mg	++	3	5	1
51	M	Bipolar II rapid cycling	Fluoxetine 20 mg	Valproate 500 mg	60	30 mg	++	3	4	1
29	M	Bipolar I	Fluoxetine 20 mg	Lithium 900 mg	120	30 mg	+	5	4	2
52	F	Major depression	Fluoxetine 40 mg	Trazodone 25 mg	90	30 mg	++	12	6	2
30	F	Bipolar II	Fluoxetine 40 mg[d]	…	60	30 mg	−	1	5	5
42	F	Major depression	Fluoxetine 40 mg[d]	Trazodone 50 mg	65	30 mg	++	9	5	1

*From reference 21, with permission.
[a]++ = good, + = fair, and − = none.
[b]CGI = Clinical Global Impressions scale.
[c]Dropped out of treatment.
[d]Failed potentiation with liothyronine 50 μg.

Table 3. Characteristics of Winter Relapsing Depressives Completing Trial of Buspirone Potentiation*

Age (y)	Sex	Axis I Diagnosis	Antidepressant	Other Medications	Days of Remission Before Buspirone Trial	Buspirone Dose	Effect[a]	Side Effects	Months Monitored on Buspirone	CGI ratings[b] Pre-trial	CGI ratings[b] Post-trial
42	F	Major depression	Fluoxetine 20 mg	Trazodone 225 mg, liothyronine 20 μg	270	30 mg	++	Sedation	3	4	1
38	M	Bipolar II	Nortriptyline 125 mg (serum level = 129 ng/mL)	Lithium 900 mg	365	30 mg	++	Nervousness, irritable mood	7	5	2
34	M	Major depression	Imipramine 200 mg (serum level = 293 ng/mL)	Lithium 750 mg, liothyronine 25 μg	60	30 mg	+	…	10	4	2
44	F	Major depression	Fluoxetine 40 mg	Trazodone 50 mg	60	30 mg	++	Sedation	4	4	1
41	F	Major depression	Fluoxetine 40 mg	Hydroxyzine 25 mg	545	30 mg	++	…	8	4	1
46	M	Bipolar I	Nortriptyline 100 mg (serum level = 143 ng/mL)	Valproate 500 mg, liothyronine 25 μg	90	30 mg	++	…	12	6	1
35	M	Bipolar I	Desipramine 200 mg (serum level = 78 ng/mL)	Carbamazepine 600 mg	210	30 mg	−	…	1	4	4
35	F	Major depression	Fluoxetine 20 mg	…	390	5 mg	+	"Spacey" feeling, insomnia	12	3	1
52	F	Bipolar II	Fluoxetine 20 mg	Liothyronine 25 μg	130	30 mg	++	…	2	5	1

*From reference 21, with permission.
[a]++ = good, + = fair, and − = none.
[b]CGI = Clinical Global Impressions scale.

with fall/winter major depression. The addition of buspirone resulted in the achievement of complete resolution of symptoms in six patients (67%) (Table 3). These patients were taking the antidepressant fluoxetine as their primary antidepressant. Two patients (22%) experienced partial response, and one patient (11%) demonstrated no response. Three patients experienced side effects associated with the addition of buspirone. These effects included drowsiness, nervousness/irritability, and spaciness.

Joffe and Schuller[22] evaluated 25 patients with major depression who had failed several antidepressant trials with the SSRIs fluoxetine (20–40 mg/day) or fluvoxamine (50–100 mg/day). Seventeen (68%) of the 25 patients showed a marked or complete response 3 weeks after a buspirone addition of 20–50 mg/day.

In another open, uncontrolled study, buspirone augmentation was studied in patients taking SSRIs or the serotonergic antidepressant clomipramine.[23] Thirty patients—14 men and 16 women—who met DSM-III-R or DSM-IV criteria for major depression (single or recurrent episodes) were included in the study. All patients had received serotonergic antidepressant medication for longer than 6 weeks with no improvement before inclusion in the study and continued the medication along with buspirone for the study duration of 4 to 5 weeks.

Of the 22 patients taking SSRIs, 60% showed improvement with buspirone addition. Six patients showed complete remission of their depressive symptoms, and 7 patients showed partial remission. Of the 8 patients taking clomipramine, 63% showed improvement with buspirone addition. Three patients showed complete remission. Of 14 responders available for a 6-month follow-up, 11 patients were asymptomatic, and 3 were mildly ill. No serious side effects were observed.

A 6-week open-label trial conducted by Barbee et al.[24] examined the safety and efficacy of adding buspirone to nefazodone. Patients exhibited partial or no response to nefazodone alone. Of 43 patients who entered the study, 16 discontinued owing to side effects, mainly dizziness, headache, or nausea. Eighteen patients completed the study. Of the 23 patients who were considered evaluable, in that they had at least 4 weeks of buspirone augmentation, 10 patients (43%) responded. The investigators speculate that the high discontinuation rate due to adverse events was related to the use of 5 mg t.i.d. of buspirone as a starting dose. They note that there is a pharmacokinetic interaction between nefazodone, which inhibits the cytochrome P450 enzyme 3A3/4, and buspirone, which is metabolized by this enzyme. This interaction resulted in higher than expected plasma levels of buspirone. Barbee and colleagues recommend a lower initial dose of buspirone—such as 2.5 mg b.i.d.—when it is used in combination with nefazodone. This should probably also be the case with fluvoxamine, which also inhibits the 3A3/4 enzyme.

A double-blind placebo-controlled trial. Only one double-blind trial of buspirone augmentation has been completed, but it has not yet been published.[29] Conducted in Sweden, the study involved 117 depressed patients who had not responded to adequate trials of SSRIs. These patients had been depressed for a mean of 465 days before recruitment into the study, despite having received antidepressant therapy for a mean of 211 days.

The overall response rate for the buspirone-treated patients in this study was comparable to the 69.4% reported in open-label studies. A high placebo response rate precluded a statistically significant difference between the active and placebo groups. Analysis of CGI ratings, however, suggests a therapeutic effect among the buspirone-treated patients. Fifty-one percent of buspirone-treated patients were either "very much improved" or "much improved," and 45% of the buspirone-treated patients were rated "not ill at all" or only "borderline ill." None of the buspirone-treated patients were rated as "markedly ill" or as "severely ill" at the end of the study (Figure 2). This study also confirmed the tolerability of buspirone as an augmentation agent. The adverse event rates were the same for buspirone and placebo. Only 3 of the 59 buspirone-treated patients dropped out because of adverse events.

Figure 2. Buspirone Versus Placebo: Clinical Global Impression of Severity at the End of 4th Week*
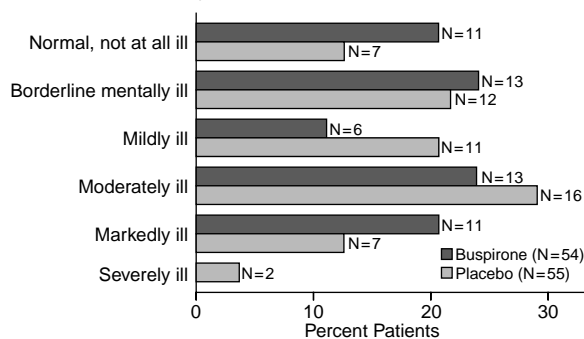
*Adapted from reference 29.

Other Studies

Some reports describe buspirone as a potential augmentation agent for conditions other than depression or in combination with drugs other than antidepressants.

One study[25] has found a "remarkably rapid response" in depressed patients treated with buspirone and pindolol. Pindolol, a 5-HT receptor antagonist, is discussed by Blier and Bergeron elsewhere in this supplement.[1] The investigators performed a study in which patients were treated with pindolol along with fluvoxamine, trimipramine, desipramine, or buspirone. Fluvoxamine is an SSRI that is used throughout the world as an antidepressant, but which is approved in the United States for the treatment of obsessive-compulsive disorder. Trimipramine and desipramine are TCAs that have minimal effects on the serotonin system. No patient was able to tolerate the pindolol-desipramine combination, but 5 patients taking pindolol-trimipramine were able to complete the 4-week study. Of these 5 patients, only 1 had a response, exhibiting a 50% reduction in his HAM-D score after 4 weeks. Of 10 patients treated with the pindolol-fluvoxamine combination, 4 improved by more than 50% after 14 days, 8 patients improved by more than 50% after 7 days, and 9 patients had a HAM-D score of less than 9 after 14 days. The investigators concluded that buspirone, in combination with pindolol, "exhibited both an efficacy and an onset of action that were superior to those of pindolol plus fluvoxamine or pindolol plus trimipramine combinations in the present study and were at least similar to those obtained with the SSRI paroxetine plus pindolol in a previous study."[25(pp335–336)]

Apart from the clinical implications of these findings, they provoke considerable questions about why drugs with apparently opposite effects—5-HT antagonism versus agonism—would produce relief of depression when used together, as in the case of buspirone and pindolol. One possibility is that the 5-HT receptors are heterogeneous, with different subtypes mediating disparate behavioral responses to different drugs. Buspirone may also produce clinical effects by increasing dopamine activity. It has

shown to increase the firing of dopaminergic neurons in the substantia nigra, through interaction with either dopamine D_2 receptors or 5-HT receptors on dopaminergic terminals.

Another study[27] examined 13 patients with body dysmorphic disorder, which has been "broadly conceptualized" as a form of mood-related disorder, and which responds to treatment with SSRIs. These patients had not responded or had only responded partially to an SSRI or clomipramine. Six (46%) of the 13 patients improved with buspirone augmentation. One patient experienced fatigue, and another experienced nausea. Those patients who had a partial response to the antidepressant before the augmentation showed the best response following the addition of buspirone.

Benefits and Risks of Buspirone Augmentation

One potential advantage of buspirone augmentation (and other drug combination strategies) is that it creates unique pharmacologic mechanisms, ones that are not present in single antidepressant agents. This might explain why one of these augmentation strategies works for a patient who is unresponsive to monotherapy. Of the more than 200 patients described in the literature as having used buspirone, there is a remarkable lack of serious side effects. One patient became manic when buspirone was added, a finding that can be regarded as evidence of the antidepressant effects of buspirone. There are case reports of patients being treated with antidepressants and buspirone who developed serotonin syndrome.[26,30]

Another appealing aspect of buspirone as an augmentation agent is its overall tolerability. Most notable is the absence of sedation, psychomotor impairment or cognitive deficits, withdrawal symptoms, and sexual dysfunction. It does not interact with alcohol or other CNS depressants. When buspirone is used alone or in combination with antidepressants, the most commonly experienced side effects associated with its use are dizziness, nausea, headache, nervousness, light-headedness, and excitement. These effects are dose related and diminish with ongoing treatment.

CONCLUSIONS

Published data strongly suggest effectiveness and safety when buspirone is used for augmentation of serotonergic antidepressants. The response rate might be as high as 65%. This is comparable to the rates reported for thyroid and lithium. All reports and studies of buspirone's augmentation properties have involved enhancement in patients not achieving a satisfactory response to ongoing treatment with an antidepressant. There are no data on the use of buspirone to accelerate response during initial antidepressant therapy.

From a risk-benefit perspective, buspirone, alone or in conjunction with antidepressants, has a highly favorable profile. Thus, safety and the absence of need for special laboratory monitoring make it a useful alternative to lithium and thyroid for patients who exhibit inadequate response to antidepressant treatment. As with all interventions, placebo-controlled, double-blind comparative studies are needed to clarify the role of buspirone in antidepressant augmentation.

Drug names: adinazolam mesylate (Deracyn), alprazolam (Xanax), amitriptyline (Elavil and others), bupropion (Wellbutrin), buspirone (BuSpar), chlordiazepoxide (Librium and others), clomipramine (Anafranil), clonazepam (Klonopin), desipramine (Norpramin and others), dexamethasone (Decadron and others), diazepam (Valium and others), fluoxetine (Prozac), fluvoxamine (Luvox), lorazepam (Ativan and others), mirtazapine (Remeron), nefazodone (Serzone), pindolol (Visken), temazepam (Restoril and others), trazodone (Desyrel and others), trimipramine (Surmontil).

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DISCLOSURE OF OFF-LABEL USAGE

The following agents mentioned in this article are *not* indicated for treatment of depression: buspirone, dexamethasone, estrogen, ketoconazole, lithium, pindolol, testosterone, T_3, T_4.

The following agents mentioned in this article are *not* indicated for treatment of depression and mania: carbamazepine, gabapentin, lamotrigine, valproate.