The Use of Antidepressants in Novel Combination Therapies

Richard C. Shelton, M.D.

Antidepressant monotherapy is used more often than other therapies to achieve symptom remission in depressed patients; however, for patients resistant to antidepressants, other strategies are necessary. Many novel combination therapies have been proposed to treat resistant depression. The efficacy of combination therapies such as lithium augmentation of antidepressants is supported by a large amount of evidence including data from controlled trials. Nonetheless, anecdotal reports suggest that these combinations are underutilized. Data from studies of the use of the combination of atypical antipsychotics and selective serotonin reuptake inhibitors suggest that this is a particularly promising therapeutic avenue. However, more research is needed to corroborate these early results.

(J Clin Psychiatry 2003;64[suppl 2]:14–18)

Estimates suggest that as many as 1 in 8 people will be treated for depression at some point in their lifetimes. Therefore, the need for effective treatments of depression cannot be overstated.[1] Historically, successful treatment of depression was equated with treatment response, typically a 50% reduction in symptoms as measured by such rating instruments as the Hamilton Rating Scale for Depression (HAM-D). However, an increasing number of physicians have become dissatisfied with such a standard. Treatment response is being replaced by the standard of symptom remission or patient wellness, which can be considered the new criterion for successful treatment of depression.[2] Wellness is usually defined as full remission of symptoms and a complete restoration of psychosocial functioning. A common operational definition is a score ≤ 7 on the HAM-D-17.[3]

Antidepressant monotherapy is used more often than other therapies to achieve remission of depressive symptoms. Although most patients with depression respond positively to antidepressant treatment, between 20% and 40% of patients exhibit only a minimal response.[4] If patients with a depressive disorder receive little or no benefit from normally effective treatments, then a diagnosis of treatment-resistant depression may be warranted. For those who receive little benefit from conventional antidepressant strategies, novel treatments are being developed.

Although many prospective therapies for treatment-resistant depression are pharmacologic, some are not. For example, vagus nerve stimulation (VNS), which has shown some benefit as a treatment for seizures,[5,6] and transcranial magnetic stimulation (TMS)[7–10] are being developed as treatments for resistant depression. However, their integration into a comprehensive treatment strategy remains in the distance.

Novel combination pharmacotherapies offer a more immediate potential for benefit for those with treatment-resistant depression. Although the terms *combination* and *augmentation* are sometimes used interchangeably, a distinction can be made. Generally, *combination* refers to the use of more than 1 type of disease-specific treatment to treat a particular illness; in the case of treatment-resistant depression, this would involve combining 2 different antidepressants. *Augmentation*, in this case, refers to the addition of a non-antidepressant medication (e.g., lithium or thyroid hormone) to an antidepressant.

An increasing amount of evidence suggests that patients with treatment-resistant depression respond favorably to combination and augmentation therapies. This evidence suggests that such pharmacologic therapies could be included in the armamentarium from which clinicians and physicians draw to produce symptom remission and induce patient wellness.

COMBINATION STRATEGIES

Combination therapies ostensibly produce their therapeutic benefit by adding an additional neurochemical action that is either different or greater than that seen with a monotherapy. However, it is not always clear what mecha-

From the Adult Psychiatry Division, Department of Psychiatry, Vanderbilt University Medical Center, Nashville, Tenn.

This article is derived from the teleconference "Treating Depression and Anxiety to Remission: Use of Algorithms," which was held April 17, 2002, and supported by an unrestricted educational grant from Wyeth Pharmaceuticals.

Corresponding author and reprints: Richard C. Shelton, M.D., Vanderbilt University Medical Center, Division of Psychopharmacology, 1500 21st Ave. S., Ste. 2200, Nashville, TN 37212-8646 (e-mail: richard.shelton@vanderbilt.edu).

nisms are responsible when combination treatment is effective. Three explanations of why a combination therapy results in positive treatment response are possible. First, in cases where a second medication is added to an ineffective antidepressant, the added medication may induce chemical mechanisms of action that may be entirely responsible for the observed clinical benefit, which would imply that the original antidepressant played no causal role in producing the response. Second, the addition of another drug, for example, adding a primarily noradrenergic agent to an agent that affects the serotonin system may produce mechanisms of action that are distinct from those of the original antidepressant. In this case, the addition of the mechanisms of the 2 agents would produce greater benefits for the patient. Third, adding a second drug to an antidepressant that is already being administered may induce a genuinely synergistic mechanism that is irreducible to the discrete mechanisms associated with each agent. However, without discontinuing the originally prescribed medication or having a clear understanding of the neurochemical mechanisms caused by particular agents, it is difficult to determine which of the explanations is applicable. Fortunately, the benefits of combination therapies do not depend on a complete understanding of the biological or chemical mechanisms that produce them.

Early indications that combined mechanisms could produce enhanced therapeutic benefits came from studies[11,12] showing that certain tricyclic antidepressants (TCAs) seemed to have a greater therapeutic effect than some selective serotonin reuptake inhibitors (SSRIs), at least in severely depressed patients.

Also, the combination of a norepinephrine reuptake inhibitor (NRI) in conjunction with SSRIs was shown to be more effective than the use of either an NRI or SSRI alone.[13,14] The findings of these early reports were replicated by a series of subsequent studies[15–17] that supported the effectiveness of combining NRIs and SSRIs. More recent research has shown that medications that have both serotonergic and noradrenergic effects, such as mirtazapine[18] and venlafaxine[19,20] can produce beneficial effects in patients who are nonresponsive to SSRIs. Evidence of this kind seems to support the idea that using drugs in combination can induce more numerous mechanisms of action and can produce greater effects in patients with treatment-resistant depression than could have been achieved by using a single agent that only affects a single chemical mechanism.

AUGMENTATION STRATEGIES

Lithium

An overwhelming amount of evidence indicates that lithium augmentation of antidepressants is an effective strategy for treating resistant depression. This was supported by a recent meta-analysis[21] of 9 placebo-controlled studies which concluded that lithium augmentation of conventional antidepressants is an effective strategy in treatment-resistant depression. Other research[22–25] into lithium augmentation seems to corroborate the findings of this meta-analysis. For example, Baumann and colleagues[25] conducted a study of the efficacy of lithium augmentation of citalopram in patients with treatment-resistant depression. Twenty-four patients were randomly assigned to groups being treated under double-blind conditions with lithium and citalopram or citalopram plus placebo. After 7 days, 6 of 10 patients being treated with lithium and citalopram responded to lithium augmentation, whereas only 2 of 14 patients responded to citalopram plus placebo. However, despite data to support the efficacy of lithium augmentation, anecdotal reports suggest this treatment strategy is underutilized.

Thyroid Hormone

Research also shows that there are other promising augmentation therapies, such as administering TCAs with thyroid hormone. Evidence from early open trials supported the efficacy of augmenting TCAs with triiodothyronine (T_3).[26] These preliminary results were reinforced by controlled data, such as the placebo-controlled study of Joffe et al.,[27] which tested the efficacy of T_3 and lithium in 51 patients with TCA-resistant depression. The study found a 59% response in patients receiving T_3 in addition to TCAs, which was comparable to the 53% response to lithium augmentation of TCAs. Both were superior to placebo, which only produced a response in 19% of cases. Unfortunately, studies on thyroid augmentation of SSRIs or monoamine oxidase inhibitors (MAOIs) are lacking, and therefore further research in this area is needed.

Antipsychotics

Conventional antipsychotics produce fairly small effects as monotherapies of depression, but are especially effective in those patients who also present psychotic symptoms. Robertson and Trimble[28] reviewed 34 double-blind trials of antipsychotics prescribed for antidepressant effect and found that typical antipsychotics deliver a modest benefit. However, the risk of adverse effects such as tardive dyskinesia makes typical antipsychotics an unacceptable therapy and complicates their use as a maintenance treatment.

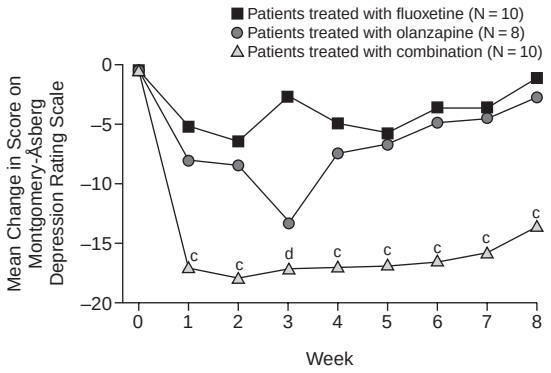
An increasing body of data has suggested that novel antipsychotics may be effective agents when used as a monotherapy or combination treatment for depression. The benefit of novel agents in bipolar or schizoaffective disorder is well-documented.[29–34] Augmenting antidepressants with atypical antipsychotics has produced some striking results. For example, Ostroff and Nelson[35] found that patients who were nonresponsive to at least one SSRI (either fluoxetine or paroxetine), as well as many who were nonresponsive to prior combination therapies, ben-

Table 1. Time to Risperidone Augmentation Response[a]

Patient No.	SSRI Trial	Prior Treatment in This Episode	Risperidone Dose	HAM-D Score		Time to Response
				Pre-Risperidone	Post-Risperidone[b]	
1	Fluoxetine 20 mg for 6 wk	None	0.5 mg hs for 1 day, increased to 1 mg[c]	19	0	1 d
2	Fluoxetine 20 mg for 2 mo	Prior trial of desipramine	0.5 mg	17	2	2 d
3	Paroxetine 20–30 mg for 8 wk	Prior trial of sertraline	0.5 mg for 1 day, increased to 1 mg	27	...[d]	1 wk
4	Fluoxetine 20–40 mg for 8 wk	3 prior trials	0.5 mg hs	21	3	4 d
5	Fluoxetine 20 mg for 4 mo	Prior trial of sertraline	0.5 mg hs	18	6	1 wk
6	Paroxetine 20 mg for 2 wk	None	1.0 mg hs	20	4	1 wk
7	Paroxetine 10 mg for 2.5 wk	Prior trial of alprazolam 0.25 mg qid	0.5 mg bid	26	4	2 d
8	Fluoxetine 20 mg for 12 wk	None	0.5 mg hs	16	0	2 d

[a]Adapted with permission from Ostroff and Nelson.[35] Abbreviations: HAM-D = Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.
[b]HAM-D performed at first follow-up visit; time to response based on patient's report of when major change occurred.
[c]Dose increased by the patient because of apparent benefit.
[d]No return visit and no HAM-D score obtained; patient and referring psychiatrist noted complete remission.

Figure 1. Weekly Change From Baseline in Response Rate (last observation carried forward) for Patients Treated With Fluoxetine, Olanzapine, or a Combination of Both[a,b]



[a]Reprinted with permission from Shelton et al.[36]
[b]Combination superior to fluoxetine or olanzapine ($p < .05$, repeated measures analysis of variance).
[c]Significantly superior to fluoxetine ($p < .05$, t test with Bonferroni correction) and olanzapine ($p < .05$, t test with Bonferroni correction).
[d]Significantly superior to fluoxetine ($p < .05$, t test with Bonferroni correction) but not olanzapine ($p < .05$, t test with Bonferroni correction).

efited dramatically from the addition of risperidone to continued administration of the SSRI. Results were measured by the HAM-D scale, and all patients had scores ≤ 4 within 1 week of the addition of risperidone to their treatment regimen (Table 1).

My colleagues and I[36] conducted an 8-week double-blind study of 28 depressed patients without psychotic symptoms who did not respond to fluoxetine. The patients were randomly assigned to treatment with olanzapine plus placebo, fluoxetine plus placebo, or olanzapine plus fluoxetine. The primary treatment outcome measure was the Montgomery-Asberg Depression Rating Scale. This study showed that there was a rapid and sustained beneficial effect in 60% of patients during the 8-week acute treatment phase, which continued in the 8-week follow-up phase (Figure 1). Neither the continuation of fluoxetine alone nor olanzapine alone produced effects similar to those produced by the combination of olanzapine and fluoxetine.

A follow-up study by Dubé and colleagues[37] was conducted with nearly 500 patients with treatment-resistant major depression. Patients were randomly assigned to 4 groups after prior failure with an SSRI or inadequate response to prospective treatment with nortriptyline. Each group received either olanzapine plus placebo, fluoxetine plus placebo, a combination of olanzapine plus fluoxetine, or a continuation of nortriptyline. Data showed that the combination of olanzapine and fluoxetine rapidly produced a therapeutic benefit. However, it did not differ from other groups at endpoint. Compared with our original trial,[36] this study[37] used appreciably lower doses of both fluoxetine and olanzapine. In the Dubé et al.[37] study, the mean daily dose of olanzapine was 8 to 8.5 mg/day and the mean daily dose of fluoxetine was 36.5 mg/day, in contrast to 12 mg/day and 50 mg/day respectively in our study.[36] Ultimately, the cause of the differences in the results of the 2 studies is unclear; but, given that olanzapine has been found to demonstrate greatest efficacy in psychosis when the daily dosage is between 10 to 15 mg/day, the reduced performance of the combination treatment in the Dubé et al.[37] study may have been a result of low daily doses of olanzapine or fluoxetine. A large-scale study that administers sufficiently higher doses of olanzapine is needed to clarify the issues.

Although data suggest that the combination of olanzapine and fluoxetine yields therapeutic benefits, there is little clinical evidence to suggest that the effect is peculiar to this combination. Further research into other combinations of atypical antipsychotics and antidepressants also is needed.

Despite the apparent effectiveness of some combinations of novel antipsychotics and antidepressants, researchers have been unable to come to a consensus on the

best account of the mechanisms of action of these drugs. However, viable hypotheses of the causal processes responsible for the benefits of combinations of atypicals and antidepressants have been developed. For example, novel antipsychotics are potent serotonin-2A receptor antagonists, which is similar to the effects of some antidepressants. The effect could explain the additive effect on depression.

Other hypotheses draw upon data that suggest that serotonin binding to 2C receptors inhibits the release of dopamine and norepinephrine in the frontal cortex. Preventing serotonin from binding to 2C receptor sites may result in increased dopamine levels in, for example, the prefrontal cortex and nucleus accumbens. Novel antipsychotics also have serotonin-2C blocking effects. As a result, the combination of novel antipsychotics and SSRIs antagonize serotonin receptors and elevate frontal cortex dopamine levels, thus producing a potentially greater therapeutic effect. Research by Zhang et al.[38] showed that the combination of fluoxetine and olanzapine was associated with increased levels of dopamine and norepinephrine in the frontal cortex of rats, which lends credence to these ideas.

Other Pharmacologic Augmentation

Limited and sometimes contradictory evidence suggests that patients may benefit from the augmentation of SSRIs using the serotonin-1A partial agonist buspirone.[39–41] Other augmentation therapies exist but have limited support or have produced mixed results. Among them is augmenting antidepressants with anticonvulsants, such as carbamazepine, which has shown variable effects in uncontrolled reports.[42–44] Other strategies include the augmentation of TCAs or MAOIs with psychostimulants such as dextroamphetamine or methylphenidate[45,46] and estrogen augmentation of antidepressants in women with resistant depression.[47]

COGNITIVE THERAPY

Evidence relevant to the efficacy of cognitive therapy is limited, but preliminary data suggest potential benefit. Keller et al.[48] have shown that patients treated with a combination of cognitive behavioral-analysis system of psychotherapy (CBASP; a variation of cognitive therapy) and nefazodone had a greater effect in patients with chronic depression than either modality given singly. Similar results were produced by a study[49] of depressed elderly outpatients. These and other data indicate that cognitive therapy and related treatments may produce benefit in treatment-resistant depression.

CONCLUSION

Most patients being treated for depression will respond well to conventional monotherapies. For those who do not, novel combination and augmentation therapies are important tools for the effective management of treatment-resistant depression. Although novel nonpharmacologic treatments such as VNS and TMS are being developed to supplement the treatment options physicians currently have, these remain relatively distant therapeutic prospects. Pharmacotherapies currently offer the widest array of proven and promising approaches to treatment-resistant depression.

Although some combination therapies, such as lithium augmentation of antidepressants, enjoy a wealth of data supporting their potential efficacy, more recent strategies, such as novel antipsychotic augmentation of antidepressants, have fewer but nevertheless exciting data supporting theirs.

Pharmacotherapies, psychotherapies, and combinations may someday be integrated into comprehensive treatment strategies, such as treatment algorithms, and could change the face of depression therapy. Algorithmic treatment strategies allow physicians to uniformly employ research-based therapies with demonstrated effectiveness that may increase the likelihood that depression will remit. The systematic application of well-tested therapies organized into treatment algorithms may help to stave off the therapeutic nihilism that sometimes emerges in both patients and their physicians when both have endured a series of failed treatments.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar and others), carbamazepine (Tegretol, Carbatrol, and others), citalopram (Celexa), desipramine (Norpramin and others), dextroamphetamine (Dexedrine, Dextrostat, and others), fluoxetine (Prozac and others), methylphenidate (Ritalin, Concerta, and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Aventyl, Pamelor, and others), olanzapine (Zyprexa), paroxetine (Paxil), risperidone (Risperdal), sertraline (Zoloft), triiodothyronine (Cytomel and others), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, buspirone, dextroamphetamine, triiodothyronine, and methylphenidate, mentioned in this article, are not approved by the U.S. Food and Drug Administration for the treatment of depression; carbamazepine is not approved for the treatment of depression and bipolar disorder; and olanzapine, risperidone, and lithium are not approved for the treatment of resistant depression.

REFERENCES

1. Kerr EA, McGlynn EA, Van Vorst KA, et al. Measuring antidepressant prescribing in a health care system using administrative data: implications for quality measurement and improvement. Jt Comm L Qual Improv 2000;26: 203–216
2. Clinical Practice Guideline Number 5: Depression in Primary Care, vol 2. Treatment of Major Depression, Rockville, Md: US Dept Health and Human Services, Agency for Health Care Policy and Research; 1993. AHCPR publication 93-0551
3. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Arch Gen Psychiatry 1991;48:851–855
4. Shelton RC. Treatment options for refractory depression. J Clin Psychiatry 1999;60(suppl 4):57–61
5. Sunderam S, Osorio I, Watkins JF III, et al. Vagal and sciatic nerve stimula-

tion have complex, time-dependent effects on chemically-induced seizures: a controlled study. Brain Res 2001;918:60–66
6. Goodnick PJ, Rush AJ, George MS. Vagus nerve stimulation in depression. Expert Opin Pharmacother 2001;2:1061–1063
7. Martin JL, Barbanoj MJ, Schlaepfer TE, et al. Transcranial magnetic stimulation for treating depression (Cochrane Review). Cochrane Database Syst Rev 2002:CD003493
8. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. Int J Neuropsychopharmacol 2002;5:73–103
9. Garcia-Toro M, Mayol A, Arnillas H, et al. Modest adjunctive benefit with transcranial magnetic stimulation in medication-resistant depression. J Affect Disord 2001;64:271–275
10. George MS, Nahas Z, Kozel FA, et al. Improvement of depression following transcranial magnetic stimulation. Curr Psychiatry Rep 1999;1: 114–124
11. Danish University Antidepressant Group. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. J Affect Disord 1990;18:289–299
12. Danish University Antidepressant Group. Citalopram: clinical effect profile in comparison with clomipramine: a controlled multicenter study. Psychopharmacology (Berl) 1986;90:131–138
13. Baron BM, Ogden AM, Siegel BW, et al. Rapid down regulation of beta-adrenoceptors by co-administration of desipramine and fluoxetine. Eur J Pharmacol 1988;154:125–134
14. Eisen A. Fluoxetine and desipramine: a strategy for augmenting antidepressant response. Pharmacopsychiatry 1989;22:272–273
15. Weilburg JB, Rosenbaum JF, Biederman J, et al. Fluoxetine added to non-MAOI antidepressants converts nonresponders to responders: a preliminary report. J Clin Psychiatry 1989;50:447–449
16. Nelson JC, Mazure CM, Bowers MB Jr, et al. A preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. Arch Gen Psychiatry 1991;48:303–307
17. Seth R, Jennings AL, Bindman J, et al. Combination treatment with noradrenaline and serotonin reuptake inhibitors in resistant depression. Br J Psychiatry 1992;161:562–565
18. Fava M, Dunner DL, Greist JH, et al. Efficacy and safety of mirtazapine in major depressive disorder patients after SSRI treatment failure: an open-label trial. J Clin Psychiatry 2001;62:413–420
19. Smith D, Dempster C, Glanville J, et al. Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. Br J Psychiatry 2002;180:396–404
20. Entsuah AR, Huang H, Thase ME. Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. J Clin Psychiatry 2001;62:869–877
21. Bauer M, Dopfmer S. Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. J Clin Psychopharmacol 1999;19:427–434
22. Bauer M, Bschor T, Kunz D, et al. Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. Am J Psychiatry 2000;157: 1429–1435
23. Heit S, Nemeroff CB. Lithium augmentation of antidepressants in treatment-refractory depression. J Clin Psychiatry 1998;59(suppl 6):28–33
24. Austin MP, Souza FG, Goodwin GM. Lithium augmentation in antidepressant-resistant patients: a quantitative analysis. Br J Psychiatry 1991;159: 510–514
25. Baumann P, Nil R, Souche A, et al. A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, pharmacogenetic investigation. J Clin Psychopharmacol 1996;16:307–314
26. Loosen PT, Shelton RC. Hormonal potentiation of antidepressants. In: Amsterdam J, ed. Antidepressant Therapy. New York, NY: Marcel Dekker; 1988:241–253
27. Joffe RT, Singer W, Levitt AJ, et al. A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. Arch Gen Psychiatry 1993;50:387–393
28. Robertson MM, Trimble MR. Major tranquilizers used as antidepressants: a review. J Affect Disord 1982;4:173–193
29. McElroy SL, Dessain EC, Pope HG Jr, et al. Clozapine in the treatment of psychotic mood disorders, schizoaffective disorder, and schizophrenia. J Clin Psychiatry 1991;52:411–414
30. Suppes T, McElroy SL, Gilbert J, et al. Clozapine in the treatment of dysphoric mania. Biol Psychiatry 1992;32:270–280
31. Dassa D, Kaladjian A, Azorin JM, et al. Clozapine in the treatment of psychotic refractory depression. Br J Psychiatry 1993;163:822–824
32. Calabrese JR, Kimmel SE, Woyshville MJ, et al. Clozapine for treatment-refractory mania. Am J Psychiatry 1996;153:759–764
33. Jacobsen FM. Risperidone in the treatment of affective illness and obsessive-compulsive disorder. J Clin Psychiatry 1995;56:423–429
34. Keck PE Jr, Wilson DR, Strakowski SM, et al. Clinical predictors of acute risperidone response in schizophrenia, schizoaffective disorder, and psychotic mood disorders. J Clin Psychiatry 1995;56:466–470
35. Ostroff RB, Nelson JC. Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. J Clin Psychiatry 1999;60: 256–259
36. Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. Am J Psychiatry 2001;158:131–134
37. Dubé S, Paul S, Sanger T, et al. Olanzapine-fluoxetine combination in treatment-resistant depression. Eur Psychiatry 2002;17(suppl 1):98
38. Zhang W, Perry KW, Wong DT, et al. Synergistic effects of olanzapine and other antipsychotic agents in combination with fluoxetine on norepinephrine and dopamine in rat prefrontal cortex. Neuropsychopharmacology 2000;23:250–262
39. Jacobsen FM. Possible augmentation of antidepressant response by buspirone. J Clin Psychiatry 1991;52:217–220
40. Appelberg BG, Syvälahti EK, Koshinen 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. J Clin Psychiatry 2001;62:448–452
41. Joffe RT, Schuller DR. An open study of buspirone augmentation of serotonin reuptake inhibitors in refractory depression. J Clin Psychiatry 1993; 54:269–271
42. Thase ME, Rush AJ. Treatment resistant depression. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven Press; 1995:1081–1097
43. Kahn D. Carbamazepine and other antileptic drugs in refractory depression. In: Roose SP, Glassman AH, eds. Treatment Strategies for Refractory Depression. Washington, DC: American Psychiatric Press; 1990:143–167
44. Ketter TA, Post RM, Parekh PI, et al. Addition of monoamine oxidase inhibitors to carbamazepine: preliminary evidence of safety and antidepressant efficacy in treatment-resistant depression. J Clin Psychiatry 1995; 56:471–475
45. Charney DS, Miller HL, Licinio J, et al. Treatment of depression. In: Schatzberg AF, Nemeroff CB, eds. The American Psychiatric Press Textbook of Psychopharmacology. Washington, DC: American Psychiatric Press; 1995:588–601
46. Fawcett J, Kravitz HM, Zajecka JM, et al. CNS stimulant potentiation of monoamine oxidase inhibitors in treatment-refractory depression. J Clin Psychopharmacol 1991;11:127–132
47. Klaiber EL, Broverman DM, Vogel W, et al. Estrogen therapy for severe persistent depressions in women. Arch Gen Psychiatry 1979;36:550–554
48. Keller MB, McCullough JP, Klein DN, et al. Comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000;342: 1462–1470
49. Thompson LW, Coon DW, Gallagher-Thompson D, et al. Comparison of desipramine and cognitive/behavioral therapy in the treatment of elderly outpatients with mild-to-moderate depression. Am J Geriatr Psychiatry 2001;9:225–240