

# Overcoming Treatment Resistance in Depression

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Treatment-resistant depression is commonly encountered by mental health professionals. Strategies for the treatment of resistant depression, including augmentation strategies and switching antidepressants, are reviewed. The potential advantages and disadvantages of each of these strategies are discussed.  
(*J Clin Psychiatry* 1998;59[suppl 16]:13-19)

**T**reatment-resistant depression is commonly encountered by mental health professionals. This is accounted for, in part, by the referral of resistant patients for treatment. But, in addition, the number of patients responding to initial treatment is no more than 50% among all patients beginning treatment, if dropouts are accounted for.<sup>1</sup> As a result, approximately half of those beginning treatment with an antidepressant will require treatment with a second agent. In addition, even among those responding to treatment, a certain percentage will fail to achieve remission, and the clinician may need to consider employing some strategy so that the patient achieves remission.

Patients vary in terms of their level of treatment resistance. Thase and Rush<sup>2</sup> have suggested a series of criteria to define relative treatment resistance, absolute treatment resistance, and treatment-refractory depression. The latter was defined by failure to respond to 2 drugs of different classes with adequate dose and duration and serves as a reminder of the importance of assuring that the initial dose and duration of antidepressant treatment were adequate before declaring any patient resistant. In practice, the clinician is likely to encounter patients ranging from those who have a less than satisfactory response to the first agent to those who have failed many drug trials.

The 2 major types of strategies employed in resistant patients are (1) augmentation and (2) switching to a different agent. For the purposes of this report, augmentation will be defined as the use of 2 agents to enhance antidepressant effects along a single dimension. These strategies

are to be distinguished from combined treatment, in which 2 agents are used to treat 2 different types of symptoms. One example of the latter is the use of antidepressants with antipsychotics for treatment of psychotic depression. In this case, the second agent is added to treat a different type of symptom rather than to enhance response along a single depressive dimension.

## AUGMENTATION STRATEGIES

Numerous augmentation strategies have now been described for use in depression (Table 1).

### Lithium Augmentation

Lithium is the best-studied strategy. Since the original description of lithium augmentation in 1981,<sup>3</sup> several case reports or series of cases have been described. To date, 9 placebo-controlled studies<sup>4-12</sup> have been reported and, of these, 7 found lithium to be more effective than placebo. The samples in these studies ranged in size from 7 to 62 patients.

While the threshold of effectiveness for lithium has not been precisely determined, a review of 2 different sets of data suggests that a level of 0.4 mEq/L or greater will usually be effective for augmentation. Stein and Bernadt<sup>10</sup> demonstrated that a dose of 250 mg/day, which produced a mean blood level of 0.25 mEq/L, was no more effective than placebo for augmentation. Alternatively, a dose of 750 mg/day, producing an average blood level of 0.77 mEq/L, was more effective than placebo. Studies in which the usual dose of 900 mg/day (300 mg t.i.d.) was administered found blood levels ranging from 0.4 to 1.0 mEq/L and, across this range, there was no relationship of levels and response. These 2 sets of data suggest that blood levels of 0.4 mEq/L or greater are likely to be effective.

Although response has been observed within 48 hours after the addition of lithium,<sup>3,5</sup> meaningful change more often occurs in the second week. Two studies suggest that improvement will continue over a 6-week period,<sup>11,13</sup> although it is unclear whether the longer trials should be viewed as augmentation.

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*Presented at the symposium "Depressive Disorders: Advances in Clinical Management," which was held May 31, 1998, in Toronto, Canada, in conjunction with the 151st Annual Meeting of the American Psychiatric Association and supported by an unrestricted educational grant from Organon Inc.*

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**Table 1. Types of Augmentation Strategies**

Lithium
Thyroid
Stimulants
Buspirone
Pindolol
Tryptophan
TCAs and MAOIs
SSRIs and TCAs
SSRIs and bupropion
SSRIs and risperidone
SSRIs and $\alpha_2$ antagonists

It was hypothesized that lithium's augmenting effects were the result of increased serotonin turnover produced by lithium. The fact that mania has been associated with the addition of lithium suggests the mechanism is different during augmentation than during treatment of bipolar disorder.<sup>14,15</sup>

In the 4 largest controlled studies of lithium augmentation, of the 107 patients enrolled, 52 (49%) of the patients responded to lithium augmentation. Although lithium has often been employed in partial responders, in the controlled studies patients were not limited to partial responders.

Few predictors of response to lithium augmentation have been identified. My colleagues and I found patients with a history suggestive of bipolar disorder (possible hypomania or family history) were more likely to respond.<sup>16</sup>

Lithium augmentation appears to be effective with a variety of antidepressants<sup>17</sup> and has been relatively well studied with the selective serotonin reuptake inhibitor (SSRI) compounds.<sup>11,12,18-20</sup> This is an important issue since most patients will begin treatment with an SSRI.

### Thyroid Augmentation

Thyroid augmentation is one of the older strategies, having been described initially in 1969.<sup>21</sup> In that initial study, T<sub>3</sub> was added to imipramine and had more rapid effects than the combination of imipramine and placebo. In that report, Prange et al. suggested the combination might be effective in refractory patients. Several open studies followed demonstrating effectiveness for T<sub>3</sub>.

Four systematic studies have been performed. In 1982, Goodwin and associates<sup>22</sup> substituted T<sub>3</sub> for placebo in a group of 12 patients, many of whom were bipolar. Eight of the 12 had a marked response. Thase et al.,<sup>23</sup> however, reported contradictory results. In an open comparison of patients who had failed 12 weeks of imipramine, they found the addition of T<sub>3</sub> to the imipramine regimen in 22 patients was not superior to the outcome of 20 patients who continued on treatment with imipramine alone.

The first controlled study was reported by Gitlin et al.<sup>24</sup> They examined 16 patients who had failed at least 4 weeks of imipramine. T<sub>3</sub> or placebo was added for 2 weeks, and then the samples were crossed over to the other agent. No difference in response was found. This study has been criti-

cized because of the crossover design. But, even after the initial 2-week parallel comparison, there was no advantage for thyroid augmentation.

The largest and best-designed study was reported by Joffe et al. in 1993.<sup>9</sup> They examined 50 patients who had failed treatment with 4 weeks of either imipramine or desipramine. Patients were randomly assigned to a double-blind addition of T<sub>3</sub>, lithium, or placebo and followed for a 2-week period. Ten (59%) of 17 of the patients receiving T<sub>3</sub> responded. Among those receiving lithium, 9 (53%) of 17 responded. Among the 16 patients receiving placebo, only 3 (19%) responded. This study demonstrated a significant effect of T<sub>3</sub> and found it comparable to lithium for augmenting response.

The mechanism of thyroid augmentation is unclear. The popular view is that thyroid hormone may be correcting a subclinical hypothyroid state. However, Joffe and Sokolov<sup>25</sup> have proposed the alternative view that depression is associated with mild hyperthyroidism and that administration of oral T<sub>3</sub> in fact reduces the effects of thyroid hormone in the brain.

During thyroid administration, the usual dose of T<sub>3</sub> administered has ranged from 25 to 50  $\mu\text{g}/\text{day}$  or, on average, 37.5  $\mu\text{g}/\text{day}$ . Although different durations of treatment have not been systematically studied, usually T<sub>3</sub> has been administered for a 2-week period to determine if it is effective. Few side effects are encountered with T<sub>3</sub> administration.

T<sub>3</sub> is the preferred form of thyroid hormone for augmentation. A controlled study, reported by Joffe and Singer,<sup>26</sup> found T<sub>3</sub> more effective than T<sub>4</sub>.

One of the factors limiting the use of T<sub>3</sub> is the lack of information about its addition to the SSRI compounds. In fact, description of its use in this situation is limited to 1 report of 3 subjects.<sup>27</sup>

### Stimulant Augmentation

Stimulant augmentation is another of the older augmentation strategies reported. Six series of cases, reviewed elsewhere,<sup>28</sup> have been described ranging in size from 4 to 32 patients in addition to a half dozen single case reports. Dextroamphetamine, methylphenidate, and pemoline have all been used as augmenting agents. These agents appear to be effective when used to augment the tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and, more recently, the SSRIs<sup>29</sup>; however, there are no controlled studies with the stimulant agents. The largest study found that the beneficial effects of adding stimulants were maintained over several months of observation.<sup>30</sup> Sustained effectiveness is an issue because of concern that tolerance develops to the stimulants. It has been hypothesized that the stimulant drugs, because of their dopaminergic action, may be particularly useful in SSRI responders who lose the effect and develop tachyphylaxis or "poop out."<sup>31</sup>

When used for augmentation, the usual dose of dextroamphetamine is 5 mg t.i.d. The typical dose of methylphenidate is 10 mg t.i.d. When used with MAOIs, lower doses are employed. It is suggested that stimulant compounds may be particularly helpful for anergic patients. Side effects encountered with stimulant augmentation are mild and tend to be primarily behavioral side effects, such as irritability, increased anxiety, and, sometimes, suspiciousness or paranoia.<sup>32</sup>

### **Buspirone Augmentation**

Buspirone augmentation is a more recent strategy, described specifically for augmentation of the SSRI compounds. Four open studies of buspirone augmentation have been reported, with samples ranging in size from 3 to 30 patients and rates of response exceeding 50%.<sup>33-36</sup> The typical dose of buspirone administered was 10 mg t.i.d., but ranged from 20 to 50 mg/day. Usually, response was observed within a 3-week period. Few side effects were observed. In addition, buspirone has the advantage of having independent effects on anxiety in some patients.

### **Pindolol Augmentation**

Pindolol augmentation is a new augmentation strategy also described for use with the SSRI antidepressants. It is proposed that pindolol blocks the presynaptic autoreceptor and thus interferes with the reduction in serotonin turnover that occurs after SSRI administration. Two initial open studies<sup>37,38</sup> described its use both for speeding response and for treating refractory patients. There have been 4 controlled trials of pindolol augmentation, with samples ranging in size from 40 to 111 patients; 3 of the 4 studies reported positive results.<sup>39-42</sup> Yet, all of these studies focused on speed of response and did not examine the use of this combination in refractory patients. One double-blind, controlled study<sup>43</sup> of 10 refractory patients has been reported. In this study, pindolol was not more effective than placebo for treatment of refractory depression. Given the current interest in pindolol, it appears likely that this agent and its mechanism of action will continue to be studied. However, its use in refractory depression currently seems questionable.

### **SSRIs and TCAs**

The effectiveness of combinations of SSRIs and a tricyclic has been reported in 3 open series of patients.<sup>44-46</sup> The hypothesis for combining these 2 compounds is that the combination of a noradrenergic tricyclic with a serotonergic SSRI compound might enhance response.

In 1989, Weilberg et al.<sup>44</sup> described 30 outpatients who had failed treatment with a variety of non-MAOI antidepressants (usually a tricyclic). Fluoxetine was then added, and 26 of the 30 patients responded. Seth et al.,<sup>45</sup> in 1992, described 8 older patients who were quite refractory to antidepressant treatment. In fact, a few of these patients had also failed electroconvulsive therapy (ECT). All of the pa-

tients described in this report responded when a tricyclic (usually nortriptyline) was added to the SSRI.

In a systematic, albeit open study, Nelson et al.<sup>46</sup> compared 14 depressed inpatients who were treated with the combination of 20 mg/day of fluoxetine and a variable dose of desipramine with 52 previously treated, depressed inpatients who had received desipramine alone. In both samples, desipramine dose was adjusted using 24-hour desipramine levels. This level was used to calculate the dose needed to achieve an adequate blood level of desipramine and to adjust the dose in anticipation of the enzyme-inhibiting effects of fluoxetine. The rate of response and rapidity of response in the 14 patients receiving the combination were superior to that observed in the 52 patients treated with desipramine alone. Although the level of side effects reported with this combination is generally higher than that of several other augmentation strategies, the combination was still tolerated by most subjects. It is advisable, during administration of this combination, to monitor the blood level of the tricyclic administered, particularly if the TCA is given with fluoxetine or paroxetine.<sup>47,48</sup> Fluoxetine and paroxetine inhibit the CYP2D6 pathway and thus raise desipramine concentrations 3- to 4-fold. Sertraline has modest effects. Venlafaxine and citalopram do not appear to inhibit CYP2D6 and would not be expected to alter desipramine levels.

### **SSRIs and Bupropion**

Two studies<sup>49,50</sup> have described the combination of SSRIs and bupropion used to augment antidepressant response. In the first, Boyer and Feighner<sup>49</sup> described a group of 23 patients who had failed treatment with either fluoxetine or bupropion given alone. The second drug was then added, and 35% (8/23) had a moderate or marked response. In this study, 39% of the sample (9/23) had a notable adverse reaction, the highest rate reported for an augmentation strategy.

In a second report, Bodkin et al.<sup>50</sup> described 27 patients who had failed to respond to either an SSRI or bupropion. The second drug was then added. In this study, the average dose of bupropion was 243 mg/day; the average dose of the SSRI was 31 mg/day of fluoxetine or its equivalent. Seventy percent of these patients improved. Only 4 of the 27 had to discontinue treatment because of a serious adverse reaction. To date, there are no controlled studies of this combination. Another potential issue is the lack of information regarding SSRI/bupropion drug interactions. Because of concern about the possibility of seizures with bupropion at higher doses or higher blood levels, information about this interaction would be most helpful.

### **Other Older Strategies**

Tryptophan augmentation has been relatively well studied, with 7 controlled studies reported and reviewed elsewhere.<sup>51</sup> Tryptophan does appear to augment the

MAOIs, but effectiveness with the TCAs was disappointing. Yet, tryptophan has been withdrawn from the market.

The combination of MAOIs and TCAs has also been described to be of value.<sup>52,53</sup> In open series, over 260 patients were studied. The safety of this combination depends on the correct sequencing of the agents (the TCA is started first or both are started together); however, this combination remains a potentially hazardous strategy. Given the availability of safer combinations, the use of these 2 drug classes together is not encouraged.

### Other Recent Strategies

The number of augmentation strategies continues to grow. A preliminary report<sup>54</sup> suggests that the addition of risperidone to an SSRI may help to augment antidepressant response. This approach appears especially effective for management of anxiety, ruminative thinking, and insomnia. Low doses (0.5 to 1 mg/day) of risperidone are employed and, at this dose, the principal effect of this drug is 5-HT<sub>2</sub> antagonism. Preclinical work suggests that a 5-HT<sub>2</sub> antagonist enhances the effects of serotonin at the 5-HT<sub>1A</sub> postsynaptic receptor.<sup>55</sup>

Alpha-2 antagonists have also been employed as an augmentation strategy. The addition of yohimbine to desipramine failed to show any effect<sup>56</sup>; however, a subsequent report found the addition of yohimbine to an SSRI compound, fluoxetine, was effective.<sup>57</sup> Two other controlled trials<sup>58,59</sup> found the combination of fluoxetine and mianserin, also an  $\alpha_2$  antagonist, was more effective than fluoxetine and placebo. Preclinical work suggests that the addition of mirtazapine to paroxetine enhances the onset of action and the magnitude of serotonergic transmission.<sup>60</sup>

### SWITCHING TO A NEW ANTIDEPRESSANT

The alternative method of managing the treatment-resistant patient is switching to a new antidepressant. A variety of switches have been described.

Prior to the introduction of the SSRIs, several open studies and 4 double-blind studies<sup>61-64</sup> found the MAOIs effective in 50% to 75% of patients failing treatment with a tricyclic. Response was particularly robust in patients with an atypical presentation or those with reversed vegetative symptoms.<sup>62,63</sup>

Response to an SSRI in patients failing treatment with a tricyclic has also been relatively well described. In 3 of these studies,<sup>65-67</sup> ranging in size from 10 to 40 patients, switching to either fluoxetine or paroxetine was effective in 43% to 51% of the patients. Alternatively, in 3 studies of fluvoxamine,<sup>68-70</sup> having a total of 96 patients, the rate of response was only 18%. Bupropion<sup>71</sup> and trazodone<sup>72</sup> also appear to be of value in patients failing an SSRI, but the number of studies is limited.

Because of the long history of tricyclic use, switches from a tricyclic have been best studied. Nevertheless, most

patients will now be started on an SSRI first, and the question arises as to what type of switch to make in patients failing an SSRI. Should you switch to another SSRI, a drug of a different class, or a drug with a different mechanism? Previous work with the tricyclics demonstrated that switching from one tricyclic to another was not likely to be very effective, with rates of response of 30% or less reported.<sup>56,65</sup>

Four studies have now examined the switch from one SSRI to another. Brown and Harrison<sup>73</sup> described a switch from fluoxetine to sertraline, noting a 74% response rate. However, their sample included both patients who had failed to respond and those who could not tolerate fluoxetine. Apter et al.<sup>74</sup> reported a series of patients either intolerant of or failing to respond to sertraline, who were switched to fluoxetine. Sixty-three percent of the 106 patients responded. Another study of patients who were either intolerant of or resistant to fluoxetine was reported by Zarate et al.<sup>75</sup> Patients were switched to sertraline, but when followed for a sufficient period in this study, only 26% of the patients were found by the authors to have maintained their response to a second SSRI. In addition, the authors found that patients who had had side effects on fluoxetine treatment tended to have similar side effects on sertraline treatment.

The only study to examine a switch to a second SSRI in which all patients were resistant to (rather than intolerant of) the first SSRI was reported by Joffe et al. in 1996.<sup>76</sup> Twenty-eight (51%) of 55 patients responded to a second SSRI. This issue remains controversial. On the one hand, proponents suggest that there are subtle differences in the neuropharmacology of the SSRIs that might explain why a switch within the class would be effective. Alternatively, others argue that switching to a drug with a different mechanism is more likely to be effective. There are no controlled data to support either argument.

Studies of other switches from an SSRI are limited. Peselow et al.<sup>67</sup> described, in a report of double-blind study, a group of 15 paroxetine nonresponders who, when switched to imipramine, had a 73% response rate.

### Alternative Antidepressants

Most patients will begin treatment with an SSRI. If treatment fails and the clinician determines that a switch from an SSRI is indicated, a variety of alternative antidepressants are available.

A switch to a tricyclic could be considered. The efficacy of the tricyclics is well established, especially in severe depression; however, the tricyclics have been associated with an increased rate of side effects<sup>77</sup> and adverse cardiac effects,<sup>78</sup> and they are lethal in overdose. If a switch to a tricyclic is considered, a theoretical argument can be made for switching to 1 of the noradrenergic agents, such as desipramine or nortriptyline, if a patient has failed to respond to a serotonergic SSRI.

Historically, the MAOIs have been used for TCA-resistant patients, but the MAOIs are particularly difficult to use because of the diet required and hazardous drug interactions. Because of the potentially fatal MAOI/SSRI interactions, an appropriate waiting period after SSRI discontinuation is required. For sertraline and paroxetine that period is 2 weeks. After fluoxetine is discontinued, 5 weeks are required before an MAOI can be administered.

Bupropion is another alternative antidepressant. Bupropion appears to be associated with fewer side effects than the tricyclics. It may be particularly useful in anergic depression. It can be started while the patient is receiving the SSRI. Its efficacy, however, in SSRI failures is not well established, and drug interactions with the SSRIs are not well described.

Another alternative antidepressant is nefazodone. Nefazodone may have particular advantages in anxious depression.<sup>79</sup> It does not increase sexual dysfunction,<sup>80</sup> and it has beneficial effects on sleep.<sup>81,82</sup> However, its efficacy in refractory depression or following a switch from an SSRI is not well established. In addition, clinicians have found switching to nefazodone difficult in the presence of an SSRI, apparently because of the enzyme-inhibiting effects of fluoxetine and paroxetine on the *m*-CPP metabolite of nefazodone, resulting in increased anxiety or restlessness.

Venlafaxine, at high doses, produces both serotonergic and noradrenergic uptake inhibition and, thus, employs a different mechanism of action than the SSRIs. A few studies suggest that venlafaxine is more effective than the SSRIs in severe depression, particularly at higher doses.<sup>83,84</sup> For example, in one 6-week multisite study of melancholic inpatients, venlafaxine, 200 mg/day, was more effective than fluoxetine, 40 mg/day. Open studies suggest that venlafaxine may be useful in refractory depression, although these studies did not employ a comparison.<sup>85,86</sup>

Another alternative antidepressant is mirtazapine. Again, like venlafaxine, it is a combined-action serotonergic-noradrenergic agent, but its mechanism of action is different. Mirtazapine's principal action is  $\alpha_2$  antagonism, which results in increased release of serotonin and norepinephrine. It has side effect advantages in that it does not produce anorexia, sexual dysfunction, or insomnia.<sup>87</sup> Its 5-HT<sub>3</sub> antagonistic effects help to block nausea. Its disadvantages are the side effects of sedation and weight gain. Data suggest that mirtazapine is more effective than the SSRIs in severe depression. In a 6-week, multisite, double-blind, comparison trial in 133 patients, mirtazapine, in doses up to 60 mg/day, was more effective than fluoxetine, given in doses up to 40 mg/day.<sup>88</sup> Hamilton Rating Scale for Depression scores were significantly lower after 3 weeks of treatment with mirtazapine, and response rates, at 4 weeks, were significantly higher in the mirtazapine group, 60% versus 30%. Data for mirtazapine in treatment-resistant patients are limited. In 1 study of

109 patients with major depression who were participating in a double-blind study of amitriptyline and mirtazapine, patients who failed initial treatment were crossed over to the other drug without breaking the blind.<sup>89</sup> In patients failing treatment with amitriptyline, 59% responded to mirtazapine. In mirtazapine failures, 55% responded to amitriptyline.

### Methodological Issues

There are a variety of methodological issues that make the comparison of the various strategies difficult. For example, the efficacy of the next treatment will be affected by how refractory the patients are. The more refractory the study population, the lower the response rate. Further, there are differences in how response is defined. In addition, the duration of prior treatment differs among studies. In some studies, patients received a minimum of 3 to 4 weeks of treatment, whereas in others, up to 12 weeks of treatment was given. Unfortunately, there are very few studies that have made a direct comparison of 2 augmentation strategies or 2 switches under similar conditions. To my knowledge, no study has compared a switch with an augmentation strategy.

### Switches Versus Augmentation

In a treatment-resistant patient, the clinician is faced with the choice of whether to augment or to switch. Switching to a new agent helps to keep treatment simple. In some patients, this may help to improve compliance (the patient only needs to take 1 drug), and there is better evidence for maintenance treatment in patients treated with a single agent.

Alternatively, augmentation may be rapid: sometimes response occurs within 48 hours. Since the second agent is added to the first, there is no time lost, unlike with switching, which may involve gradual dose reduction of the first agent and a delayed onset of action of the second. In patients who have a partial response, adding the augmenting agent may improve the response without losing the initial gain achieved with the first agent. Some augmentation agents may have additional beneficial effects, e.g., buspirone, which has anxiolytic effects. Finally, some of the combination strategies employed to augment response can be used as a bridge to a second agent. In other words, a tricyclic, bupropion, or mirtazapine can be added to treatment with an SSRI and, if the patient improves, an attempt can be made to switch over to the new agent. An algorithm for augmentation strategies is presented elsewhere.<sup>90</sup>

In terms of side effects and cost, the advantages of switching or augmenting depend on the specific agents employed. For example, the side effects of buspirone and T<sub>3</sub> addition are minimal, whereas those associated with bupropion or desipramine addition are greater. With respect to cost, some augmentation strategies, such as lithium, T<sub>3</sub>, and stimulant drugs, are inexpensive. In fact,

adding 1 of these agents to an SSRI may be less expensive than doubling the dose of the SSRI.

It makes sense that in a patient who has minimal treatment resistance, switching to a different agent may help to keep treatment simple. On the other hand, in patients who are refractory, the clinician may wish to employ augmentation strategies before switching in order to exhaust the possibilities of each drug trial before moving on.

What is sorely needed in the field are studies directly comparing different augmentation strategies, comparing various switches, or comparing augmentation with switching in similar patients under similar conditions.

*Drug names:* amitriptyline (Elavil and others), bupropion (Wellbutrin), buspirone (BuSpar), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), methylphenidate (Ritalin), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), pemoline (Cylert), pindolol (Visken), risperidone (Risperdal), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor), yohimbine (Yocon and others).

## REFERENCES

- Agency for Health Care Policy and Research. Clinical Practice Guideline Number 5: Depression in Primary Care, vol 2. Treatment of Major Depression. Rockville, Md: US Dept Health Human Services, Agency for Health Care Policy and Research; 1993. AHCPR publication 93-0551
- 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
- de Montigny C, Grunberg F, Mayer A, et al. Lithium induces rapid relief of depression in tricyclic antidepressant drug nonresponders. *Br J Psychiatry* 1981;138:252-256
- Heninger GR, Charney DS, Sternberg DE. Lithium carbonate augmentation of antidepressant treatment: an effective prescription for treatment-refractory depression. *Arch Gen Psychiatry* 1983;40:1335-1342
- Courmoyer G, de Montigny D, Ouellette J, et al. Lithium addition in tricyclic-resistant unipolar depression: a placebo-controlled study. Presented at the 14th Collegium Internationale Neuropsychopharmacologicum; June 19-23, 1984; Florence, Italy
- Kantor D, McNevin S, Lechner P, et al. The benefit of lithium carbonate adjunct in refractory depression—fact or fiction? *Can J Psychiatry* 1986; 31:416-418
- Zusky PM, Biederman J, Rosenbaum JF, et al. Adjunct low dose lithium carbonate in treatment-resistant depression: a placebo-controlled study. *J Clin Psychopharmacol* 1988;8:120-124
- Schopf J, Baumann P, Lemarchand T, et al. Treatment of endogenous depressions resistant to tricyclic antidepressants or related drugs by lithium addition: results of a placebo-controlled double-blind study. *Pharmacopsychiatry* 1989;22:183-187
- 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
- Stein G, Bernadt M. Lithium augmentation therapy in tricyclic-resistant depression: a controlled trial using lithium in low and normal doses. *Br J Psychiatry* 1993;162:634-640
- Katona CLE, Abou-Saleh MT, Harrison DA, et al. Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. *Br J Psychiatry* 1995;166:80-86
- 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 and pharmacogenetic investigation. *J Clin Psychopharmacol* 1996;16:307-314
- Thase ME, Kupfer DJ, Frank E, et al. Treatment of imipramine-resistant recurrent depression, II: an open clinical trial of lithium augmentation. *J Clin Psychiatry* 1989;50:413-417
- Louie AK, Meltzer HY. Lithium potentiation of antidepressant treatment. *J Clin Psychopharmacol* 1984;4:316-321
- Price LH, Charney DS, Heninger GR. Manic symptoms following addition of lithium to antidepressant treatment. *J Clin Psychopharmacol* 1984;4: 361-362
- Nelson JC, Mazure C. Lithium augmentation in psychotic depression refractory to combined drug treatment. *Am J Psychiatry* 1986;143:363-366
- Price LH, Charney DS, Heninger G. Variability of response to lithium augmentation in refractory depression. *Am J Psychiatry* 1986;143:1387-1392
- Ontiveros A, Fontaine R, Elie R. Refractory depression: the addition of lithium to fluoxetine or desipramine. *Acta Psychiatr Scand* 1991;83: 188-192
- Delgado PL, Price LH, Charney DS, et al. Efficacy of fluvoxamine in treatment-refractory depression. *J Affect Disord* 1988;15:55-60
- Dinan TG. Lithium augmentation in sertraline-resistant depression: a preliminary dose-response study. *Acta Psychiatr Scand* 1993;88:300-301
- Prange AJ, Wilson IC, Rabon AM, et al. Enhancement of imipramine antidepressant activity by thyroid hormone. *Am J Psychiatry* 1969;126: 457-469
- Goodwin FK, Prange AJ, Post RM, et al. Potentiation of antidepressant effects by L-triiodothyronine in tricyclic nonresponders. *Am J Psychiatry* 1982;139:34-38
- Thase ME, Kupfer DJ, Jarrett DB. Treatment of imipramine-resistant recurrent depression, I: an open clinical trial of adjunctive L-triiodothyronine. *J Clin Psychiatry* 1989;50:385-388
- Gitlin MJ, Weiner H, Fairbanks L, et al. Failure of T<sub>3</sub> to potentiate tricyclic antidepressant response. *J Affect Disord* 1987;13:267-272
- Joffe RT, Sokolov STH. Thyroid hormones, the brain, and affective disorders. *Crit Rev Neurobiol* 1994;8:45-63
- Joffe RT, Singer W. A comparison of triiodothyronine and thyroxine in the potentiation of tricyclic antidepressants. *Psychiatry Res* 1990;32:241-251
- Joffe RT. Triiodothyronine potentiation of fluoxetine in depressed patients. *Can J Psychiatry* 1992;37:48-50
- Ayd FJ Jr, Zohar J. Psychostimulant (amphetamine or methylphenidate) therapy for chronic and treatment-resistant depression. In: Zohar J, Belmaker RH, eds. Treating Resistant Depression. New York, NY: PMA Publishing; 1987:343-355
- Stoll AL, Pillay SS, Diamond L, et al. Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series. *J Clin Psychiatry* 1996;57:72-76
- 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
- McGrath PJ, Quitkin FM, Klein DF. Bromocriptine treatment of relapses seen during selective serotonin re-uptake inhibitor treatment of depression. *J Clin Psychopharmacol* 1995;15:289-291
- Satel SL, Nelson JC. Stimulants in the treatment of depression: a critical overview. *J Clin Psychiatry* 1989;50:241-249
- Jacobsen FM. Possible augmentation of antidepressant response by buspirone. *J Clin Psychiatry* 1991;52:217-220
- Bakish D. Fluoxetine potentiation by buspirone: three case histories. *Can J Psychiatry* 1991;36:749-750
- Joffe RT, Schuller DR. An open study of buspirone augmentation of serotonin reuptake inhibitors in refractory depression. *J Clin Psychiatry* 1993;54: 269-271
- Dimitriou EC. Augmentation of antidepressant effect with the addition of buspirone. Presented at the Xth World Congress of Psychiatry; August 23, 1996; Madrid, Spain
- Artigas F, Perez V, Alvarez E. Pindolol induces a rapid improvement of depressed patients treated with serotonin reuptake inhibitors. *Arch Gen Psychiatry* 1994;51:248-251
- Blier P, Bergeron R. Effectiveness of pindolol with selected antidepressant drugs in the treatment of major depression. *J Clin Psychopharmacol* 1995; 15:217-222
- Berman RM, Darnell AM, Miller HL, et al. Effect of pindolol in hastening response to fluoxetine in the treatment of major depression: a double-blind, placebo-controlled trial. *Am J Psychiatry* 1997;154:37-43
- Tome MB, Isaac MT, Harte R, et al. Paroxetine and pindolol: a randomized trial of serotonergic autoreceptor blockade in the reduction of antidepressant latency. *Int Clin Psychopharmacol* 1997;12:81-89
- Perez V, Gilberte I, Faries D, et al. Randomized, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. *Lancet* 1997;349:1594-1597
- Zanardi R, Artigas F, Franchini L, et al. How long should pindolol be asso-

- ciated with paroxetine to improve the antidepressant response? *J Clin Psychopharmacol* 1997;17:446–450
43. Moreno FA, Gelenberg AJ, Bachar K, et al. Pindolol augmentation of treatment-resistant depressed patients. *J Clin Psychiatry* 1997;58:437–439
  44. 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
  45. 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
  46. Nelson JC, Mazure CM, Bowers MB, 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
  47. Preskorn SH, Alderman J, Chung M, et al. Pharmacokinetics of desipramine co-administered with sertraline or fluoxetine. *J Clin Psychopharmacol* 1994;14:90–98
  48. Brøsen K, Hansen JG, Nielsen KK, et al. Inhibition by paroxetine of desipramine metabolism in extensive but not in poor metabolizers of sparteine. *Eur J Clin Pharmacol* 1993;44:349–355
  49. Boyer WF, Feighner JP. The combined use of fluoxetine and bupropion. Presented at the 146th annual meeting of the American Psychiatric Association; May 27, 1993; San Francisco, Calif
  50. Bodkin JA, Lasser RA, Wines JD Jr, et al. Combining serotonin reuptake inhibitors and bupropion in partial responders to antidepressant monotherapy. *J Clin Psychiatry* 1997;58:137–145
  51. Jones JS, Stanley M. Serotonergic agents in the treatment of refractory depression. In: Roose SP, Glassman AH, eds. *Treatment Strategies for Refractory Depression*. Washington, DC: American Psychiatric Press; 1990: 145–167
  52. Lader M. Combined use of tricyclic antidepressants and monoamine oxidase inhibitors. *J Clin Psychiatry* 1983;44:20–24
  53. Devlin MJ, Walsh BT. Use of monoamine oxidase inhibitors in refractory depression. In: Tasman A, Goldfinger SM, Kaufman CA, eds. *American Psychiatric Press Review of Psychiatry*, vol 9. Washington, DC: American Psychiatric Press; 1990:74–90
  54. Ostroff R, Nelson JC. Risperidone augmentation of SSRIs in depression. *J Clin Psychiatry*. In press
  55. Lakoski JM, Aghajanian GK. Effects of ketanserin on neuronal responses to serotonin in the prefrontal cortex, lateral geniculate and dorsal raphe nucleus. *Neuropharmacology* 1985;24:265–273
  56. Charney DS, Price LH, Heninger GR. Desipramine-yohimbine combination treatment of refractory depression. *Arch Gen Psychiatry* 1986;43: 1155–1161
  57. Cappiello A, Oren D, Anand A, et al. Yohimbine plus fluoxetine combination for rapid treatment of depression. Presented at the 36th annual meeting of the American College of Neuropsychopharmacology; Dec. 8–12, 1997; Waikoloa, Hawaii
  58. Dam J, Ryde L, Svejsjo J, et al. Morning fluoxetine plus evening mianserin versus morning fluoxetine plus evening placebo in the acute treatment of major depression. *Pharmacopsychiatry* 1998;31:1–7
  59. Maes M, Libbrecht I, vanHumsel F, et al. Pindolol and mianserin augment the antidepressant activity of fluoxetine in hospitalized major depressed patients even in those with treatment resistance. *J Clin Psychopharmacol*. In press
  60. Besson A, Haddjeri N, Debonnel G, et al. Effects of the mirtazapine-paroxetine combination on 5-HT neurotransmission in the rat forebrain. Presented at the 27th annual meeting of the Society for Neuroscience; October 1997; New Orleans, La
  61. Nolen WA, van de Putte JJ, Dijken WA, et al. Treatment strategy in depression, II: MAO inhibitors in depression resistant to cyclic antidepressants. *Acta Psychiatr Scand* 1988;78:676–683
  62. McGrath PJ. Treatment of tricyclic refractory depression with a monoamine oxidase inhibitor antidepressant. *Psychopharmacol Bull* 1987;23:169–172
  63. Thase ME, Malinge AG, McKnight D, et al. Treatment of imipramine-resistant recurrent depression, IV: a double-blind crossover study of tranlycypromine for anergic bipolar depression. *Am J Psychiatry* 1992;149: 195–198
  64. Nolen WA, Haffmans PMJ, Bouvy PF, et al. Monoamine oxidase inhibitors in resistant major depression: a double-blind comparison of brofaromine and tranlycypromine in patients resistant to tricyclic antidepressants. *J Affect Disord* 1993;28:189–197
  65. Reimherr FW, Wood DR, Byerley B, et al. Characteristics of responders to fluoxetine. *Psychopharmacol Bull* 1984;20:70–72
  66. Beasley CM Jr, Saylor ME, Cunningham GE, et al. Fluoxetine in tricyclic refractory major depressive disorder. *J Affect Disord* 1990;20:193–200
  67. Peselow ED, Filippi AM, Goodnick P, et al. The short and long term efficacy of paroxetine HCl, B: data from a double-blind crossover study and from a year long trial vs imipramine and placebo. *Psychopharmacol Bull* 1989;25:272–276
  68. Nolen WA, van de Putte JJ, Dijken WA, et al. Treatment strategy in depression, I: non-tricyclic and selective reuptake inhibitors in resistant depression: a double-blind partial crossover study on the effects of oxaprotiline and fluvoxamine. *Acta Psychiatr Scand* 1988;78:668–675
  69. Delgado PL, Price LH, Charney DS, et al. Efficacy of fluvoxamine in treatment-refractory depression. *J Affect Disord* 1988;15:55–60
  70. White K, Wyckoff W, Tynes LL, et al. Fluvoxamine in the treatment of tricyclic-resistant depression. *Psychiatr J Univ Ottawa* 1990;15:156–158
  71. Stern WC, Harto-Truax N, Bauer N. Efficacy of bupropion in tricyclic-resistant or intolerant patients. *J Clin Psychiatry* 1983;44:148–152
  72. Cole JO, Schatzberg AF, Sniffin C, et al. Trazodone in treatment-resistant depression: an open study. *J Clin Psychopharmacol* 1981;1:49–54
  73. Brown WA, Harrison W. Are patients who are intolerant to one SSRI intolerant to another? *Psychopharmacol Bull* 1992;28:253–256
  74. Apter JT, Thase ME, Birkett M. Fluoxetine treatment in depressed patients who failed treatment with sertraline. Presented at the American Society of Clinical Psychopharmacology President's Day Educational Program; Feb. 18, 1986; Montego Bay, Jamaica
  75. Zarate CA Jr, Kando JC, Tohen M, et al. Does intolerance or lack of response with fluoxetine predict the same will happen with sertraline? *J Clin Psychiatry* 1996;57:67–71
  76. Joffe RT, Levitt AJ, Sokolov STH, et al. Response to an open trial of a second SSRI in major depression. *J Clin Psychiatry* 1996;57:114–115
  77. Montgomery SA, Henry J, McDonald G, et al. Selective serotonin reuptake inhibitors: meta-analysis of discontinuation rates. *Int Clin Psychopharmacol* 1994;9:47–53
  78. Glassman AH, Bigger JT Jr. Cardiovascular effects of therapeutic doses of tricyclic antidepressants. *Arch Gen Psychiatry* 1981;38:815–820
  79. Fontaine R, Ontiveros A, Elie R, et al. A double blind comparison of nefazodone, imipramine, and placebo in major depression. *J Clin Psychiatry* 1994;55:234–241
  80. Feiger A, Kiev A, Shrivastava RK, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. *J Clin Psychiatry* 1996;57(suppl 2):53–62
  81. Armitage R, Rush AJ, Trivedi M, et al. The effects of nefazodone on sleep architecture in depression. *Neuropsychopharmacology* 1994;10:123–127
  82. Gillin JC, Rapaport M, Erman MK, et al. A comparison of nefazodone and fluoxetine on mood and on objective, subjective, and clinician-rated measures of sleep in depressed patients: a double-blind, 8-week clinical trial. *J Clin Psychiatry* 1997;58:185–192. Correction 1997;58:275
  83. Clerc GE, Ruimy P, Verdeau-Pailles J. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. *Int Clin Psychopharmacol* 1994;9:138–143
  84. Dierick M, Martin A, Ravizza L, et al. A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. *Prog Neuropsychopharmacol*. In press
  85. Nierenberg AA, Feighner JP, Rudolph R, et al. Venlafaxine for treatment-resistant unipolar depression. *J Clin Psychopharmacol* 1994;14:419–423
  86. de Montigny C, Debonnel G, Bergeron R, et al. Venlafaxine in treatment-resistant depression: an open-label multicenter study. Presented at the 34th annual meeting of the American College of Neuropsychopharmacology; Dec. 11, 1995; San Juan, Puerto Rico
  87. Nelson JC. Safety and tolerability of the new antidepressants. *J Clin Psychiatry* 1997;58(suppl 6):26–31
  88. Wheatley DP, van Moffaert M, Timmerman L, et al. Mirtazapine: efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe major depressive disorder. *J Clin Psychiatry* 1998;59:306–312
  89. Catterson ML, Preskorn SH. Double-blind crossover study of mirtazapine, amitriptyline and placebo in patients with major depression. In: *New Research Program and Abstracts of the 149th Annual Meeting of the American Psychiatric Association*; May 6, 1996; New York, NY. Abstract NR157:110
  90. Nelson JC. Augmentation strategies for treatment of unipolar major depression. In: Rush AJ, ed. *Mood Disorders: Systematic Medication Management*. Basel, Switzerland: Karger; 1997:34–55. *Modern Problems of Pharmacopsychiatry*; vol 25