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.

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**Treatment-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. 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 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, several case reports or series of cases have been described. To date, 9 placebo-controlled studies 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 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, meaningful change more often occurs in the second week. Two studies suggest that improvement will continue over a 6-week period, although it is unclear whether the longer trials should be viewed as augmentation.
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.1,12

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.16

Lithium augmentation appears to be effective with a variety of antidepressants17 and has been relatively well studied with the selective serotonin reuptake inhibitor (SSRI) compounds.11,12,18,20 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 1969.21 In that initial study, T₃ 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 T₃.

Four systematic studies have been performed. In 1982, Goodwin and associates substituted T₃ for placebo in a group of 12 patients, many of whom were bipolar. Eight of the 12 had a marked response. Thase et al.,23 however, reported contradictory results. In an open comparison of patients who had failed 12 weeks of imipramine, they found the addition of T₃ 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. They examined 16 patients who had failed at least 4 weeks of imipramine. T₃ 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 criticized 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. 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 T₃, lithium, or placebo and followed for a 2-week period. Ten (59%) of 17 of the patients receiving T₃ 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 T₃ 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 have proposed the alternative view that depression is associated with mild hyperthyroidism and that administration of oral T₃ in fact reduces the effects of thyroid hormone in the brain.

During thyroid administration, the usual dose of T₃ administered has ranged from 25 to 50 µg/day or, on average, 37.5 µg/day. Although different durations of treatment have not been systematically studied, usually T₃ has been administered for a 2-week period to determine if it is effective. Few side effects are encountered with T₃ administration.

T₃ is the preferred form of thyroid hormone for augmentation. A controlled study, reported by Joffe and Singer, found T₃ more effective than T₄.

One of the factors limiting the use of T₃ 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.

### Stimulant Augmentation

Stimulant augmentation is another of the older augmentation strategies reported. Six series of cases, reviewed elsewhere, 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; 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. 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."
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.

**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%. 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 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. 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 described 10 refractory patients who 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. 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. 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., 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 patients described in this report responded when a tricyclic (usually nortriptyline) was added to the SSRI.

In a systematic, albeit open study, Nelson et al. 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. 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 have described the combination of SSRIs and bupropion used to augment antidepressant response. In the first, Boyer and Feighner described a group of 23 patients who had failed treatment with either fluoxetine or bupropion given alone. The second drug was then added, and 33% (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. 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. 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.\textsuperscript{52,53} 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\textsuperscript{54} 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\textsubscript{2} antagonism. Preclinical work suggests that a 5-HT\textsubscript{2} antagonist enhances the effects of serotonin at the 5-HT\textsubscript{1A} postsynaptic receptor.\textsuperscript{55}

Alpha-2 antagonists have also been employed as an augmentation strategy. The addition of yohimbine to desipramine failed to show any effect;\textsuperscript{56} however, a subsequent report found the addition of yohimbine to an SSRI compound, fluoxetine, was effective.\textsuperscript{57} Two other controlled trials\textsuperscript{58,59} 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.\textsuperscript{60}

**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\textsuperscript{61–64} 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.\textsuperscript{62,63}

Response to an SSRI in patients failing treatment with a tricyclic has also been relatively well described. In 3 of these studies,\textsuperscript{65–67} 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,\textsuperscript{68–70} having a total of 96 patients, the rate of response was only 18%. Bupropion\textsuperscript{71} and trazodone\textsuperscript{72} 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.\textsuperscript{56,65}

Four studies have now examined the switch from one SSRI to another. Brown and Harrison\textsuperscript{73} 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.\textsuperscript{74} 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.\textsuperscript{75} 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.\textsuperscript{76} 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.\textsuperscript{67} 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\textsuperscript{77} and adverse cardiac effects,\textsuperscript{78} 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 treatment-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. It does not increase sexual dysfunction, and it has beneficial effects on sleep. 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. 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.

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 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. Its 5-HT, 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. 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. 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., bupropion, 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.

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 bupropion and T3 addition are minimal, whereas those associated with bupropion or desipramine addition are greater. With respect to cost, some augmentation strategies, such as lithium, T3, 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), pimoline (Cylet), pindolol (Visken), risperidone (Risperdal), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor), yohimbine (Yocop and others).

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