Treatment of Antidepressant Nonresponders: Augmentation or Switch?

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Selective serotonin reuptake inhibitors (SSRIs) are now commonly used in the treatment of major depression. In all patients starting treatment, the intent-to-treat response rate is about 50%. The other 50% will require some change in treatment, either augmentation or switch to a different agent. In this report, augmentation strategies are reviewed, with special attention to those strategies that have been used with the SSRIs. The data for switching antidepressants also are reviewed. Although there are no direct comparison studies of augmentation strategies versus switching that address the question of relative efficacy, the tactical issues that pertain to augmentation or switching are discussed.

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The treatment of refractory depression is a common challenge for the psychiatrist. There are several reasons for this. First, a substantial portion of all patients starting pharmacologic treatment either fail to respond or cannot tolerate the drug. A comprehensive review of 102 controlled trials of tricyclic antidepressants found that the overall intent-to-treat response rate in depressed outpatients was 51%.[1] This means that about half of those starting one antidepressant will need another. The overall intent-to-treat rate for selective serotonin reuptake inhibitors (SSRIs) was 47% in 39 studies. In addition, the most common methods of defining response, 50% improvement over baseline or a Clinical Global Impressions (CGI) rating of much improved, result in a level of response that would be unacceptable for many patients. Further, clinical trial patients are usually carefully selected and are less complicated than the patients clinicians often treat. Finally, psychiatrists are likely to treat a disproportionate number of treatment-resistant patients since this is a common reason for referral.

When faced with a refractory patient, the clinician has essentially 2 choices—to switch to another antidepressant or to augment the first medication. Ideally, this decision would be based on data that indicate the most effective treatment. Yet, at this time there are no parallel comparison studies that directly test these 2 approaches. The available data, presented subsequently, do not indicate a clear advantage for switching or augmentation in terms of efficacy. For these reasons, the decision to switch or augment is based more on practical issues than efficacy data.

Switching to another antidepressant is simpler. For a patient who is reluctant to take medication, monotherapy may improve compliance. In addition, there are reasonably good data on continuation and maintenance treatment for most marketed antidepressants used alone, while the information on continuation treatment following augmentation is scant.

Cost and side effects are also important considerations but do not necessarily favor one strategy over another. Costs vary with the specific antidepressants and augmenting agents. Several of the augmenting agents, e.g., lithium and thyroid hormone, are inexpensive. Thus, the combination of lithium and low-dose SSRI treatment may be less expensive than another SSRI given at a higher dose. Side effects of the augmenting strategies also vary considerably. Thyroid and buspirone appear to cause fewer side effects than a higher dose of an SSRI. Alternatively, combinations of 2 antidepressants, for example, an SSRI plus a tricyclic antidepressant (TCA) or an SSRI and bupropion may have more side effects than monotherapy.

Augmentation strategies have some advantages. First, they may be rapidly effective. Effects within 48 hours have been reported.[2] Second, patients who have had some degree of response may be reluctant to risk losing this improvement, and, in this situation, augmentation may be preferred. Augmentation with another marketed antidepressant may improve response and ultimately "bridge" to monotherapy with the second agent. Finally, in very refractory patients, the psychiatrist may wish to exhaust each drug trial with augmentation before switching to another agent, especially if most drug classes have already been tried.

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AUGMENTATION STRATEGIES

Several augmentation strategies have been described and the list continues to grow. Described below are those for which there are multiple reports in the literature. They are presented roughly in the order that controlled trials support their efficacy. In this report the term *augmentation* is used to describe the use of 2 agents to enhance the response of the core symptoms of depression. These combinations include the use of an established antidepressant with an agent not approved for use as an antidepressant, e.g., fluoxetine and pindolol, and combinations of 2 marketed antidepressants, e.g., fluoxetine and bupropion. These combinations are to be distinguished from combinations in which the second agent is used for other target symptoms, for example, the addition of a benzodiazepine to reduce anxiety or the addition of an antipsychotic to treat delusions. Special attention will be given to the issue of augmentation of the SSRIs, although some of the early augmentation strategies were tested before the SSRIs became the first-line drugs for depression.

Lithium augmentation is the best studied approach. Since its initial description in 1981,[2] it has been studied in 9 placebo-controlled trials, of which 7 were positive.[3–11] It is effective with essentially all types of antidepressants including the SSRIs—fluoxetine,[10,12] citalopram,[11] fluvoxamine,[13] and sertraline.[14] Recent work indicates a single dose of 250 mg/day is no more effective than placebo, but in that study, 250 t.i.d. was effective.[9] In most North American studies, the dose has been 300 mg t.i.d. At this dose, serum levels vary between 0.4 mEq/L and 1.0 mEq/L, and within this range there appears to be no relationship of serum levels to response.[15] These data suggest that levels above 0.4 mEq/L will usually be adequate but that 1 pill a day or levels below 0.4 mEq/L are not likely to be effective. Although response can occur within 48 hours, 2 weeks has been the usual period of observation and 2 studies suggest patients continue to improve over a 3- to 6-week period.[16,17]

In 4 of the largest controlled lithium augmentation studies,[7–10] response rates of 44%, 48%, 52%, and 53% were reported. In other words, about 50% of patients will show at least much improvement. This is likely to vary with how refractory the patients are. Less treatment-resistant patients are likely to have a higher response rate,[15] while patients who have failed several prior trials will have a lower rate.[13] There is little information available about predictors of response to lithium. We have reported that lithium augmentation was most effective in patients with a possible history of hypomania or a family history of bipolar illness,[18] but this observation has not been replicated.

Lithium at the doses used has mild side effects. Tremor is most common. In my experience, a more common obstacle to the use of lithium is the patient's view that lithium is used for serious mental illness and, as a result, the patient is reluctant to take it.

Thyroid augmentation is the next best studied strategy in refractory patients. Thyroid augmentation has a long history. It was first suggested by Prange et al. in 1969.[19] Several open studies in refractory patients followed, and to date, 4 systematic or controlled studies have been reported.

Goodwin et al.[20] substituted T_3 for placebo in 12 patients who had failed at least 4 weeks of tricyclic treatment. Eight had marked response. Thase et al.,[21] however, failed to observe any effect of T_3 addition in 20 patients who had failed 12 weeks of imipramine and psychotherapy. In this study, patients receiving T_3 augmentation were compared with a group of historical controls who continued on imipramine treatment.

Gitlin et al.[22] reported the first placebo-controlled study. Sixteen patients who had failed prior tricyclic treatment were given either T_3 or placebo for 2 weeks and were then crossed over. No difference between T_3 and placebo was observed. The most recent controlled study[8] compared T_3 with lithium and placebo in 50 depressed outpatients who had failed a tricyclic. Both T_3 and lithium were effective with rates of response of 59% and 54%, respectively, while response to placebo was low at 19%. The latter study provides the best support for T_3 augmentation and indicates it is comparable to lithium.

All of the systematic studies added T_3 to patients who had not responded to a TCA. There are few data addressing T_3 augmentation of SSRIs, although Joffe has reported 3 cases.[23]

T_3 is the preferred form of thyroid (a comparison study[24] found T_3 more effective than T_4), and Joffe and Sokolov[25] have suggested that T_3 acts by lowering circulating T_4, the form of thyroid that enters the brain. They argue that contrary to the usual view that the addition of thyroid is treating something akin to subclinical hypothyroidism, in fact, depressed patients display relative hyperthyroidism. They note that depressed patients have elevated T_4 levels and that most antidepressant treatments lower T_4 levels. While this remains an area of controversy, T_3 is the form of thyroid usually employed. The usual dose of T_3 has been 25 to 50 μg/day. Despite the controlled evidence supporting its use, thyroid augmentation does not appear to be a popular strategy according to a poll of northeastern psychiatrists.[26]

Pindolol augmentation was first reported by Artigas and colleagues in 1994,[27] but has already received considerable attention. In theory, pindolol would block the presynaptic 5-HT_{1A} autoreceptor at the outset so that the compensatory reduction in the presynaptic firing rate, which usually occurs following the administration of an SSRI, would not occur or would be attenuated. This would help to reduce the delay in effect of the antidepressant. Artigas also suggested this might be an effective strategy for refractory patients and presented a small open series of pa-

tients. Subsequently Blier and Bergeron[28] reported similar results from an open trial.

Five placebo-controlled studies have now been reported. Berman et al.[29] described a comparison of pindolol and placebo in 40 outpatients with major depression. They found no difference between the 2 groups of patients in the rate of response. Alternatively, Tome et al.,[30] in a placebo-controlled study of pindolol and paroxetine in 80 patients with major depression, found an early advantage of pindolol over placebo but no difference at the end of treatment. In the third controlled study, Perez et al.[31] reported a positive placebo-controlled trial of pindolol and fluoxetine in 111 patients in Barcelona. Pindolol reduced the mean time to response (50% improvement) from 29 days to 19 days and resulted in a higher response rate (75% vs. 59%). In another study,[32] the Barcelona group compared the effects of paroxetine 20 mg/day given with placebo for 4 weeks, with pindolol for 4 weeks, or with pindolol for the first week only. Sixty-three patients with major depression were recruited and equally distributed among the 3 groups. Patients receiving paroxetine and pindolol for the full 4 weeks did significantly better than those taking paroxetine and placebo after each week of treatment. The group receiving paroxetine and pindolol for 1 week showed greater improvement at weeks 1 and 2 than those taking paroxetine and placebo, but at weeks 3 and 4 did not differ from the group receiving paroxetine and placebo. The study suggests pindolol does augment response as early as week 1, but that pindolol needs to be continued to sustain the improved response. In each of these studies, the usual dose of pindolol was 2.5 mg t.i.d., and at this dose, side effects were minimal.

The study of pindolol has generated considerable interest and has led to preliminary reports describing the value of adding pindolol to nefazodone[33] and buspirone.[34] Yet, it should be noted that the controlled studies of pindolol, described above, focus on speed of response. They do not address the issue of the effectiveness of pindolol augmentation in refractory patients. In fact, in 1 of these studies,[29] the patients were treatment naive. Data on the use of pindolol in refractory patients are limited. A recent placebo-controlled trial in 10 refractory patients found no advantage of pindolol over placebo.[35] Consequently, the status of pindolol as an augmentation strategy in refractory depression remains unclear.

SSRI-TCA combinations were first suggested by Weilburg et al. in 1989.[36] They described 30 patients who had been refractory to prior antidepressant treatment, usually with a tricyclic. Fluoxetine was added and 26 patients had a good response. Subsequently, Seth et al.[37] described 8 very refractory elderly patients who had failed various treatments including ECT. All responded to a combination of an SSRI and nortriptyline.

We described the first systematic comparison study of a TCA-SSRI combination.[38] We treated 14 severely depressed inpatients with the combination of fluoxetine and desipramine for 4 weeks and compared these patients with 52 similar patients treated with desipramine alone. This was not a randomized parallel comparison study; however, patients were similar descriptively, were treated in the same setting, and were rated during treatment with the same instrument. In all patients, desipramine dose was adjusted using a 24-hour blood level to achieve a therapeutic plasma desipramine level and, in the combined group, to anticipate the effect of fluoxetine on desipramine levels. In this comparison, the combination of fluoxetine and desipramine was more effective than desipramine alone. The advantage of the combination was significant and meaningful at 1 week and continued through the trial. For example, at 2 weeks, the mean improvement in the patients taking desipramine alone was 30% versus 60% for the patients taking desipramine and fluoxetine. The combination appeared effective in some patients who had been quite refractory to other treatments including ECT. Because dose was adjusted early with blood level monitoring, the desipramine levels achieved were reasonably comparable in the 2 groups. The usual dose of desipramine required during combined treatment was 75 to 125 mg/day.

Usually the combination was well tolerated although side effects can result from either the SSRI or the TCA. There is the potential for more serious adverse reactions because of the effect of the SSRI on tricyclic metabolism.[39] Paroxetine and fluoxetine both raise desipramine levels 3- to 4-fold.[38,40,41] Sertraline has a more modest effect, on average raising desipramine levels 30% to 40%.[40] Citalopram appears to have a modest inhibitory effect on desipramine metabolism similar to that of sertraline.[42] Fluvoxamine has minimal effects on the 2D6 isoenzyme, which metabolizes desipramine.[43] The effects of the SSRIs on nortriptyline have not been well studied but interactions do occur.[44] The effects of the SSRIs on the tertiary tricyclics differ because the demethylation of these compounds is mediated by different isoenzyme pathways; however, if the intent of combined treatment is to use a potent norepinephrine reuptake blocker with an SSRI, there is no reason to use a tertiary tricyclic. Desipramine or nortriptyline would be the TCAs of choice. Because of potential drug interactions, this strategy is best administered with blood level monitoring and/or the use of an SSRI less likely to interact with a TCA.

From a practical perspective, combined treatment can be a very useful strategy for patients admitted to the hospital who have failed treatment with an SSRI. In these patients, there may not be time to withdraw the SSRI before starting a new treatment. A noradrenergic TCA can be added to ongoing SSRI treatment. This combination has another advantage. In a responding patient, the SSRI can be tapered and the patient continued on the TCA. Thus the augmentation period serves as a bridge to the new treatment.

There are yet no controlled data supporting the SSRI-TCA combination. One small controlled study failed to find augmentation of fluoxetine with desipramine or lithium effective[45]; however, as we have argued elsewhere, the doses used in that study were below those usually found to be effective.[46] While controlled studies are needed, the rationale for combining a potent serotonergic blocking agent with a noradrenergic reuptake blocker is compelling.

Stimulant augmentation has been described in several open cases or series of cases previously reviewed.[47] In 2 of the largest series, stimulants were used to augment monoamine oxidase inhibitor (MAOI) agents. In one, Fawcett and colleagues reported that 78% of the 32 patients responded.[48] The patients had all been clearly refractory to prior treatment, and the authors documented that the response was sustained. The usual dose of stimulants used was 10 mg t.i.d. for methylphenidate or 5 mg t.i.d. for dextroamphetamine. When coadministered with the MAOIs, lower doses usually have been used. Most of the stimulant augmentation reports involved the addition of stimulants to either the TCAs or the MAOIs. One recent report suggests they are effective when given with the SSRIs.[49] There are no controlled studies of stimulant augmentation; however, there have been controlled studies of the use of stimulants in depressed patients. Although the extended use of a stimulant as the primary antidepressant has been disappointing,[50] the acute effects of stimulants in depressed patients have been well established in controlled studies, which have been reviewed elsewhere.[51] Thus, the addition of stimulants might be expected to have rapid effects.

Side effects of stimulants are usually mild.[50] At the doses reported, cardiovascular effects are minimal. Those side effects that do occur are usually behavioral and include irritability, anxiety, and sometimes paranoia. Stimulants are usually not given to patients already anxious or agitated.

Buspirone augmentation has been described in 3 reports,[52–54] based on the idea that a 5-HT_{1A} partial agonist might add to the postsynaptic effects of a serotonergic agent. In each of the 3 reports, buspirone 10 mg t.i.d. was added to an SSRI, usually fluoxetine. In the 2 larger studies,[52,54] 10 of 17 patients and 17 of 25 patients responded over a 3-week period. The advantages of buspirone augmentation are that it has minimal side effects, it has independent anxiolytic effects, and it has been studied primarily with the SSRIs.

Bupropion augmentation has been described in 2 reports.[55,56] In each study, patients were refractory to either an SSRI or bupropion. The second agent was then added. In the first study, 8 (35%) of 23 responded. In the second, 19 (70%) of 27 responded. In the second study, the mean dose of bupropion was 243 mg/day. Side effects with this combination are mild to moderate. A disadvantage of this combination is that the kinetic interaction of bupropion and SSRIs is not well described; yet, there are reports of bupropion being of benefit for the reversal of sexual dysfunction occurring with the SSRIs.[57]

Other augmentation strategies have been described. In fact, tryptophan augmentation has been studied in 7 previously reviewed placebo-controlled studies.[58] Tryptophan was an effective adjunct when used with the MAOIs or with clomipramine. It was not more effective than placebo when used with other tricyclics. Tryptophan, however, has been withdrawn from the U.S. market because of its association with eosinophilia-myalgia syndrome.[59] The use of tryptophan with the SSRIs has not been well studied, but clinicians should be aware that 5 cases of severe serotonergic side effects were reported when tryptophan was added to high dose (50 to 100 mg/day) fluoxetine treatment in OCD patients.[60] Although the addition of tryptophan appeared to trigger the side effects, it seems likely that the high doses of the SSRI were a contributing factor.

MAOI-TCA combinations have also been reported in refractory depression. In 6 open series, over 200 patients were studied. Only one study[61] reported a controlled comparison and in that study the combination of an MAOI and trimipramine was no more effective than trimipramine alone; however, this study was not limited to refractory patients. Although this combination can be safely administered, it is potentially hazardous. Certainly its use should be restricted to clinicians experienced in the use of the MAOI compounds. Because there are many other safer alternatives, the use of this combination is not recommended. Given the current infrequent use of the MAOIs, the clinician would be better advised to consider whether an MAOI alone would be a worthwhile alternative.

The list of augmentation strategies continues to grow. Those with favorable findings, reported by more than one group, have been described. The reader is referred to other sources for a further discussion of augmentation strategies.[62–64]

SWITCHING STRATEGIES

The most common approach to patients who are treatment-resistant is to switch to another drug. Prior to the introduction of the SSRIs, the best studied switch was from a TCA to an MAOI. Four controlled studies[65–68] found rates of response for switching from TCA to MAOI of 50%, 59%, 65%, and 75%; however, the higher rates of response were noted in atypical depressed patients[66] or anergic bipolar patients.[67] This was further illustrated in a systematic study reported by Thase et al.,[69] who found that 55% (23 of 42) of patients who failed imipramine therapy responded to either phenelzine or tranylcypromine. However, the rate in atypical anergic patients was higher, 67% (18 of 27), than in typical patients, 31% (4 of 13).

Surprisingly, switching from one TCA to another has not been well studied, and when studied, has not been found to be very effective. Two small studies[70,71] found

rates of response of 9% and 27% when TCA failures were treated with another TCA. These low rates are consistent with the rationale for switching to a drug with a different mechanism.

Following the introduction of the SSRIs, several studies, reviewed elsewhere,[72] examined the switch from a TCA to an SSRI. Beasley et al.[73] reported that 51% (18 of 35) of patients who failed a TCA responded to an open-label trial with fluoxetine. Reimherr et al.[71] observed that 17 (43%) of 40 patients who failed a TCA responded to fluoxetine. The rate was higher among the atypical patients. In a small series of 10 patients who failed a TCA, Peselow et al.[74] found 50% (N = 5) responded to paroxetine. Rates of response to fluvoxamine following TCA failure have been variable, with rates of 4%, 28%, and 75% reported in 3 studies,[75–77] giving an overall pooled rate of 18.5%.

Other agents have also been examined in patients failing TCAs. Both bupropion[78] and trazodone[79] appear to be effective following a switch.

Perhaps the most controversial current question is the value of switching from one SSRI to another. The data from the TCA studies argue against a switch within a class. The logic is that if a patient fails to respond to a drug whose primary mechanism is serotonin reuptake blockade, then giving another drug with the same mechanism is less likely to work than a drug with a different action. The counter argument is that the secondary effects of the SSRIs are sufficiently different that there may be differences in efficacy. The empirical data are limited and mixed. Two studies examined this switch in patients intolerant of the first drug. Brown and Harrison[80] found sertraline effective in fluoxetine-intolerant patients, while Apter et al.[81] found fluoxetine effective in patients who failed or were intolerant of sertraline. Another report was less favorable. Zarate et al.[82] examined 42 patients treated with sertraline who had previously failed to respond or were intolerant of fluoxetine. Among the 31 patients with unipolar or bipolar depression at follow-up, only 8 (26%) of 31 responded. Patients with side effects on sertraline tended to have had the same side effects on fluoxetine therapy. Only 1 study examined a switch to another SSRI in a sample limited to nonresponders. Joffe et al.[83] found 55 patients with unipolar nonpsychotic major depression in their mood disorders clinic who failed 1 SSRI and then received a second. Twenty-eight (51%) of the 55 patients responded.

There are few data on other switches in patients starting treatment with an SSRI. In a study of 15 patients failing paroxetine, Peselow et al.[74] found 11 (73%) responded to imipramine in a double-blind crossover study.

COMPARISON OF SWITCHING AND AUGMENTATION

The practical considerations bearing on the question of whether to switch or augment have been discussed above. One other issue might be raised. Clinical lore suggests that augmentation may be more useful in partial responders with the implication that augmentation should not be used in patients showing little response. It does seem likely that partial responders are more apt to respond to future interventions of any sort than patients having no response, but it is not clear that patients having minimal response will necessarily respond better to a switch. In a large open study[16] that provided detailed data, 84 depressed inpatients received lithium augmentation after failing a 4- to 6-week tricyclic trial. The average improvement on the tricyclic was only 13% or 4.5 points on a 25-item Hamilton Rating Scale for Depression. Yet, after 3 weeks of lithium augmentation, 56% were at least much improved. There was essentially no difference between lithium responders and nonresponders with respect to their prior improvement on the TCA (15% vs. 11%). Thus, while it may be that augmentation is beneficial in partial responders in order to maintain improvement, it is not clear that augmentation will be ineffective in patients with minimal prior improvement.

As mentioned above, no controlled study has directly compared an augmentation strategy with a switch under similar conditions. Response rates of separate studies can be compared. As noted, the response rates for lithium augmentation in controlled studies are about 50%. In the single positive controlled study of T_3, the response rate was 59%.[8] The rates of response for switching from a TCA to an MAOI, from a TCA to an SSRI, or from an SSRI to another SSRI are about 50%. These data suggest the efficacy of the 2 approaches is similar but comparisons across studies are hazardous. A response rate of 50% in a sample of 30 patients means that it is 95% likely that the true rate is between 32% and 68%, a fairly large range. In addition, the studies vary in terms of how refractory the samples were, how response was defined, and other factors. The safest conclusion is that the relative efficacy of augmentation and switching is unknown, and that until there are data to the contrary, treatment decisions are likely to be based on practical considerations rather than differences in efficacy.

Drug names: bupropion (Wellbutrin), buspirone (BuSpar), citalopram (Celexa), clomipramine (Anafranil), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil), methylphenidate (Ritalin), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), pindolol (Visken), sertraline (Zoloft), tranylcypromine (Parnate), trazodone (Desyrel and others), trimipramine (Surmontil).

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