Augmentation Strategies in Depression 2000

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Augmentation strategies and combination treatments have become a popular method of treating refractory depression, enhancing therapeutic response in partial responders and increasing the likelihood of more rapid response. The evidence supporting these strategies will be reviewed, their methods of administration discussed, and the relative advantages and disadvantages considered.

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Combined pharmacologic strategies have become popular in depression. They have been used to enhance antidepressant response in refractory patients, to achieve remission in partial responders, and to speed up response. In this article, the evidence for these strategies will be reviewed and their advantages and disadvantages discussed.

The terms *augmentation strategies* and *combination treatments* will be used in this article somewhat interchangeably. Some reviewers have limited the use of *augmentation strategies* to those strategies in which an agent not approved for use as an antidepressant is added to a marketed antidepressant; for example, the use of triiodothyronine (T_3) with a tricyclic. Alternatively, the term *combination treatment* is sometimes employed when 2 approved antidepressants are used together. This review will focus on both types of strategies, as long as the 2 agents are both used to enhance antidepressant response. These combinations should be distinguished from the use of 2 drugs when the second agent is used for a different purpose. For example, in psychotic depression, the antipsychotic drug is used to treat psychotic symptoms, or a second agent may be used as a hypnotic or as an anxiolytic.

In reviewing the augmentation and combination treatment strategies, there are a few general issues to keep in mind. The majority of augmentation studies have been of short duration, usually 2 weeks. Rates of response might be higher with treatment of longer duration. Placebo controls are important in the exploration of the efficacy of a new augmentation strategy because some patients will respond to continued treatment with the first agent alone. In placebo-controlled trials with lithium,[1,2] approximately 20% of the patients responded to placebo during a 2-week interval. Efficacy of the combination strategy varies with how refractory the sample is. In one study of lithium augmentation, Delgado et al.[3] found that only 28% of the patients who had failed an average of 4 prior drug trials had a marked response. Alternatively, de Montigny et al.[4] found that 74% of their patients responded to lithium augmentation, but they selected treatment-naive patients. For some strategies, the dose of the augmenting agent has been fairly well established, but for others, the appropriate dose for combination treatment has not been determined. Finally, it should be noted that the earlier strategies (e.g., thyroid augmentation) were studied primarily with tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), and little is known about their use with selective serotonin reuptake inhibitors (SSRIs). This is of obvious importance currently since initial treatment is most often begun with an SSRI.

THE EARLY STRATEGIES

Tryptophan

Historically, the use of tryptophan was one of the first strategies described. Four positive controlled studies[5–8] document the efficacy of tryptophan augmentation when used with an MAOI. In the studies combining tryptophan with a TCA,[6,9–11] only 1 of 4 demonstrated efficacy,[10] although in some studies the dose of the TCA was quite low. There is little information about the use of tryptophan with SSRIs. Walinder et al.[12] reported a negative study of tryptophan with zimelidine, and Steiner and Fontaine[13] described 5 patients who developed severe adverse events with the combination of L-tryptophan and high-dose fluoxetine (60 to 100 mg/day). Currently, tryptophan is not approved for use in the United States.

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Stimulant Drugs

The use of stimulant drugs to augment response has also had a long history. Stimulants themselves have acute antidepressant effects that occur within the first few days of treatment and that have been well documented in controlled studies.[14–16] Yet, their use as antidepressants in primary depression has been limited by concerns about tolerance and disappointing efficacy in controlled studies.[17] It has been suggested that stimulants might be used early in treatment to "jump start" response while the second antidepressant is being started.[17] While a prior open study adding methylphenidate to a TCA at the beginning of treatment supported this strategy,[18] a recent study adding methylphenidate to sertraline showed no advantage.[19]

Stimulants have also been used in refractory patients to augment initial treatment. Five open studies,[20–24] including a total of 63 patients, reported positive results with stimulant augmentation of a TCA or an MAOI. When used with an MAOI, low doses of methylphenidate or dextroamphetamine were carefully added to the MAOI to ensure that no adverse blood pressure changes occurred. In the largest of these studies,[23] it was also observed that the effects of stimulant augmentation were sustained for several months; in other words, tolerance was not observed. Yet, there are no controlled studies using stimulants in refractory patients, and reports of their use with SSRIs are limited.[24–26]

Thyroid Augmentation

Thyroid augmentation also has a long history. The first study, reported by Prange and associates[27] in 1969, administered T_3 at the beginning of imipramine treatment. Patients receiving the combination showed greater improvement at 2 weeks, although differences at the end of the 4-week trial were not significant. Prange and colleagues suggested that the combination might be effective in refractory patients. Subsequently, a number of open studies and 4 systematic studies[1,28–30] were reported. Goodwin et al.[28] substituted T_3 for placebo in 12 patients who had failed to respond to at least 4 weeks of TCA treatment, and 9 responded. In contrast, Thase et al.[29] compared response in 20 patients who received T_3 after failing to respond to 12 weeks of treatment with imipramine with the response observed in 22 patients who continued with imipramine alone. Although this was not a double-blind or random assignment study, no differences were observed.

The placebo-controlled studies also found mixed results. Gitlin and associates[30] found no difference in response when T_3 or placebo was added to a TCA in 16 patients. In the best designed and largest study to date, Joffe et al.[1] compared the addition of T_3 with that of lithium and placebo in 51 patients for whom treatment with TCAs had failed. T_3 and lithium augmentation appeared comparable, with slightly more than 50% of the patients responding, and both were superior to placebo. In these studies, the usual dose of T_3 varied between 25 and 50 μg/day. T_3 appears to be superior to thyroxine (T_4).[31] Reports of the use of T_3 with the SSRIs are limited to a few cases.[32]

Lithium Augmentation

Lithium augmentation has been one of the most popular strategies and is the best established augmentation strategy. One of the earliest studies of lithium augmentation examined the addition of lithium from the onset of treatment to enhance initial response.[33] Three studies[33–35] have now been conducted using lithium with a TCA from the beginning of treatment, and all of these studies found the combination more rapid but not necessarily more effective.

Lithium has also been widely used in refractory patients or partial responders. Since the initial report by de Montigny and colleagues in 1981,[36] several open studies and controlled trials have been reported. To date, 7 placebo-controlled studies[1,2,37–41] have found positive evidence for the efficacy of lithium augmentation. In 4 of the larger of these,[1,2,39,41] the rate of response was approximately 50% (52 of 107 patients). The combination of lithium use and SSRIs has been relatively well studied.[3,40,41]

A moderate amount of information has now been generated about methods of administration. Although positive effects have been observed within 48 hours, response has been more commonly observed during a 2-week trial. Two studies[42,43] demonstrated further improvement with treatment up to 6 weeks.

In early studies of lithium augmentation,[4,36,37] the usual dose was 300 mg 3 times a day. At this dose, serum lithium levels were usually above 0.4 mEq/L, and no relationship between serum levels and response was observed.[4,37] A subsequent study[2] employing a low dose (250 mg/day) and a moderate dose (250 mg t.i.d.) demonstrated that the low dose was no more effective than placebo, whereas the moderate dose was significantly more effective. Considering these data, it appears that serum lithium levels above 0.4 mEq/L are sufficient for response, but that lower serum levels are not.

Few predictors of lithium response have been demonstrated, although our group[44] suggested lithium augmentation might be most useful in probable or possible bipolar patients, for example, patients with a first-degree relative with bipolar disorder or patients with a probable history of hypomania. (Definite bipolar patients were already likely to receive lithium or another mood stabilizer.) However, our observation has not been replicated by others.

Lithium augmentation has played an important role in establishing the legitimacy of augmentation strategies. de Montigny and associates[36] had proposed a neurochemical hypothesis for this synergistic interaction. Previous animal work had suggested that administration of TCAs increased postsynaptic serotonin receptor sensitivity,[45] and de Montigny et al.[36] reasoned that the addition of lithium,

which quickly increases serotonin turnover, would augment serotonin transmission. This hypothesis predicted the clinical outcome and suggested that "polypharmacy" could be rational and effective.

MAOI-TCA Combination

Another combination strategy of historical interest is the combination of an MAOI with a TCA. This is a potentially hazardous combination. Fatalities have been reported when a large dose of a TCA was given to a patient already taking an MAOI. Thus, sequencing this combination is important, i.e., the TCA should be started first or the 2 drugs should be started together.[46] Ironically, it has been demonstrated that the reuptake blockade that occurs with the TCA may protect the patient from the effects of tyramine.[47] The problem is that, although the data supported a group effect consistent with this hypothesis, nevertheless, one could not be assured that every individual patient would be fully protected. As a result, a diet and the usual MAOI restrictions were still necessary.

The use of MAOI-TCA combinations in refractory depression is well described in open studies. Six open series of cases, previously reviewed,[48,49] describe treatment outcome in 233 patients with rates of response from 54% to 100%. One controlled study[50] compared response to the combination with response to either a TCA or MAOI alone. In this particular study, trimipramine alone was slightly more effective than the MAOI or the combination. Because of the potential hazards of this combination and the availability of a variety of other combinations that are simpler to use, this treatment cannot be recommended as either a first- or second-line treatment, and it should be reserved to those clinicians who are quite familiar with the use of MAOI medications.

STRATEGIES INVOLVING COMBINATIONS WITH SSRI ANTIDEPRESSANTS

Buspirone

A variety of agents have been reported to be useful when combined with SSRI antidepressant drugs. Buspirone augmentation was one of the first strategies described. Five open studies[51–55] supported the potential utility of this treatment, although Fischer et al.[56] found weak effects. The usual dose of buspirone was 30 mg/day (10 mg t.i.d.), and response rates of approximately 60% were observed. Recently, a controlled trial of buspirone augmentation was reported in 119 patients with major depression who had failed at least 4 weeks of paroxetine or citalopram.[57] These patients were randomly assigned to buspirone or placebo, which was administered in double-blind fashion. The buspirone dose was flexible, with an average dose of 49 mg/day and a range of 10 to 60 mg/day. The response to buspirone augmentation was neither statistically nor meaningfully different from that for placebo, 51% versus 47%.

TCA-SSRI Combinations

Another early strategy described for use with the SSRIs involved the combination of a TCA with an SSRI. In 1989, Weilburg and associates[58] described a group of 30 outpatients who had failed prior treatment, usually with a TCA. Fluoxetine was then added. Response was observed in 26 of the patients. Others have reported open studies using combinations of tricyclics or heterocyclics with an SSRI in refractory patients.[59,60]

In 1991, Nelson et al.[61] reported a study comparing the effectiveness of the combination of desipramine and fluoxetine with that for desipramine alone. The combination was initially given with the idea of improving speed of response, but overall efficacy was also examined. In this preliminary study, 14 patients who received the combination were compared with 52 previously treated patients who received desipramine alone. This was not a double-blind parallel comparison study, and patients were not randomly assigned. Yet, all the patients were inpatients, rated prospectively with similar instruments, and treated with rapid desipramine dosing based on an initial blood level. The combination appeared to be more rapidly effective, but the most robust finding was that remission was much more likely with the combination.

Subsequently, a prospective study was completed in depressed inpatients.[62] In this study, the combination of desipramine and fluoxetine was compared with either drug given alone. The dose of desipramine was adjusted to rapidly achieve an effective blood desipramine level and to compensate for the enzyme-inhibiting effects of fluoxetine. The combination was significantly more likely to result in remission (50% for the combination vs. 7% and 0% for fluoxetine and desipramine, respectively). Although the group receiving the combination showed greater improvement at 2 weeks, this was primarily a reflection of overall efficacy and did not indicate more rapid response among responding patients.

Not all SSRI-TCA studies have been positive. Fava et al.[63] reported a small controlled study comparing desipramine and lithium augmentation with fluoxetine dose increase. In this study, desipramine augmentation was not effective, but as previously noted,[64] the desipramine doses were low, 25 to 50 mg/day. In our previous studies, desipramine dose was adjusted to achieve an effective blood drug level[65] and was usually between 75 and 125 mg/day.

The combination of an SSRI with a noradrenergic antidepressant may be particularly potent, but it is noted that drug interactions complicate their use and may result in toxicity.[66] Fluoxetine and paroxetine are cytochrome P450 (CYP) 2D6 inhibitors and raise desipramine levels 3- to 4-fold. If this effect is anticipated, the combination can be used safely although blood level monitoring is advised. Citalopram and sertraline have modest effects on CYP2D6 and should be less problematic.

Bupropion-SSRI Combinations

The combination of bupropion and an SSRI has also been described. The basis for this combination appears to be similar to that for an SSRI and desipramine, i.e., the addition of a noradrenergic agent to a serotonergic agent may enhance effects. Bupropion may also have dopaminergic actions. Three open series of cases[67–69] and 2 other case reports[70,71] have described beneficial results with the combination. Patients had been either refractory to prior treatment with one agent or were partial responders. A relatively high adverse response rate (39%) was observed in one of these trials,[67] but not the others. In the largest study,[68] the usual dose of bupropion during combined treatment was 243 mg/day. Although the interactions of bupropion and SSRIs have not been well described, it has recently been discovered that bupropion is a CYP2D6 inhibitor.[100] This suggests that bupropion might affect concentrations of paroxetine, a CYP2D6 substrate; however, because paroxetine inhibits its own metabolism, further inhibition with bupropion may be relatively unimportant. Bupropion itself is reportedly metabolized by CYP2B6,[100] and the effects of the SSRIs on this enzyme have not been reported. Although no controlled studies have been reported for this combination, it appears to be a popular choice.[72]

Pindolol

In 1994, Artigas and colleagues[73] suggested pindolol might be a useful augmentation strategy when used with SSRI agents. The concept was that pindolol at low doses, 2.5 mg t.i.d., would block the presynaptic serotonin-1A (5-HT_{1A}) autoreceptor in the serotonin system, which otherwise reduces the firing rate of the presynaptic neuron in the presence of serotonin reuptake blockade.[74] As a result, a normal firing rate would be maintained in the presence of reuptake blockade, and serotonin transmission would be quickly enhanced. Five controlled studies[75–79] have been reported that have employed pindolol at the outset of treatment. Four of the 5 studies[76–79] demonstrated more rapid improvement with the combination. Efficacy at the end of the study was more variable, with only 2 of the 5 studies showing an overall advantage.[76,78] Nevertheless, this series of studies documents more rapid improvement with the combination.

Although initial open studies suggested that pindolol might also be useful in refractory patients,[73,80] controlled studies have not confirmed this observation.[81,82] In a crossover study of 10 patients, Moreno et al.[81] found no advantage of the addition of pindolol over placebo in refractory patients. In a larger study of 80 outpatients with major depression who had not responded to at least 6 weeks of treatment with an SSRI, Perez et al.[82] found that pindolol was no more effective than placebo when added to ongoing SSRI treatment. Thus, while pindolol appears to speed up initial response, its utility in refractory depression has not been demonstrated.

Mirtazapine

Another strategy recently reported for use in augmenting SSRI drugs is the addition of the α_2 antagonist mirtazapine. A preclinical study by Besson et al.[83] reported that the combination of mirtazapine and paroxetine more rapidly shortened the delay to tonic activation of postsynaptic 5-HT_{1A} receptors. Three controlled studies[84–86] using 2 α_2 antagonists, yohimbine or mianserin, found evidence for more rapid effects. Recently, Carpenter et al.[87] described 20 patients with major depression or dysthymia who had failed at least 4 weeks of aggressive antidepressant treatment with SSRIs; 15 to 30 mg of mirtazapine was added, and about 50% of the patients responded, most within 2 weeks. The combination appeared easy to use, in part because the beneficial effects of mirtazapine on some symptoms (for example, sleep disturbance and nausea) may offset the side effects of the SSRI agent.

Risperidone

Recently, another strategy has been reported in a preliminary study. Ostroff and Nelson[88] described 8 patients with major depression who had failed initial treatment with an SSRI. Low-dose risperidone, 0.5 or 1 mg h.s., was added. Patients were rated with the Hamilton Rating Scale for Depression before and after the initiation of risperidone. These 8 patients demonstrated relatively robust and early changes following the addition of risperidone. The hypothesis was that low-dose risperidone acts primarily as a 5-HT_2 antagonist, and other preclinical data suggest that 5-HT_2 antagonists enhance the effects of serotonin.[89] These preliminary findings have not been replicated. However, similar effects of the combination of risperidone and SSRIs have been observed in obsessive-compulsive disorder.[90–92]

Other Strategies

Numerous other augmentation strategies have been attempted. Noteworthy are controlled studies that showed no advantage of fenfluramine augmentation of TCAs,[93] yohimbine augmentation of desipramine,[94] and reserpine augmentation of desipramine.[95] A controlled study of estrogen augmentation, used acutely and in nonselected women, showed no efficacy[96]; however, a recent retrospective review indicated that postmenopausal women who were receiving estrogen replacement therapy were more likely to respond to treatment with fluoxetine.[97] The potential value of combining a mood-stabilizing anticonvulsant such as carbamazepine or valproate with an antidepressant deserves mention. The rationale for this strategy has been recently reviewed elsewhere.[98] Stated simply, the logic is that combining 2 agents with different mechanisms of action both having effects on mood might be beneficial. Unfortunately, whereas the pharmacokinetic interactions of these combinations have been well described,[98] the clinical efficacy of these combinations in major depression has not.

PROS AND CONS OF AUGMENTATION

The use of augmentation or combination strategies has a variety of advantages and disadvantages. Combination treatment is more complicated than treatment with a single agent, drug interactions may be involved, side effects may be increased, and some combinations are costly. Perhaps most important is that the complexity of treatment is increased, and in a patient with questionable compliance, treatment with a single agent is simpler and might improve compliance. These considerations might be most important during the initial treatment of depression in a patient who has not been particularly refractory and whose depression is not terribly severe.

Alternatively, augmentation or combination strategies have some advantages. First, response may be rapid. For some types of augmentation, for example, lithium augmentation, response has been observed within 48 hours. From a practical perspective, the addition of a second agent in a patient with partial response may help to maintain the improvement associated with the initial agent, but it is worth noting that the efficacy of augmentation strategies is not necessarily limited to partial responders. One study[42] suggested that lithium augmentation was useful in patients with minimal initial response to a TCA. Another advantage of combining a second agent is that no time is lost tapering the first drug and then gradually increasing the other. The patient may benefit from combined treatment, and then consideration can be given to withdrawing the initial antidepressant. Thus, combination treatment can be used as a bridge to final treatment with the second agent.

In addition to their effectiveness in partial responders or refractory patients, augmentation and combination treatments can be useful in improving speed of response. This is particularly an issue for psychiatric inpatients, but it is also a general concern to severely depressed patients for whom more rapid response may be important in reducing risk of suicide, improving nutrition, or treating a variety of symptoms associated with severe depression. More rapid effects have been observed in controlled trials with lithium, pindolol, and combinations of α_2 antagonists, such as mirtazapine, with SSRIs.

The augmentation strategies reviewed here differ in their side effects. T_3, L-tryptophan, buspirone, and pindolol have minimal side effects when combined with antidepressants. Stimulants, lithium, risperidone, and combinations of SSRIs and bupropion or mirtazapine are associated with relatively mild side effects. Side effects with the SSRI-TCA combination are moderate, and blood level monitoring is likely to be required. The combination of MAOIs and TCAs is potentially hazardous, and its use should be restricted. It is this author's view that the severity of adverse effects observed to some extent mirrors the potency of the combination.

It seems reasonable to expect that if the use of combination treatments increases, there is likely to be increased interest in what to do with responding patients. The literature on this topic is sparse. One small study[4] and a second larger one[99] each found that about 50% of the patients who responded to augmentation or combined treatment maintained their response after the second agent was withdrawn. Alternatively, 50% relapsed and required reinitiation of combined treatment. However, the total number of patients involved in these studies is small. The number of augmentation strategies studied is limited, and there are few data about the timing of withdrawal in relation to maintaining response.

In summary, it appears that augmentation and combination treatments are useful in refractory depression, in patients who had partial response, and for accelerating response. Some of these studies have not been examined under controlled conditions, and this will be required. Few predictors of response have been identified for these various augmentation or combination treatments, so there is little to guide the clinician in where to start. Finally, almost no studies have directly compared the efficacy of these various augmentation or combination treatments, nor has the efficacy of combination treatment with switching to a single agent been well studied. Until direct comparison studies have been conducted, it will be difficult to provide guidelines for clinicians about where to start in selecting from these augmentation strategies.

Drug names: bupropion (Wellbutrin), buspirone (BuSpar), carbamazepine (Tegretol and others), citalopram (Celexa), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), fluoxetine (Prozac), methylphenidate (Ritalin), mirtazapine (Remeron), paroxetine (Paxil), reserpine (Serpasil and others), risperidone (Risperdal), sertraline (Zoloft), trimipramine (Surmontil), yohimbine (Yocon and others).

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