Augmentation Strategies With Serotonergic-Noradrenergic Combinations

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Combinations of antidepressants with both serotonergic and noradrenergic activity may be especially effective and thus useful in treating refractory patients and severely depressed patients. In the current report, studies of combinations of serotonin selective reuptake inhibitors (SSRIs) and noradrenergic tricyclics or of SSRIs and bupropion are reviewed, and practical issues pertaining to their use are discussed.

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Augmentation strategies have become popular to treat refractory patients, to improve response in partial responders, and to enhance the chances that severely depressed patients will respond during the first drug trial. A variety of augmentation strategies have been described in the literature. One of these strategies involves the combination of a serotonergic agent—a serotonin selective reuptake inhibitor (SSRI)—with a noradrenergic antidepressant (tricyclics such as desipramine or nortriptyline or bupropion).

THEORETICAL BASIS FOR SSRI-NORADRENERGIC COMBINATIONS

Two lines of evidence suggest that combinations of SSRIs with noradrenergic antidepressants may be especially effective. Clinically, there has been speculation that the selective serotonergic agents might have a narrower spectrum of action and be less effective than the tricyclic antidepressants (TCAs). The two Danish university studies,[1,2] which have often been cited, demonstrated that clomipramine was more effective than paroxetine or citalopram. These studies, conducted in severely depressed melancholic inpatients, suggested that a combined-action tricyclic is more effective than a selective SSRI.

Studies comparing the TCAs and SSRIs have been previously reviewed.[3] Recently, Anderson[4] updated this review. He found 101 TCA-SSRI comparison studies and performed a meta-analysis of their findings. Overall, differences between the two classes were slight, although they favored the TCAs. The individual TCA for which differences were greatest was clomipramine, and the patient group for which differences were most likely to be demonstrated was severely depressed inpatients. The finding that the difference in efficacy related primarily to clomipramine is consistent with the hypothesis that combined-action tricyclic agents may be more effective than selective agents.

Another set of data supporting the value of combined treatment comes from studies investigating the mechanism of antidepressant action. Delgado and associates, in a series of studies, examined the effects of tryptophan depletion on antidepressant response.[5–7] The method of their studies, described elsewhere,[5] involved administration of an amino acid drink to rapidly deplete tryptophan. Patients, who had been successfully treated with antidepressants, experienced a relapse in their depressive symptoms when tryptophan was depleted. When the investigators examined which patients were likely to relapse, they found those treated with serotonergic agents were those who relapsed following tryptophan depletion, while patients who had been treated with noradrenergic antidepressants were relatively resistant.[5] In untreated depressed patients, tryptophan depletion had essentially no effect.[6] They then examined the effects of α-methylparatyrosine (AMPT), which rapidly depletes catecholamines.[7] Again, they demonstrated relapse in successfully treated patients, but now those who relapsed were patients who had been successfully treated with a noradrenergic agent. Patients responding to serotonergic drugs were relatively unaffected. These studies did not address the neurophysiology of depression, but the findings suggested that serotonin and norepinephrine mediate the action of these two classes of antidepressant compounds. These studies raise the question that if both neurotransmitters do mediate antidepressant response, would the combination of drugs that act on each neurotransmitter enhance response?

SSRI-TCA COMBINATIONS

The first clinical study of this combination was reported by Weilburg and associates[8] from Massachusetts General Hospital. Their sample of 30 outpatients had been refractory to antidepressants commonly used at that time, usually the tricyclic antidepressants. The average duration of prior treatment was 11 months. Fluoxetine was then added to the prior

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antidepressant. Twenty-six of the 30 patients showed a favorable response. This was the first study suggesting that combined treatment might be particularly effective.

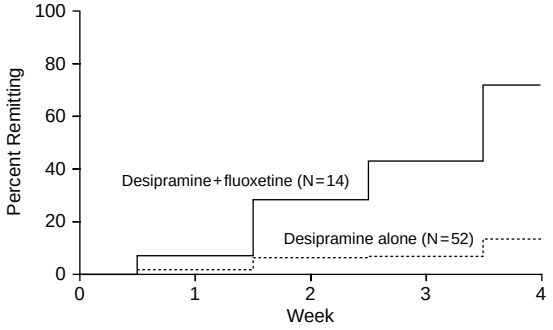
In a smaller, open series, Seth et al.[9] described the response of eight patients, seven of whom were elderly, to similar combinations. These patients were notable for having been refractory to a variety of treatments, including ECT. SSRIs, including fluoxetine, sertraline, or fluvoxamine, were added to nortriptyline. All of these patients responded.

In the first systematic study of this serotonergic-noradrenergic combination, Nelson et al.[10] reported the results of a preliminary study in which the combination of desipramine and fluoxetine was administered to 14 severely depressed inpatients. All patients received desipramine over a 4-week period. Dose was rapidly adjusted using a 24-hour blood level to achieve a desired blood desipramine level and to anticipate the interactive effects of fluoxetine. Fluoxetine was administered for the first 2 weeks of the study; however, given the long half-life of the drug, levels of fluoxetine and norfluoxetine persisted for the subsequent 2 weeks. The patients were compared with another group of 52 severely depressed inpatients, treated in the same setting. All patients were rated with a similar 17-item Hamilton Rating Scale for Depression (HAM-D). Demographic and other characteristics of the patients were similar in the two groups.

Patients receiving the combination of desipramine and fluoxetine responded more rapidly. At the end of the first week, patients in the combined treatment group achieved 42% improvement on the HAM-D versus 20% improvement in patients taking desipramine alone (Mann-Whitney U test, $p = .02$). After 2 weeks, the patients in the combined treatment group demonstrated 60% improvement on the HAM-D, while those receiving desipramine alone showed 30% improvement ($p = .006$). In order to further investigate the effect of the combination on speed of response, patients who did not respond at all were excluded. Patients who at the end of 4 weeks demonstrated at least much improvement on a CGI scale were then compared. Even in this group of responders, speed of response was significantly more rapid in patients receiving combined treatment. Finally, time to remission (> 75% improvement in the HAM-D and HAM-D < 7) was examined in the two groups (Figure 1). The combined treatment group more rapidly achieved this criterion. Remission for patients taking desipramine alone was relatively uncommon during the first 4 weeks of treatment.

Because of the concern that improvement in the combined treatment group might have been explained by differences in blood levels, total desipramine plus hydroxydesipramine levels were examined closely. At Week 1, total blood levels in the two groups were nearly identical. Through the remainder of the trial, they were not meaningfully or significantly different in the two groups. Because plasma desipramine levels in both groups were generally above the

Figure 1. Time to Remission in Patients on Combined Treatment and Patients Taking Desipramine Alone*



*From reference 25. Remission defined as > 75% improvement in HAM-D score and final HAM-D score < 7.

therapeutic threshold,[11] there was no relationship of desipramine levels to response.

It has also been questioned whether desipramine may have some effect on blood fluoxetine levels. Although desipramine is an enzyme inhibitor, it has a relatively weak effect on other drugs. Even if there was some increase in fluoxetine levels, fixed-dose studies of fluoxetine indicate that response is not increased at higher doses.[12,13] Further, dose adjustment studies with fluoxetine suggest that early adjustment of fluoxetine dose does not enhance response.[14,15] Thus, even if desipramine had a modest effect on fluoxetine levels, there is little in the literature to suggest that higher blood levels of fluoxetine will enhance response during the first 4–8 weeks.

Preliminary evidence from a small controlled study did not find the combination of fluoxetine and desipramine effective. Fava and associates[16] reported the results of a study comparing the effects of lithium augmentation, desipramine augmentation, and a dose increase in fluoxetine. Patients included had been treated for 8 weeks with fluoxetine 20 mg/day without adequate response. They found that neither desipramine nor lithium augmentation was particularly effective; however, as we have previously suggested,[17] the augmentation dose of both lithium and desipramine may have been too low. Desipramine was added at a dose of 25 to 50 mg/day. In our studies with desipramine, we found average doses of 75 to 125 mg were required in order to achieve an adequate blood desipramine level in the presence of fluoxetine 20 mg/day. When their data and our data are combined, the findings suggest that during combined desipramine-SSRI treatment, low desipramine doses and blood desipramine levels are not effective, but if dose is adjusted to achieve an adequate desipramine concentration, the combination will be effective.

SSRI-BUPROPION COMBINATIONS

The first report of this combination was described by Boyer and Feighner in 1993.[18] They described 23 patients

who had had only a partial response to either fluoxetine (20–60 mg/day) or bupropion (150–450 mg/day) administered alone. In these 23 patients, the other drug was then added to the first. Eight (35%) of the 23 patients had a moderate or marked response. However, 9 (39%) of the 23 patients were unable to tolerate the combination. This is one of the highest adverse discontinuation rates reported for an augmentation strategy.

More recently, Bodkin et al.[19] described response to bupropion and an SSRI in a series of 27 depressed outpatients. Patients included were those who had had a partial response to either drug given alone. Again, as in the previous study, patients might have first received either an SSRI or bupropion. The second was then added to the first. Seventy percent of the patients appeared to benefit from the combination. In this study, a lower adverse event discontinuation rate, 4 (15%) of 27, was observed. No seizures occurred. When the authors examined the characteristics of patients likely to respond to each drug, bupropion appeared more likely to improve energy or cognition. The SSRI was more useful for anxiety and ruminative worry or obsessive symptoms. The mean dose of bupropion administered was 243 mg/day. The mean SSRI dose was equivalent to 31 mg/day of fluoxetine.

PRACTICAL CONSIDERATIONS DURING COMBINED TREATMENT

One of the advantages of both of these strategies is that since the combination of drugs involved includes two marketed antidepressants, in patients responding to the combination, it may be possible to switch over to monotherapy with the second agent. For example, in a patient who has failed to respond to an SSRI, but responds to the combination of an SSRI and desipramine, it may be possible to discontinue the SSRI and maintain monotherapy with desipramine. There are few data pertaining to the question of how many patients can ultimately be switched to monotherapy with the second agent or when this is best accomplished. In our experience with desipramine-fluoxetine combinations, approximately half of the subjects required continued treatment with both drugs. However, this conclusion was based on clinical impression, not systematic study. Weilburg et al.[8] noted that 8 of 12 patients responding to combined treatment in their study relapsed when the non-SSRI was withdrawn, but improved again when that drug was reinstituted. It seems likely that the need for continued combined therapy will in part depend on how refractory the patient has been to prior treatment.

Because of the interactive effects of the SSRIs, during combined treatment, the dose of the second agent will usually be reduced. Our data, and those of others, suggest that when fluoxetine is administered with desipramine, blood desipramine levels will be increased by about 3 to 3.5 times.[10] The degree of inhibition relates to the metabolic status of the patient. Slow metabolizers are relatively unaffected. Rapid metabolizers show the greatest change. In our own studies, it was necessary to administer a dose of desipramine usually between 75 and 125 mg in order to achieve an adequate blood desipramine level, although some patients required higher doses. Interactions with nortriptyline are less well described. We recently observed an increase in the nortriptyline level from 100 ng/mL to 278 ng/mL after the addition of 20 mg of paroxetine (J.C.N. 1997. Unpublished data). Until further data become available, it would be reasonable to assume a threefold increase in nortriptyline levels. Because the average dose of nortriptyline required to reach a blood level of 100 ng/mL is approximately 75 mg/day, an augmentation dose of 25 mg/day will usually be sufficient. However, there will be variability between patients, and blood level monitoring is likely to be required both to avoid unnecessarily high levels and to assure that an adequate level is achieved. If sertraline is the SSRI employed, more modest elevation of TCA levels would be expected on average, and thus the TCA dose might be reduced by only 25%, or not at all. Venlafaxine and fluvoxamine have little effect on the 2D6 pathway, and usual TCA doses would be employed.

Interactions of the SSRIs with bupropion have not been described, although that does not mean they do not occur. There are no published reports describing the metabolic pathway for bupropion. Unpublished data from the company suggest the drug is metabolized by 2B6 (data on file. Glaxo Wellcome). However, it is unclear if this is the only pathway or the major pathway of bupropion. 2B6 is a minor hepatic isoenzyme. The lack of knowledge about potential interactions takes on added importance when one considers that the maximum dose of bupropion has been limited because of the potential risk of seizures at high doses or, presumably, high blood levels.[20] This would be a situation in which blood level monitoring of bupropion might be useful, although data to guide the clinician are limited. The three studies[21–23] that described blood bupropion levels in relation to response were not fixed-dose studies and were not designed to determine a blood level–response relationship. Nevertheless, the blood levels obtained in responders were generally below 75 ng/mL. In another report,[24] 13 patients who had a seizure while receiving bupropion had a mean plasma drug level of 170 ng/mL. These findings suggest that keeping the blood level of bupropion below 75 ng/mL would appear to be indicated.

There has been much discussion about the actual value of blood level monitoring and its cost. Nevertheless, the patients who are likely to receive the combinations discussed in this report are usually patients who have been refractory to treatment, often for several months, or are patients who are severely depressed and may require inpatient treatment. In these patients, a blood sample may be very cost-effective if it helps to avoid costly serious adverse reactions and if it helps to avoid prolonged ineffective treatment.

SUMMARY

Combinations of SSRIs with noradrenergic tricyclics or with bupropion would appear to be effective for refractory patients and for severely depressed patients. These combinations are likely to be accompanied by a somewhat higher level of side effects than those found with some of the more benign augmentation strategies. However, it is possible that potent serotonergic-noradrenergic treatment may be more effective than some other strategies. The lack of comparison studies examining the efficacy of different strategies leaves these questions open to debate. Administration of combined treatment is more complicated. Dose adjustment and blood level monitoring are likely to be required, and this will require a higher level of expertise on the part of the physician.

It might be questioned whether single agents with combined action, such as venlafaxine, mirtazapine, or clomipramine, might be just as effective, more convenient, and, for these reasons, preferred. It seems reasonable to think that if this question is encountered at the initiation of treatment, a single, combined-action drug might be selected. It is noted, however, that the relative effectiveness of these agents with each other or with combined treatment is not established, and, theoretically, it is unclear if these agents have as potent a noradrenergic effect as desipramine.

In practical terms, it seems more likely that the value of combinations would primarily be for patients who have already started and failed an SSRI trial. Because of the popularity of these agents, most depressed patients do begin treatment with an SSRI, and, as a result, patients who have failed an SSRI are commonly encountered. In these patients, the addition of a noradrenergic tricyclic or bupropion to the SSRI may offer an alternative to switching drugs. As others have noted,[19] patients who have achieved some improvement may prefer adding a second agent in order not to lose the improvement gained with the first agent. Combinations may result in more rapid response, either because of synergistic effects or because of the time saved; i.e., the second drug can be added to the first rather than tapering the first compound and then starting the second. If combined treatment is effective, the patient may go on to try monotherapy with the second agent. In this situation, the augmentation phase serves as a bridge to treatment with the second agent given alone. Decisions about when to switch or when to combine will best be made by patients who have been well advised by their physicians.

Drug names: bupropion (Wellbutrin), clomipramine (Anafranil), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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