

Augmentation and Combination Strategies in Treatment-Resistant Depression

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A substantial proportion of depressed patients show only partial or no response to antidepressants, and even among responders to antidepressant treatment, residual symptoms are rather common. When depressions do not respond adequately to treatment with an antidepressant, clinicians may choose to keep the same antidepressant and add another “augmenting” compound. Such augmentation strategies involve the use of a pharmacologic agent that is not considered to be a standard antidepressant but may boost or enhance the effect of an antidepressant. Alternatively, clinicians may choose combination strategies, in which they combine the antidepressant that did not produce adequate response with another antidepressant, typically of a different class. There are only a few controlled clinical trials of these 2 strategies among patients with treatment-resistant depression or among patients who have only partially benefited from antidepressant treatment. Most of the time, clinicians’ decisions are, therefore, guided by anecdotal reports, case series, and by some relatively smaller, uncontrolled clinical trials. These augmentation and combination strategies appear to be relatively safe and effective approaches to treatment-resistant depressions, although there is a relative paucity of controlled studies to support their efficacy. These strategies typically aim at obtaining a different neurochemical effect than the one obtained with the antidepressant that has not produced adequate response. While drug-drug interactions may limit the use of some of these strategies, the potential loss of partial benefit from the failed drug inherent in switching may increase the acceptability of augmentation and combination strategies among partial responders. Further studies are clearly needed to evaluate the comparative efficacy and tolerability of these different approaches in treatment-resistant depressions.

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Several studies suggest that 29% to 46% of depressed patients show only partial or no response to antidepressants,¹ and even among responders to antidepressant treatment, residual symptoms are common² and have been shown to be associated with greater likelihood of relapsing and perhaps having a poorer prognosis.³ While there are many good studies showing the efficacy of antidepressants in placebo-controlled trials of outpatients or inpatients with major depressive disorder, there are only a few controlled clinical trials among patients with treatment-resistant depression or among patients who have only partially benefited from antidepressant treatment. Most of the time, clinicians’ decisions are guided by anecdotal reports, case series, and relatively small, uncontrolled clinical trials. When one surveys psychiatrists to assess their perceptions of what treatments are effective in treatment-resistant depression, in the absence of data on the newer

strategies, the best-studied strategies to manage patients with partial or no response do not seem to reflect current psychopharmacologic practice.⁴

When depressed patients do not respond adequately to treatment with an antidepressant, clinicians may choose to keep the same antidepressant and add another “augmenting” compound. Such augmentation strategies involve the use of a pharmacologic agent that is not considered to be a standard antidepressant but that may boost or enhance the effect of an antidepressant. Alternatively, clinicians may choose to combine the antidepressant that did not produce adequate response with another antidepressant, typically of a different class. The popularity of these combination strategies has increased over time with the introduction of newer antidepressants that have fairly benign side effect profiles and are associated with fewer concerns about drug-drug interactions. My colleagues and I⁵ recently surveyed 402 psychiatrists from all over North America, asking them what they would do when a patient fails to respond to 8 weeks or more of an adequate dose of a selective serotonin reuptake inhibitor (SSRI); even though the most- and best-studied strategies are lithium and thyroid augmentation, the approaches combining either bupropion or a tricyclic antidepressant (TCA) with an SSRI were the first and third most popular augmentation/combination strategies. These findings confirm the impression

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that there is indeed a discrepancy between how physicians treat nonresponders and what is recommended in the literature.

Augmentation and combination strategies are often favored by clinicians over switching in the case of partial response, since patients may be reluctant to discontinue an antidepressant that has produced some benefit. On the other hand, a recent study by Joffe and Levitt⁶ has shown in a reanalysis of 2 double-blind trials that the augmentation response is not related to the degree of nonresponse to the preceding antidepressant trial, with partial and nonresponders having comparable chances of response.

This article will review some of the studies concerning both augmentation and combination strategies in treatment-resistant depression.

AUGMENTATION STRATEGIES

General Principles

Over the past few decades, numerous compounds have been used as augmenting agents with antidepressants. Although the majority of the studies of this therapeutic approach are open-label, many investigations are also double-blind, often placebo-controlled, allowing us to draw relatively firm conclusions on the efficacy of some of the augmenting agents, such as lithium and thyroid hormones. It appears that the improvement following antidepressant augmentation tends to occur within 3 to 4 weeks, so it may be too premature to decide in the first few days or couple of weeks whether an augmentation strategy is working. Almost all the studies on the efficacy of these augmentation strategies have focused on the short-term outcome, and very little is known about the minimum duration of the augmentation trial in responders to such strategy. A typical approach is to maintain the augmenting agent for 6 to 9 months after obtaining remission and then to attempt a gradual discontinuation of the augmenting agent.

Lithium

Lithium augmentation is not as popular now as it was in the 1980s, although many studies have clearly shown that the addition of 600 mg/day or more of lithium, typically in divided doses and with adequate blood levels, leads to a robust increase in the chances of response in treatment-resistant patients who do not respond to TCAs, monoamine oxidase inhibitors (MAOIs), or SSRIs.⁷⁻¹³ Eleven double-blind controlled trials of lithium augmentation in depression have been published; of those, 10 reported the observed response rate, which averaged 52% for a total of 135 lithium-treated patients.¹³⁻²⁴ Why is it that in spite of these studies, lithium is not often used? In 2 studies, lithium led to little antidepressant response when added to SSRIs.^{15,19} Furthermore, there is a risk of toxicity with lithium,²⁵ and a significant proportion of lithium-treated patients may report bothersome side effects, particularly patients who are used to the

fairly benign side effect profile of the SSRIs. Because of the need for blood monitoring and the risk of hypothyroidism, significant weight gain, and nephrotoxicity, lithium augmentation is often perceived by patients and clinicians to be not as user-friendly as other augmentation strategies. All of these reasons might contribute to lithium's diminished popularity among clinicians.

Thyroid Hormone

In depression studies, liothyronine (T_3) has been used in preference to thyroxine (T_4) because of its rapid onset and offset of action.²⁶ T_3 augmentation, in doses of 25 to 50 $\mu\text{g}/\text{day}$, has been used successfully among depressed patients refractory to TCAs.^{17,27} This strategy does not appear to be very popular today,⁵ perhaps because all published studies concern TCAs and not SSRIs²⁷ or because thyroid augmentation is associated with the possible side effects of nervousness and insomnia.

Buspirone

A commonly used strategy in treatment-resistant depressed patients is buspirone augmentation. Buspirone is a typically well-tolerated anti-anxiety drug, with serotonin-1A (5-HT_{1A}) partial agonist properties. Studies using 5 to 15 mg twice a day of buspirone have shown significant improvement in treatment-resistant patients.²⁸⁻³¹ The main issue concerning the use of buspirone augmentation is its efficacy. In fact, in 1 study,³² the response rate was very low among depressed patients with treatment-resistant depression, and the only placebo-controlled study in treatment-resistant depression comparing buspirone and placebo augmentation³³ found no statistically significant difference in response rates between these 2 treatments (51% vs. 47%, respectively). One possible advantage of buspirone augmentation is that the addition of this compound has been shown to be more effective than placebo in alleviating SSRI-induced sexual dysfunction among treatment-resistant depressed patients.³⁴

Pindolol

Pindolol augmentation is rarely used in the United States, but is relatively more popular in Europe and Canada. Pindolol is a β -blocker and a 5-HT_{1A} antagonist. A dose of 2.5 mg 3 times a day has been used in most studies. This agent has generated a lot of interest because it has been shown to accelerate antidepressant response when combined with SSRIs in some,³⁵⁻³⁹ but not all⁴⁰ the studies. A study by Moreno and colleagues⁴¹ found no response among 10 refractory depressed patients, and a study by Perez and colleagues⁴² showed no difference from placebo in a very short (10-day) trial of augmentation in a refractory depressed population. Another issue concerning the use of this augmentation strategy is that findings by Blier and Bergeron³⁹ have shown some increased irritability with the use of pindolol in treatment-resistant depression.

Dopaminergic Drugs

Augmentation with dopaminergic drugs is an interesting strategy. In an open trial, Bouckoms and Mangini⁴³ used with some success the antiparkinsonian drug pergolide, 0.25 to 2 mg/day. Similarly, there are reports of the usefulness of antidepressant augmentation with the dopaminergic drugs amantadine (100–200 mg twice a day)⁴⁴ and pramipexole (0.125–0.25 mg 3 times a day).⁴⁵ A recent prospective, open study of pramipexole (mean dose = 0.84 mg/day) augmentation of TCAs and SSRIs showed a 55% response rate among 31 inpatients with unipolar or bipolar depression.⁴⁶ Unfortunately, these studies concerning the augmentation of antidepressants with dopaminergic agents are uncontrolled and have relatively small sample sizes. The effectiveness of these augmenting agents, therefore, remains to be established. The use of dopaminergic drugs as augmentors of antidepressants may offer a theoretical advantage in that dopamine in animal models may stimulate sexual function and that these agents have been shown anecdotally to alleviate the sexual dysfunction induced by SSRIs.⁴⁵

Psychostimulants

In line with the potential role of dopaminergic agents as augmentors of antidepressants, psychostimulants, which have significant effects on dopamine neurotransmission, have been used to augment TCAs,⁴⁷ MAOIs,⁴⁸ SSRIs,^{49,50} and even venlafaxine.⁵¹ Clinicians typically use methylphenidate, 10 to 40 mg/day, or dextroamphetamine, 5 to 20 mg/day, in divided doses. The main issues concerning the use of psychostimulant augmentation are the potential for abuse in some patients with history of substance abuse and the relatively short half-life of psychostimulants. Psychostimulants may also worsen anxiety and irritability and may cause significant insomnia; therefore, it is important to prescribe the use of stimulants earlier and not later during the day. Even though the response may be transient,⁴⁸ these agents tend to work quite rapidly as augmentors.

Modafinil

Modafinil is a novel psychostimulant with pharmacologic actions somewhat different from those of the amphetamines. In a retrospective case series, Menza et al.⁵² reported the usefulness of modafinil (in doses up to 200 mg/day) as an adjunct to antidepressants in refractory depression. A recent report by DeBattista et al.⁵³ showed that 57% of 14 patients not responding to SSRIs or venlafaxine regarded themselves as much improved following augmentation with up to 400 mg/day of modafinil. The effectiveness of modafinil as an augmenting agent remains to be established, since these studies concerning its use are uncontrolled and have relatively small sample sizes.

Atypical Antipsychotics

Both risperidone⁵⁴ and olanzapine⁵⁵ have shown good responses in some small trials in SSRI nonresponders. The

typical doses in augmentation of antidepressants are 0.5 to 2 mg/day for risperidone and 5 to 20 mg/day for olanzapine. In addition, olanzapine augmentation has been shown to be efficacious in a placebo-controlled study of refractory obsessive-compulsive disorder,⁵⁶ and the combination of fluoxetine and olanzapine has produced marked increases in the levels of dopamine, serotonin, and norepinephrine in the prefrontal cortex of the rat.⁵⁷ The rapid antianxiety and anti-irritability effects of these drugs have made them relatively popular among clinicians in the treatment of agitated or insomniac refractory patients. The main disadvantage of these strategies is the risk of sedation and weight gain.

Anticonvulsants

Many of the anticonvulsants used in bipolar illness (i.e., valproic acid, carbamazepine, lamotrigine, gabapentin, and topiramate) are also used as adjuncts in resistant unipolar depression, although there are no studies in the literature on this strategy. The main issues with this strategy are sedation and, in the case of valproic acid and carbamazepine, the need for blood monitoring.

Inositol

Despite initial anecdotal positive reports of the usefulness of augmentation of antidepressants with doses of inositol up to 12 g/day, a recent controlled, double-blind augmentation trial did not support its use in SSRI treatment failures,⁵⁸ and a study by Levine et al.⁵⁹ showed no difference in outcome between patients treated with SSRIs and placebo versus those treated with SSRIs and inositol.

Opiates

There is very modest evidence, mostly based on case reports and case series, for the usefulness of augmentation of antidepressants with opiates, such as oxycodone, oxycodone,⁶⁰ and buprenorphine.⁶¹ The lack of adequate studies and the potential risk for abuse markedly limit the use of these augmenting agents.

Estrogen

Estrogen exerts profound effects on behavior by interacting with neuronal estrogen receptors.⁶² There is mostly anecdotal evidence for the efficacy of estrogen augmentation of antidepressants in resistant depression among postmenopausal women. In addition, as pointed out by Stahl⁶³ in his review of the literature, there are no guidelines on how to optimize antidepressant administration with estrogen, especially in women insufficiently responsive to antidepressants.

Dehydroepiandrosterone (DHEA)

DHEA, a major circulating corticosteroid in humans, has an unclear physiologic role. In addition to serving as a precursor to testosterone and estrogen, DHEA and its sulfated metabolite, DHEA-S, most likely have important

biological roles and have been hypothesized to be involved in regulating mood and sense of well-being.⁶⁴ A very small, preliminary, double-blind study suggests its usefulness up to 90 mg/day as an adjunct to antidepressants in refractory depression.⁶⁴ Further studies are clearly necessary, given the small number of patients studied.

Folate and S-Adenosyl-Methionine (S-AMe)

Folate, in particular its active form methyltetrahydrofolate (MTHF), and S-AMe are compounds closely involved in the one carbon cycle and in methylation processes of the brain. These compounds have been studied extensively in depression, and the literature suggests that they may have antidepressant properties.^{65,66} An open trial of methylfolate (up to 30 mg/day) in SSRI-refractory patients suggested its usefulness as an adjunct,⁶⁷ and a recent study by Coppen and Bailey⁶⁸ showed that adding folate (0.5 mg/day) to fluoxetine led to significantly higher response rates among depressed women (but not among depressed men) than fluoxetine plus placebo. A double-blind study showed an earlier onset of efficacy among patients receiving treatment with the TCA imipramine plus S-AMe compared with patients treated with imipramine and placebo.⁶⁹ However, there have been no studies of S-AMe augmentation of antidepressants in resistant depression, despite some positive anecdotal experiences.

Omega-3 Fatty Acids

Given the recent report of the usefulness of omega-3 fatty acids in improving the short-term course of illness among patients with bipolar disorder,⁷⁰ there has been an increased interest in the use of natural compounds as augmentors of antidepressants in treatment-resistant major depressive disorder. Unfortunately, there are no published studies of the use of these augmenting agents.

Table 1 provides a summary of the pertinent review of the literature concerning augmentation strategies in treatment-resistant depression.

COMBINATION STRATEGIES

General Principles

Combination strategies are those involving the concomitant use of 2 agents with well-established antidepressant efficacy. Although the combination of MAOIs and TCAs was used in the 1970s and early 1980s in treatment-resistant depression, the risk of lethal hypertensive crises related to drug-drug interactions and the introduction of newer antidepressants have led to the disappearance of this combination from clinical practice. The typical rationale of combination strategies is that of broadening the central nervous system (CNS) effect by combining agents affecting different neurotransmitter systems. While there are numerous double-blind studies of augmentation strategies, there are only 2 double-blind studies of combination

Table 1. Overview of Augmentation Strategies^a

Efficacy	Augmentation Strategy
Clear	Lithium, T ₃
Suggested	Dopaminergic agents, psychostimulants, atypical antipsychotics, folate/methylfolate
Anecdotal	Modafinil, anticonvulsants, opiates, S-AMe, DHEA, estrogens
Disputed	Buspirone, pindolol, inositol

^aAbbreviations: DHEA = dehydroepiandrosterone, S-AMe = S-adenosyl-methionine, T₃ = liothyronine.

strategies, reflecting the need for further study in this area. It appears that the improvement following the combination of antidepressants tends to occur within 4 to 6 weeks, so it may be premature to decide in the first few days or couple of weeks whether a combination strategy is working. Almost all the studies on the efficacy of these strategies have focused on the short-term outcome, and very little is known about the minimum duration of combination trials in responders to such strategies. A typical approach is to maintain the combination for 6 to 9 months after obtaining remission and then to attempt a gradual discontinuation of 1 of the 2 antidepressants.

Bupropion and SSRIs

As mentioned above, bupropion (sustained-release formulation, 100–150 mg once or twice a day) combined with SSRIs was the first strategy chosen by the psychiatrists that we surveyed.⁵ On the other hand, the evidence for this combination is based primarily on anecdotal reports, case series, or small open trials.^{71–74} The main disadvantages of this approach are that the combination of bupropion and SSRIs may lead to tremor⁷³ or panic attacks.⁷⁵ However, the positive effects of bupropion on SSRI-induced sexual dysfunction reported in some studies^{76,77} may be a significant advantage for this strategy.

Mirtazapine and SSRIs

Mirtazapine is a dual-action antidepressant that increases both serotonergic and noradrenergic activity by blocking the α_2 -adrenergic autoreceptors and heteroreceptors and the serotonergic 5-HT₂ and 5-HT₃ receptors. Mirtazapine (15–30 mg q.h.s.) combined with SSRIs has been reported to be helpful in an open study of nonresponders to SSRIs⁷⁸ and to be more effective than placebo plus SSRIs in a subsequent double-blind study of refractory depressed patients.⁷⁹ A recent study by Debonnel et al.⁸⁰ showed a significantly higher response rate to the combination of paroxetine and mirtazapine than monotherapy with either drug and a 64% response rate to the switch to combination therapy for patients not responding to monotherapy. The combination of mirtazapine and SSRIs may also help manage SSRI-induced sexual dysfunction.⁸¹ The main disadvantages of this strategy are the weight gain and sedation that have been reported with its use.⁷⁸

Desipramine or Other TCAs and SSRIs

An early study by Nelson et al.⁸² showed that the TCA-plus-SSRI combination may produce a rapid onset of action, while a more recent study by the same author⁸³ has shown that remission rates are significantly higher with desipramine plus fluoxetine than with either drug alone. This is consistent with reports that desipramine and other TCAs were effective in combination with SSRIs in small cohorts of patients.^{84–86} The main issue related to combining TCAs with SSRIs is that TCAs are substrates of the cytochrome P450 2D6 isoenzyme (CYP2D6), so there may be accumulation of TCAs when coadministered with SSRIs, which inhibit this pathway, potentially leading to cardiac toxicity. Low doses of TCAs (25–75 mg/day) are therefore typically used, and monitoring of blood TCA levels is necessary. Despite the promising response rates reported in previous open trials, in a double-blind study from our group,¹⁵ we observed fairly low response rates with desipramine (up to 50 mg/day) combined with fluoxetine among patients who had not responded to 8 weeks of fluoxetine, 20 mg/day.

Reboxetine and SSRIs

After an initial anecdotal report from our group⁸⁷ that the addition of reboxetine, a relatively selective norepinephrine reuptake inhibitor, was helpful in patients resistant to SSRI treatment, 2 open trials, using doses up to 8 mg/day, have suggested the usefulness of this agent combined with SSRIs in refractory depression.^{88,89} The hypothesis by Nelson⁹⁰ that combining drugs that affect both serotonin and norepinephrine may be uniquely helpful among nonresponders to drugs that affect only the serotonergic system may provide further support to the use of this strategy. Furthermore, there is one drug-drug interaction study of fluoxetine and reboxetine suggesting safety of this combination.⁹¹

Nefazodone and SSRIs

There have been only anecdotal reports suggesting the efficacy of combining SSRIs with nefazodone, typically 100 or 200 mg twice a day. One possible issue concerning this strategy is related to some reports of serotonin syndrome,^{92,93} not particularly severe, due to the fact that nefazodone is a mildly potent uptake blocker of serotonin. The biotransformation pathways of nefazodone are mediated mainly by the CYP3A system, whereas clearance of meta-chlorophenylpiperazine (*m*-CPP), a nefazodone metabolite, is mediated by CYP2D6.⁹⁴ Therefore, when nefazodone is coadministered with SSRIs that inhibit the CYP2D6 system, there may be an accumulation of *m*-CPP, which by itself may cause some irritability and anxiety in some patients.⁹⁵ The advantage of adding nefazodone to SSRIs in the event of nonresponse is that it has been shown, again anecdotally, to alleviate sexual dysfunction related to treatment with SSRIs.⁹⁶

Table 2. Overview of Combination Strategies^a

Efficacy	Combination Strategy
Suggested	Bupropion and SSRIs, mirtazapine and SSRIs, desipramine or TCAs and SSRIs, reboxetine and SSRIs
Anecdotal	Venlafaxine and SSRIs, nefazodone and SSRIs
Disputed	SSRIs and SSRIs

^aAbbreviations: SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Venlafaxine and SSRIs

There are only anecdotal reports of venlafaxine augmentation (75–300 mg/day) in SSRI nonresponders. The main disadvantage is that venlafaxine is a substrate of CYP2D6, and there have been reports of accumulation of venlafaxine when coadministered with some SSRIs inhibiting the 2D6 pathway, leading to serotonin syndrome⁹⁷ or to marked blood pressure elevation and severe anticholinergic side effects.⁹⁸

SSRI Plus Another SSRI

Given that SSRIs vary in potency and specificity of serotonin reuptake inhibition in vitro, that paroxetine and fluoxetine are relatively more potent norepinephrine uptake inhibitors than the other SSRIs, and that sertraline is a relatively more potent dopamine uptake inhibitor than the other SSRIs,⁹⁹ it is not surprising that SSRIs have been anecdotally reported to be useful when combined with other SSRIs¹⁰⁰ and that this strategy has been reported to be infrequently used by clinicians in a recent survey.⁴ The main disadvantages of this approach are an increase in the intensity of serotonergic side effects and a theoretical risk of serotonin syndrome.¹⁰¹ A report by Bondolfi and colleagues¹⁰⁰ suggests that there may be an interesting drug-drug interaction when fluvoxamine is combined with citalopram, as the addition of fluvoxamine increases the ratio of S-citalopram versus the R-citalopram, with S-citalopram being a more potent uptake inhibitor of serotonin.

Table 2 provides a summary of the pertinent review of the literature concerning combination strategies in treatment-resistant depression.

SUMMARY

In conclusion, many augmentation and combination strategies are available to psychopharmacologists and psychiatrists. Most of these strategies appear to be relatively safe and effective approaches to treatment-resistant or intolerant patients, although there is a paucity of controlled studies to support their efficacy. Most of these strategies aim at obtaining a different neurochemical effect than the one obtained with the antidepressant that has not produced adequate response. While drug-drug interactions may limit the use of some of the combination strategies, the potential loss of partial benefit from the failed drug may

increase their acceptability. Further studies are clearly needed to evaluate the comparative efficacy and tolerability of these different strategies.

Drug names: amantadine (Symmetrel and others), buprenorphine (Buprenex), bupropion (Wellbutrin), buspirone (BuSpar), carbamazepine (Tegretol and others), citalopram (Celexa), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), inositol (Megadose and others), lamotrigine (Lamictal), liothyronine (Cytomel, Triostat), methylphenidate (Ritalin and others), mirtazapine (Remeron), modafinil (Provigil), nefazodone (Serzone), olanzapine (Zyprexa), oxycodone (Percodan and others), oxymorphone (Numorphan), paroxetine (Paxil), pergolide (Permax), pramipexole (Mirapex), risperidone (Risperdal), sertraline (Zoloft), L-thyroxine (Levothroid, Synthroid), topiramate (Topamax), valproic acid (Depakene and others), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, amantadine, buprenorphine, buspirone, carbamazepine, dextroamphetamine, gabapentin, inositol, lamotrigine, liothyronine, methylphenidate, modafinil, olanzapine, oxycodone, oxymorphone, pergolide, pramipexole, risperidone, L-thyroxine, topiramate, and valproic acid are not approved by the U.S. Food and Drug Administration for augmentation of antidepressants; and bupropion, citalopram, desipramine, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine are not approved for combination treatment in depression.

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