Antidepressant Augmentation: Conclusions and Recommendations

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All of the strategies reviewed in this supplement warrant particular attention because they either have a long history of use or have recently become more widely cited in the literature and are used increasingly in clinical practice. These strategies to augment inadequate antidepressant response include the adjunct use of lithium, thyroid, anxiolytics, pindolol, anticonvulsants, dopamine agonists, stimulants, and supplemental antidepressants.

In their articles, the authors conclude that each of the strategies they reviewed has been shown to enhance the response to antidepressant drugs. There is, however, no basis to conclude that any one strategy is more often effective than the others. As Joffe[1] (this supplement) points out in his discussion, "there is no evidence to guide the decision about which augmentation strategy is preferable at which stage of treatment or which may be particularly useful in a particular patient group or subtype of depression." The absence of controlled trials that directly compare the treatments makes it difficult to rank the options in an algorithmic fashion. Based on the literature, all interventions might be effective in up to about 60% of cases, or be no more effective than placebo. This is evident for the best-studied add-on agents, lithium and thyroid. In the nine placebo-controlled studies of lithium augmentation reviewed by Rouillon and Gorwood[2] in this supplement, three were inconclusive. A review of open studies of T_3 response rates by Joffe[1] shows that the results have varied from as low as 25% to almost 100%. A critical review of lithium and thyroid augmentation concluded that efficacy was not supported by the clinical trials, mainly due to methodological considerations.[3]

There are, nevertheless, differences in each approach with respect to safety and tolerability. In the absence of a well-established augmentation algorithm based on efficacy, the significance of other factors becomes more prominent. Decisions about potential interventions need to be made with regard to the patient's clinical status and the benefits and risks associated with each add-on agent.

Thus, to provide some basis for selecting one strategy, certain factors need to be considered. These include:

1. The nature of the evidence regarding efficacy. Higher levels of evidence reflect the availability of double-blind trials in addition to open-label studies and anecdotal reports
2. Safety
3. Tolerability

The various clinical considerations are summarized for each treatment approach in Table 1.

LITHIUM

Lithium augmentation has the largest body of evidence to support its effectiveness. It is the best-established and probably most frequently used treatment for antidepressant nonresponse. Side effects and toxicity can, however, occur even at the lower doses used in augmentation. Accordingly, monitoring of blood lithium levels, thyroid status, and renal function do add a layer of cost and inconvenience to the use of lithium.

THYROID HORMONE

As for lithium, there is an extensive body of research data for thyroid hormone that addresses the safety and efficacy of its use. An advantage of using T_3 is that a response can be evident within a few days. The therapeutic effects of T_3 should be evident within 3 weeks. Few patients will respond after that time. It is also now recognized that the necessary dose is 25 µg/day, a dose that generally does not produce adverse effects.[4] The major disadvantages of thyroid are that it does require laboratory monitoring, a consideration that adds cost and complexity to the treatment.

BUSPIRONE

Considerable preclinical and clinical evidence suggests that buspirone possesses intrinsic antidepressant activity. These effects have never been tested in placebo-controlled

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Table 1. Clinical Considerations for Selecting Antidepressant Augmentation Strategies*

Treatment	Level of Supporting Evidence	Safety	Tolerability	Cautions or Special Monitoring
Lithium	+++	++	++	Lithium levels, thyroid function, and renal function monitoring
Thyroid	+++	++	++	Thyroid function monitoring
Buspirone	++	+++	+++	No specific safety concerns or need for special laboratory monitoring
Pindolol	++	+	++	Blood pressure and heart rate monitoring. Caution in patients with asthma, severe allergies, and cardiac conduction problems
Dopamine agonists and stimulants	+	+	+	Abuse, regulatory concerns. Activation, nausea, blood pressure changes
Anticonvulsants	+	+	++	Pharmacokinetic interactions
Antidepressant combinations	+	+	+	Safety varies according to combination. Risk of drug interactions requires plasma monitoring

*Symbols: +++ = very positive, ++ = positive, + = problematic.

comparisons with standard antidepressants, but reports have continued to appear in the literature to the effect that the addition of buspirone to antidepressants produces an antidepressant effect in patients not responding to the treatment. Most clinical experience and published reports have involved augmentation of serotonin selective reuptake inhibitors (SSRIs). Accounts of buspirone-associated enhancement of response in patients being treated for depressive spectrum disorders and the apparent effectiveness of a pindolol-buspirone combination have generated further interest in this approach.

The anecdotal reports and open studies of buspirone suggest response rates comparable to those found with lithium and thyroid. Properties of buspirone that increase its relative rank on the list of augmentation agents are its remarkable safety and the absence of need for any special laboratory testing. The data supporting the efficacy of buspirone, while highly consistent and interesting, would benefit from positive findings in double-blind, controlled studies.[5]

BENZODIAZEPINES

Benzodiazepines appear to complement treatment with antidepressants. Prescription of benzodiazepines in the treatment of depression is largely limited to helping to manage the symptoms of agitation, anxiety, and insomnia that accompany depression. Augmentation for the purpose of converting nonresponders or partial responders is not documented in the literature.

PINDOLOL

Pindolol is a recent addition to the list of drugs used for augmentation. Many clinicians are still surprised to find a β-blocker included on a list of treatments for depression, considering that these agents have been cited in the past as a cause of depression and increased antidepressant use. Yet, both open-label and double-blind studies suggest that pindolol is effective in both accelerating the rate of response to antidepressants and in converting nonresponders to responders. Like buspirone, pindolol plays a homeostatic role in controlling the levels of serotonin in the extracellular space. The addition of pindolol blocks the decrease in serotonergic neuronal activity associated with SSRIs, thus possibly enhancing the action of these drugs. Pindolol is generally well tolerated at the doses used for augmentation and has few contraindications. Pindolol does carry a potential risk when used by patients with asthma or severe allergies. It can also produce bradycardia and orthostatic hypotension. This intervention is not without controversy—which has been fueled by a recent double-blind study that showed lack of efficacy for pindolol in augmentation.[6] A more recent controlled study, however, found pindolol to be effective and well tolerated.[7]

ANTIDEPRESSANT SUPPLEMENTATION

Since every class of antidepressants differs to some extent in its effects on monoamine neurotransmitter activity—and in other effects—there has been a rationale for combining antidepressant drugs. This is probably the most appealing strategy on an intuitive level. The most common strategies involve the combination of drugs that are serotonergic and noradrenergic. This is a so-called "broad spectrum" approach that presumes that both norepinephrine and serotonin are involved in the pathogenesis of depression. Although limited in number of subjects, studies of SSRI–tricyclic antidepressant (TCA) or SSRI-bupropion combinations show effectiveness in highly refractory patients. The major risk with this strategy is that SSRIs can raise levels of tricyclic agents. Blood levels of the tricyclic need to be monitored. This combination may be especially useful in an inpatient setting, since blood levels, vital signs, and cardiac status can be monitored. Arrhythmias and delirium represent potentially serious consequences of elevated tricyclic levels.

DOPAMINERGIC AGENTS AND STIMULANTS

Dopaminergic agents and stimulants tend to be underused because of their potential for abuse. This is despite

the fact that doses remain stable even after long-term use and are rarely abused in the context of augmentation. As noted by Nierenberg and colleagues,[8] the information available on the potential risks of combining these agents with antidepressants is limited. Controlled data, however, are lacking. Nausea, vomiting, blood pressure changes, activation, and psychosis may occur in some patients, especially when higher doses are used.

ANTICONVULSANTS

The anticonvulsants represent a diverse group of agents. Because of their CNS activity, it is not surprising that they can also have effects on mood. Valproate and carbamazepine both have been reported to act as mood stabilizers and antidepressants. They are rarely used in the latter role because of their side effects and an absence of supporting research. Both agents also require laboratory monitoring. More recently, the anticonvulsants lamotrigine and gabapentin have been reported to produce antimanic and antidepressant activity.[9] Gabapentin appears to be both safe and well tolerated, but lamotrigine requires careful dosing and close monitoring because of potentially serious skin rash. Neither of these drugs has been studied as an augmentation agent.

UNANSWERED QUESTIONS

A number of questions about augmentation remain unanswered. Foremost among these are the following: Is it better to switch to a second primary antidepressant than to add a second drug? How many different antidepressants should be tried before resorting to augmentation? Once started, how long should adjunctive medication be continued? Which approach carries the highest probability of success? Do some combinations produce dramatic improvement when they work, but have lower response rates than the other interventions? Do patient characteristics exist that might predict response to any particular treatment? Are some combinations better at improving the speed of response, others in inducing a response in refractory cases, and others at preventing recurrence?

CONCLUSIONS

It is difficult to explain why different clinicians and researchers have formed disparate perceptions about the relative merits of augmentation strategies. It may depend on highly subjective factors, such as a highly positive patient response to an intervention the first time it is used. Isaac and Tome[10] have commented on these "rapid, almost miraculous sustained symptomatic recoveries" after addition of a second agent. This has been described as the conversion experience, wherein the clinician subsequently develops a bias toward the use of that combination in the future.

Despite the influence of clinical experience, there is no substitute for well-done double-blind, placebo-controlled studies. Yet, with respect to augmentation, the investment of time and money needed to study large populations treated with different strategies has not been and is unlikely to be forthcoming. As Bodkin and associates[11] recently observed with respect to treatment alternatives for partially responsive depressed patients, research to demonstrate and quantify the possible benefits, risks, and costs of each of the varied approaches is virtually nonexistent.

Thus, there is no consensus algorithm for nonresponse to antidepressants. In this supplement, Thase and associates[12] include these options as the common and better-studied augmentation strategies: lithium, thyroid, buspirone, stimulants, and pindolol. Potential, experimental, or targeted augmentation strategies are antidepressant combinations, estrogen, testosterone, dexamethasone, ketoconazole, and dopamine agonists. Amsterdam and Horning-Rohan[13] have offered general criteria for a strategy to warrant inclusion in an empirically based algorithm for treatment nonresponse. A particular intervention, they suggest, "should be (1) shown to be either superior to a comparative treatment in controlled drug trials or superior to other treatments in a series of uncontrolled case reports and (2) based on sound psychopharmacologic theory." They do not recommend any one augmentation strategy as being first-line per se, but rather they offer examples of options that appear to be comparable in terms of efficacy. Those options may, however, vary according to their relative risk:benefit ratio based on the clinical profile of the patient.

Treatment decisions involving patients who do not respond to initial antidepressant therapy thus need to be made with regard to available evidence and factors such as relative safety and convenience. By those standards, some of the more established interventions, such as lithium and thyroid hormone, as a practical matter, may not be as useful as some other strategies that require no special monitoring and have few serious side effects.

Drug names: bupropion (Wellbutrin), buspirone (BuSpar), carbamazepine (Tegretol and others), dexamethasone (Decadron and others), estrogen (Premarin and others), gabapentin (Neurontin), ketoconazole (Nizoral), lamotrigine (Lamictal), pindolol (Visken), testosterone (Oreton and others).

REFERENCES

1. Joffe RT. The use of thyroid supplements to augment antidepressant medication. J Clin Psychiatry 1998;59(suppl 5):26–29
2. Rouillon F, Gorwood P. The use of lithium to augment antidepressant medication. J Clin Psychiatry 1998;59(suppl 5):32–39
3. Patten SB, Lupin DA, Boucher SA, et al. Pharmacologic management of refractory depression. Can Med Assoc J 1992;146:483–487
4. Sokolov ST, Levitt AJ, Joffe RT. Thyroid hormone levels before unsuccessful antidepressant therapy are associated with later response to T3 augmentation. Psychiatry Res 1997;69:203–206
5. Joffe RT, Levitt AJ, Sokolov TH. Augmentation strategies: focus on anxiolytics. J Clin Psychiatry 1996;57(suppl 7):25–31
6. Berman RM, Darnell AM, Miller HL, et al. Effect of pindolol in hastening

response to fluoxetine in the treatment of major depression: a double-blind, placebo-controlled trial. Am J Psychiatry 1997;154:37–43
7. Perez V, Gilaberte I, Faries D, et al. Randomized, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. Lancet 1997;349:1594–1597
8. Nierenberg AA, Dougherty D, Rosenbaum JF. Dopaminergic agents and stimulants as antidepressant augmentation strategies. J Clin Psychiatry 1998;59(suppl 5):60–63
9. Sussman N. Gabapentin and lamotrigine in the treatment of bipolar disorder. Primary Psychiatry 1997;4:25–42
10. Isaac MT, Tome MB. Selective serotonin reuptake inhibitors plus pindolol [letter]. Lancet 1997;350:288–289
11. Bodkin JA, Lasser RA, Wines JD, et al. Combining serotonin reuptake inhibitors and bupropion in partial responders to antidepressant monotherapy. J Clin Psychiatry 1997;58:137–145
12. Thase ME, Howland RH, Friedman ES. Treating antidepressant nonresponders with augmentation strategies: an overview. J Clin Psychiatry 1998;59(suppl 5):5–12
13. Amsterdam JD, Hornig-Rohan M. Treatment algorithms in treatment-resistant depression. Psychiatr Clin North Am 1996;19:371–386