Treating Antidepressant Nonresponders With Augmentation Strategies: An Overview

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This paper provides an overview of antidepressant nonresponse and the role of augmentation strategies in the management of treatment-resistant depression. When effective, the more widely used augmentation strategies, including lithium salts, thyroid hormones, pindolol, buspirone, and psychostimulants, share two important advantages when compared with "switching" strategies: avoidance of ill effects associated with discontinuing the initial antidepressant and rapidity of onset of action. Ideally, advances in the understanding of the neurobiology of mood disorders and mechanisms of antidepressant response will permit a more efficient and specific matching between patient, initial antidepressant, and subsequent strategy for enhancing response to treatment.

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Patients with major depressive disorder respond variably and, at times, unpredictably to different antidepressant treatments. Moreover, among those who begin a trial of antidepressant medication, only about 40% to 50% will both remain on the therapy for 4 to 6 weeks and respond to that medication.[1,2] Development of effective alternate strategies for antidepressant nonresponders has, by necessity, become an important area of clinical research. Various augmentation strategies are often used to treat patients who do not respond to monotherapies.[1,2] This paper will review these strategies in order to set the stage for the subsequent papers on specific antidepressant augmentation strategies.

DEFINING NONRESPONSE

Patients generally need to experience at least a 40% to 50% reduction of symptom severity during the first 6 weeks of therapy in order for the treatment outcome to be considered a success.[3] Unfortunately, busy practitioners seldom quantify symptomatic outcome, and, not infrequently, progress is overestimated. Patients thus may remain on ineffective dosages of antidepressants for weeks without appropriate changes in the treatment plan. Periodic administration of rating scales such as the patient-rated Beck Depression Inventory (BDI),[4] the clinician-administered Hamilton Rating Scale for Depression (HAM-D),[5] or the Inventory for Depressive Symptomatology (IDS)[6] (which has both patient and clinician versions) could provide clinicians reliable, quantitative assessments of their patients' symptomatic outcome. The patient and clinician Clinical Global Impressions (CGI) scales[7] are even simpler, 7-point, Likert-type rating scales, with "much" (+2) and "very much" (+3) improvement scores representing the desired outcomes. Alternatively, the Global Assessment of Functioning (GAF)[8] and its ancestor, the Global Assessment Scale (GAS),[9] provide straightforward 0–100 point ratings of overall functional status. One of the few welcomed benefits of managed behavioral health care and capitation is the growing interest in documenting and monitoring symptomatic outcomes as a means to prompt more timely changes in treatment regimens.

Achieving a significant reduction in symptom scores is only the initial goal of antidepressant pharmacotherapy. Ideally, such a treatment response is followed within a few weeks by a more complete remission of symptoms. A remission describes a reduction of symptom scores and an improvement of global functioning to levels that are virtually indistinguishable from those of people who are not depressed.[10] Failure to achieve a full remission conveys an increased risk of relapse as well as a greater level of persistent social and vocational impairment.[11] A partial

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remission therefore warrants consideration for revisions in the treatment plan.

Ongoing treatment aimed at producing a complete and sustained remission and preventing relapse is called continuation phase therapy.[12] In recent years, a period of sustained remission of 4 to 6 months' duration has been presumed to be necessary before the patient can be said to have recovered.[12] This duration has been estimated by examining relapse rates following 4 to 8 weeks of acute phase antidepressant therapy.[13] Typically, the cumulative probability of relapse following discontinuation of acute phase antidepressant therapy increases rapidly up to about 6 months, at which point the slope of the curve decreases significantly.

Conceptually, relapse represents renewed activity of the index (treated) depressive episode, whereas a recovery denotes the end of that episode. If this assumption were fully accurate, most recovered patients could be tapered off antidepressant medications after a reasonable course of continuation therapy without a high risk of relapse. However, a recent study of unipolar depression documented that the risk of recurrence was as high when imipramine was withdrawn after 40 months of remission as it was when comparable patients were withdrawn after only 4 months of treatment.[14] Clearly, the number of months of remission on medication may not lessen risk of recurrence among such vulnerable patients, at least during the first 6 months following antidepressant discontinuation. Therefore, it is possible that patients with highly recurrent depressions may require indefinite or even lifetime prophylactic therapy.[12–15]

Fava[16] has suggested that continuation and maintenance phase pharmacotherapy may actually prolong vulnerability by suppressing, but not reversing, state-dependent neurophysiologic abnormalities associated with depression. This important and provocative hypothesis has not yet been subjected to a definitive empirical test.

CHARACTERISTICS OF ANTIDEPRESSANT NONRESPONDERS

Major depressive disorder is such a heterogeneous condition that it is unreasonable to expect that any particular treatment will be uniformly effective. Although antidepressant response cannot be predicted with a clinically useful degree of precision, a number of replicable correlates of antidepressant nonresponse have been identified.[17,18] Among the subtypes of depression less responsive to tricyclic antidepressants (TCAs), the following are particularly important because they identify patients who are often responsive to alternate treatments (also listed): psychotic depression (i.e., adding a neuroleptic or switching to electroconvulsive therapy [ECT]), bipolar depression (i.e., adding or substituting a mood stabilizer or treating with a monoamine oxidase inhibitor [MAOI] or bupropion), and atypical depressions characterized by reversed neurovegetative features (i.e., switching to a serotonin selective reuptake inhibitor [SSRI], bupropion, or an MAOI).[2]

Other clinical correlates of antidepressant nonresponse are probably better understood as more global indicators of a poorer prognosis.[19] These correlates include most forms of Axis I comorbidity, the more severe and well-established personality (Axis II) disorders, and chronic, burdensome medical diseases (e.g., diabetes, hypertension, osteoarthritis). Substance abuse and dependence are often overlooked by treating physicians (many people are ashamed to reveal their drug or alcohol problem, whereas others flatly deny that the problem exists). When possible, the complicating or comorbid conditions must be treated or stabilized in conjunction with antidepressant therapy. It should be kept in mind that personality pathology may be exaggerated by a protracted, unremitting depressive episode and that an oversimplistic case formulation could result in an underemphasis of alternate pharmacotherapies.[20]

Diagnostic complexity also increases the risk of medication noncompliance, another major determinant of antidepressant nonresponse.[21] Of course, alternate medications also will be unlikely to work if the patient is noncompliant. An approach to patient care providing psychoeducation, frequent inquiry about the type and severity of side effects, and ongoing concern about the frequency of missed doses is the best way to minimize noncompliance.[21]

Noncompliance is particularly problematic for patients who must take complex medication regimens and among those with significant Axis II pathology.[20,21] It is useful to ascertain if the patient's nonadherence is the result of disorganization and globally poor functioning or if it is an act of volitional (willful) noncompliance. In the former case, streamlining dosing schedules and using prompts (e.g., a compartmentalized pill box, reminder notes on the refrigerator or medicine cabinet, or a watch with a digital alarm to denote dosing times) may have beneficial effects.[21]

Pharmacotherapists and collaborating psychotherapists usually must deal more directly with volitional noncompliance. An open discussion with the patient about his or her thoughts and feelings about having depression, needing to take medication, or having to see a psychiatrist may reveal the patient's rationale for noncompliance and creates the opportunity to address misinformation and dysfunctional beliefs about the illness and/or the treatment process.[20,21] Indeed, the skills necessary to build and maintain a strong treatment alliance may be nearly as important to a pharmacotherapist as they are to a psychotherapist.

UNDERSTANDING TREATMENT RESISTANCE

The term *resistance* in psychopharmacology has its roots in both medical microbiology and psychoanalysis. In the former case, the analogy is to a species of infectious

Table 1. Staging Criteria for Treatment-Resistant Depression*

Stage I: Failure of at least one adequate trial of one major class of antidepressant
Stage II: Stage I resistance plus failure of an adequate trial of an antidepressant in a distinctly different class from that used in Stage I
Stage III: Stage II resistance plus failure of an adequate trial of a TCA
Stage IV: Stage III resistance plus failure of an adequate trial of an MAOI
Stage V: Stage IV resistance plus failure of a course of bilateral ECT

*From reference 23.

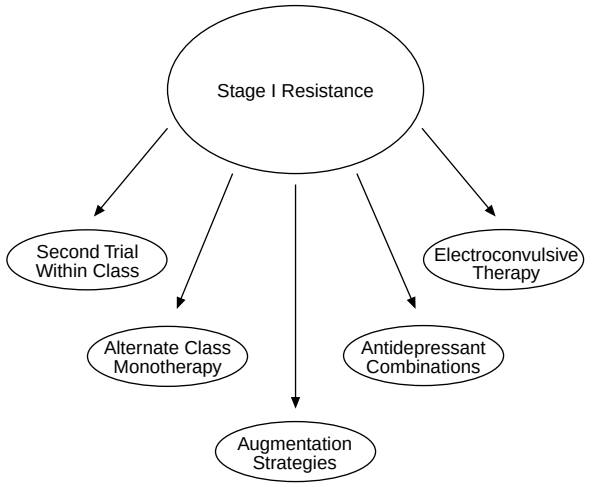
organism that has developed the capacity to withstand the cytotoxic effects of a particular antibiotic. Of course, the psychopharmacologist currently lacks the methodology to explicate the mechanism(s) underlying antidepressant resistance with the precision of the microbiologist. However, knowledge about the neurobiology of antidepressant nonresponse is increasing. For example, patients who do not respond to TCAs do not experience as robust suppression of rapid eye movement sleep as responders, despite comparable blood levels.[22] Nonresponders to antidepressants or ECT also are more likely to manifest persistent hypercortisolism when compared with responders. These examples illustrate how research integrating serial assessments of depressive pathophysiology and treatment response may eventually lead to more specific targets for alternate treatments.

Psychodynamic therapists use the term *resistance* when describing patients who are unable to engage productively in treatment because of unconscious defenses against conflict. This model of resistance is probably more likely to be invoked by frustrated clinicians when the antidepressant nonresponder exhibits disagreeable interpersonal or therapy-interfering behaviors suggestive of more longstanding character pathology.[20] Beyond psychodynamic conflicts, however, the lower probability of antidepressant response observed in personality disordered patients may be attributable to noncompliance (i.e., a conscious process) or a constellation of psychosocial correlates of poor prognosis (i.e., a lower level of social support, greater level of life stress, and poorer coping abilities). Indeed, comorbid personality disorders are associated with the onset of mood disorders at an early age, which in turn conveys higher risks of chronicity and a "loaded" family pedigree.[20] Thus, rather than reflexively viewing personality disordered depressed patients as resisting the treatment process, it may be that complex person-environment interactions have pathoplastic effects that alter treatment responsivity.

STAGING TREATMENT RESISTANCE

In the absence of a compelling unitary theoretical model to guide research on treatment resistance, scientific progress can still be made by careful clinical observations of our patients' phenomenology, clinical course, and treatment response. Thase and Rush[2,23] have proposed a descriptive classification that borrows heavily from the method used by oncologists to stage the clinical progression of malignancies. As summarized in Table 1, this simple approach stages the patient's degree of resistance on the basis of the number and type of prior adequate treatment trials. Selection of alternate treatment strategies may then follow logically from this hierarchical classification by moving from simpler to progressively more complex strategies. The most advanced stage of treatment resistance in this framework, Stage V, is synonymous with the older terms such as refractory or intractable depression.

Figure 1. Treatment Options for Patients Who Fail an Optimal Trial of Antidepressant Medication



Our intention was not to suggest slavish adherence to a particular treatment algorithm. For example, ECT certainly should be considered a first-line treatment for an incapacitated melancholic patient, and MAOIs may be used earlier in the treatment strategy for patients with reversed neurovegetative features. As knowledge about differential therapeutics and mechanisms of action continues to expand, more precise staging models undoubtedly will emerge.

CHARACTERIZING STRATEGIES USING MULTIPLE MEDICATIONS

Depressed people who do not respond adequately to an optimal trial of an antidepressant may be treated in a number of different ways (Figure 1). For example, they may be switched to another antidepressant within the same class, switched to a dissimilar type of antidepressant, treated with ECT, or kept on the ineffective antidepressant and "augmented" by the addition of various psychoactive compounds.[1,2] With at least seven major classes of antidepressants, including multiple FDA-approved agents within three of the classes, as well as a wide array of potential

Table 2. Common and Better Studied Augmentation Strategies

Augmentation Strategy	Decade Introduced	Proposed Mechanism(s) of Action
Stimulant	1960s	Potentiation of noradrenergic neurotransmission Increase of blood TCA levels (?)
Thyroid	1970s	Potentiation of noradrenergic neurotransmission Correction of subclinical hypothyroidism Down-regulation of intracellular thyroid activity
Lithium	1980s	Potentiation of serotonergic neurotransmission Modulation of phosphatidyl-inosital pathway
Buspirone	1990s	Partial 5-HT_{1A} receptor agonism (somatodendritic, heteroceptor, and postsynaptic) α_2-adrenergic antagonism [via metabolite, 1-(2-pyrimidinyl) piperazine]
Pindolol	1990s	Selective 5-HT_{1A} antagonism (somatodendritic)

Table 3. Potential, Experimental, or Targeted Augmentation Strategies

Strategy	Comment/Limitation
Antidepressant combinations	Popular but unproven
Estrogen	Probably only useful for peri- or postmenopausal women
Testosterone	Worrisome side effects for women
Dexamethasone	Probably indicated only to suppress persistent hypercortisolism
Ketoconazole	Same as above
Dopamine agonists	Possibly effective for retarded depressions

augmentors, one seldom encounters a treatment-resistant patient who has failed all viable options.

In the late 1970s and early 1980s, the practice of using multiple medications for treatment of a single psychiatric disorder was anathema. Polypharmacy, which perhaps should have been called polypharmacotherapy, was a standard target of quality assurance reviews as an indicator of poor psychiatric practice. Nevertheless, even in that earlier era there were examples of the rational use of combinations of TCAs, MAOIs, lithium, and neuroleptics for treatment of antidepressant-resistant depression. Over the past 2 decades, the distinction between rational and irrational medication combinations has evolved substantially, such that the term *polypharmacy* should now be reserved for the concomitant prescription of two or more agents from the same class of medications.

What, then, are the current rational antidepressant strategies that employ multiple medications, and which ones are best described as augmentation? At the risk of engaging in an exercise of semantic silliness, we would like to suggest that the term *augmentation* be used to describe only those strategies that are intended to enhance, mechanistically, an ineffective standard antidepressant compound. Such enhancement, in turn, may work via pharmacodynamic or pharmacokinetic actions.

Within this framework, the best-studied or most promising augmentation agents are lithium salts, thyroid hormones, pindolol, buspirone, and the psychostimulants (Table 2).[2] These will be discussed in more detail subsequently. Less common augmentation strategies include the addition of gonadal hormones, anticonvulsants, monoaminergic agonists, and potent glucocorticoids or glucocorticoid synthesis inhibitors (Table 3). These latter approaches probably benefit smaller subgroups of depressed people. For example, estrogen augmentation is generally not used to treat depressed men, and its efficacy may be limited to women who are peri- and postmenopausal. Similarly, the potent synthetic glucocorticoid dexamethasone and the steroid synthesis inhibitor ketoconazole are probably indicated only for treatment of severely depressed patients with persistent hypercortisolism.

Interventions intended to provide complementary clinical effects, such as the addition of a benzodiazepine to help control anxiety or insomnia, do not really augment the mechanism of action of the primary antidepressant treatment. Therefore, we would suggest that these strategies be referred to as *adjunctive therapy*. The use of a second psychotropic medication to reverse treatment-emergent side effects could be viewed as yet another type of adjunctive therapy. The concomitant use of two medications for two different indications is probably best described as *combined therapy*. Examples of combined therapy include the prescription of a mood stabilizer and an antidepressant for treatment of bipolar depression or an antidepressant and a neuroleptic for treatment of psychotic depression. Not all potential additive strategies utilize medication. Phototherapy with bright white light may be added to pharmacotherapy of seasonal depression, and some antidepressant-resistant patients benefit from sustained partial sleep deprivation.[2] This latter approach is labor-intensive and subjectively unpopular and is probably most feasible for treatment of hospitalized patients. The addition of a focused, problem-oriented psychotherapy provides another nonpharmacologic alternative that may be added to enhance the treatment-resistant patient's coping skills, stress management, interpersonal difficulties, or persistent depressive symptoms.[19]

It is not yet clear if using two different antidepressants concurrently is more accurately described as an augmentation or combination therapy. Moreover, it is not certain that the currently popular practice of combining SSRIs with tricyclics, bupropion, nefazodone, or mirtazapine is more effective than the simpler strategy of monotherapy with a broader spectrum antidepressant, such as clomipramine or venlafaxine. Indeed, the practice of combining a

sedating TCA and an MAOI has not been proven to be more efficacious than therapy with an MAOI alone, more than 30 years after the initial applications of this combined strategy.

Sometimes combinations of medication are prescribed to try to speed up or accelerate the time to response. This highly desirable goal may reduce the cost of acute phase therapy, a particular advantage for inpatient treatment, as well as decrease the amount of misery and impairment experienced by the patient. Concomitant therapy with thyroid, lithium, benzodiazepines, and dissimilar antidepressants have all been used to try to accelerate the time to response.[2]

WHEN IS IT TIME TO AUGMENT?

Effective antidepressant pharmacotherapy involves a balance of judgments about the adequacy of the dosage and duration of treatment. If one must err, it usually should be on the side of providing a longer trial at higher dosage before changing treatment strategies. Unless speed of response is paramount, it does not seem reasonable to augment an ineffective antidepressant before first attempting to achieve the maximally tolerated therapeutic dosage.[23] Nevertheless, a series of prolonged courses of ineffective medications at maximal tolerated dosages can be demoralizing to both the patient and the clinician, and researchers are now examining if early response characteristics can be used to predict subsequent outcome 4 or 6 weeks later.

Katz et al.[24] have demonstrated that a constellation of relatively modest improvements during the first week of high-dose TCA therapy can predict the subsequent response of severely depressed inpatients. These correlates, of course, must include an admixture of predictors of response to TCAs and nonspecific factors, because rapid early improvement is also characteristic of placebo response.[25] This method has not yet been applied to depressed outpatients nor to patients treated with newer generation antidepressants. In an early study of fluoxetine treatment (20 mg/day), nonresponse at Week 3 did not predict a more favorable response to upward dosage titration when compared with continued therapy at the lower dosage.[26] Fixed-dosage studies of fluoxetine,[27] sertraline,[28] and paroxetine[29] similarly indicate that there is no advantage for routinely starting patients at higher dosages of the SSRIs. This is not true for all classes of newer antidepressants, however, as venlafaxine shows semilinear dose-response characteristics between 75 mg/day and 375 mg/day.[30]

So, the question remains: when to increase the dosage, when to augment, and when to switch? Fava et al.[31] found that, after 8 weeks of therapy with fluoxetine (20 mg/day), increasing the dosage to 40 or 60 mg/day was more effective than adding low dosages of either lithium or desipramine. Increasing the fluoxetine dosage was particularly effective for patients who had obtained partial responses by Week 8 (i.e., 25%–49% improvement in Hamilton Rating Scale for Depression [HAM-D] scores). In a subsequent paper from the same data set, Nierenberg et al.[32] found that a virtual lack of symptomatic response after 4 weeks of fluoxetine therapy was a strong indicator that a change was necessary. Quitkin et al.[25] similarly found that patients who were "complete nonresponders" to 4 weeks of antidepressant therapy (principally with imipramine or phenelzine, at optimized doses for at least 2 weeks) were unlikely to benefit from 2 more weeks of therapy. Thus, it appears that a 4-week trial at usual clinical doses, followed by at least 1 to 2 more weeks at maximally tolerated dosages, serves as a useful rule of thumb to guide transitions in treatment strategies.

AUGMENTATION VERSUS ALTERNATE MONOTHERAPY

Augmentation strategies have two potential advantages when compared with switching to an alternate monotherapy: avoidance of symptomatic exacerbation resulting from discontinuation of the initial antidepressant and a more rapid response. When effective, the augmentation strategy thus benefits both the patient (i.e., less discomfort, less ill time) and the provider (i.e., fewer office visits may offset the increase in costs of adding a second medication). Moreover, the two best-studied augmentation agents, lithium and L-triiodothyronine (T_3), can be prescribed in generic form, which greatly limits additional drug costs.

Higher drug costs are, however, among the potential disadvantages that augmentation strategies have vis-à-vis alternate monotherapies. Another is confidence in the effectiveness of the strategy. Specifically, all FDA-approved antidepressants have a sounder empirical basis of efficacy, derived from both placebo- and active comparator-controlled clinical trials, than any of the augmentation strategies. Studies of switching antidepressants from an ineffective class to a novel or dissimilar medication typically document response rates at least as high as the better studied augmentation strategies.[2] Moreover, several recent studies suggest that a second SSRI trial after the failure of a classmate, whether due to intolerance or nonresponse, may yield comparable response rates.[33–35]

Following withdrawal of the ineffective initial antidepressant, alternate monotherapies have the additional potential advantages of simplicity, lower risk of drug interactions, and fewer side effects. However, when the initial antidepressant is fluoxetine, the washout is prolonged by the extremely long elimination half-life of norfluoxetine, its active metabolite. This virtually eliminates the possibility of switching from fluoxetine to an MAOI, although a trial with another antidepressant, including either another SSRI or a dissimilar antidepressant with a lower risk of pharmacokinetic and pharmacodynamic interactions (e.g.,

bupropion, venlafaxine, mirtazapine) can be undertaken. Some clinicians prefer to use alternate monotherapies when the patient has had a virtual lack of response (e.g., < 20% improvement on the HAM-D) and augmentation strategies when there has been a partial response at maximally tolerated dosages.[23] Consistent with this practice, the amount of improvement during an initial trial of sertraline was *inversely* correlated with the response to imipramine in a recent double-blind crossover study of patients with chronic depression.[36]

PICKING AN AUGMENTATION STRATEGY

Of all augmentation strategies for treating antidepressant nonresponders, lithium augmentation has received the greatest empirical support and probably could "pass muster" for approval if FDA criteria for registration for this indication were applied.[2] Lithium salts also have a modest primary antidepressant effect, particularly for patients with bipolar spectrum disorders.[37] As a result, it may be justified to continue lithium augmentation for a longer period of time than the other augmentation strategies.[38]

As a large majority of lithium augmentation studies investigated patients treated with TCAs, there is still some concern that lithium augmentation may not be as effective for patients who have not responded to SSRIs.[2] Specifically, there may be little room for enhancement of serotonergic neurotransmission after a high-dose SSRI trial. Potentiation of serotonin-mediated side effects also may be a concern during lithium augmentation of an SSRI.

Thyroid augmentation is one of the oldest strategies. Yet, despite several positive controlled studies,[39,40] it has a checkered past.[41,42] Moreover, practitioners give it relatively low marks for perceived effectiveness.[43] Originally thought to enhance noradrenergic function, T_3 may actually decrease intracellular thyroid function and/or suppress thyrotropin-releasing hormone levels in the brain.[44] Not infrequently, thyroid "augmentation" is effective because the patient has unrecognized subclinical hypothyroidism (i.e., right drug/wrong reason).[44] Thus, a thyroid-stimulating hormone level is a very appropriate part of the workup for an antidepressant nonresponder. Patients at higher risk for thyroid dysfunction include younger women, those who have received lithium, and those who manifest anergia, weight gain, and cold intolerance. Thyroxine (T_4) is typically used instead of T_3 when hormone replacement therapy is intentional.

Stimulant augmentation has an even weaker track record. Psychostimulants may augment antidepressant response via a number of mechanisms, including both pharmacokinetic (increased blood antidepressant levels) and pharmacodynamic (enhancement of noradrenergic or dopaminergic neurotransmission) effects.[45] They may also be useful as an adjunctive therapy (e.g., to improve concentration, energy, libido). Psychostimulants have well-recognized abuse potential, and their augmentation efficacy has not been determined by carefully controlled studies. For this reason, many clinicians reserve stimulant augmentation for treatment of more advanced stages of resistance.[46]

Buspirone[47,48] and pindolol augmentation[49,50] are currently widely used, and randomized controlled clinical trials are underway to establish their efficacy versus placebo. These agents have complementary neurochemical actions on pre- and postsynaptic serotonergic neurotransmission, and, as described by Blier and Bergeron in this supplement, they may also be used together as a "double barreled" augmentation strategy.[51]

HOW LONG SHOULD THE AUGMENTATION STRATEGY BE CONTINUED?

There is little certainty about the optimal length of therapy with any of the augmentation strategies. Sustained treatment with lithium salts does convey some degree of prophylactic efficacy for unipolar depression over and above an augmentation effect.[37] However, no such assumption can be made about buspirone, psychostimulants, pindolol, or thyroid hormone. In fact, beyond the clinical reality that a number of augmentation responders will relapse after the agent is withdrawn,[52] there are essentially no empirical data to help decide whether or not the augmentor should be maintained concomitantly with the antidepressant or tapered after a minimally adequate period of stable remission (e.g., ≤ 4 months).

RESEARCH CONSIDERATIONS

Research on antidepressant nonresponse is difficult to conduct, and, as a result, far fewer well-controlled studies are conducted than are warranted by the public health significance of the problem.[1,2] As illustrated by Nierenberg,[1] at least 200 untreated patients would need to be enrolled in order to conduct an adequately powered, placebo-controlled study of one novel treatment strategy for Stage I–resistant depression. Response to an initial standard antidepressant (e.g., 40%–60%), attrition from the protocol (e.g., 10%–20%), and exclusion of patients because of noncompliance (e.g., 10%–20%) or previously unrecognized serious comorbidities (e.g., 5%–10%) cause a progressive loss of potential subjects. Following this logic to plan a study of Stage IV resistance, at least 1000 new patients would need to begin treatment in order to conduct a single prospective study.

Alternatively, investigators often study patients who present with a history of antidepressant nonresponse, i.e., a sample of convenience. This strategy, however, may be compromised by difficulties ascertaining the adequacy of the patient's prior treatment(s).[1,2] Such studies also typically enroll patients at different stages of antidepressant resistance, introducing a critical source of heterogeneity that

can have marked effects on treatment response rates. For example, ECT response rates are significantly lower in Stage IV resistance than after a single antidepressant failure.[53] Nierenberg et al.[54] similarly found a venlafaxine response rate of 41% among Stage III–resistant depressions, as compared with only 9% among patients who had failed to respond to ECT. It is recommended that future studies focus on groups of patients with more homogeneous treatment histories.

Another methodological issue involves the choice of the comparison group. A valid comparison group must be credible and engender comparable demand characteristics among both patients and clinical staff. Thus, a waiting list or historical control group, in which patients receive continued treatment with an ineffective strategy for a comparable period of time, does not suffice because patients receiving the novel treatment would undoubtedly have higher expectations of improvement.

The most critical question faced by researchers concerns the ethics of exposing patients with a history of treatment nonresponse to a placebo condition.[2] Generally, a placebo condition is justified only if it is necessary to answer a question of sufficient public health significance. It is also essential that the patient understands the consent form and agrees to accept the possible risks associated with a defined period of placebo therapy. These risks can be minimized in a research milieu that provides psychoeducation, careful monitoring, and supportive clinical management. Whenever possible, patients randomly assigned to a placebo group should be given the opportunity to receive the experimental intervention after their participation in the double-blind portion of the study is completed.

Are clinicians eager to refer patients for participation in placebo-controlled trials? Usually not. However, one "reality check" is to ask clinicians to consider the ethics of providing unproven treatments. The patient's hope for symptom relief, coupled with the wish to help to identify more effective interventions for other long-suffering patients, provides both pragmatic and altruistic reasons for research participation.

Research on augmentation strategies is particularly well suited for the ethical use of placebo control groups. For example, the straightforward two-group design that contrasts continued antidepressant therapy plus either placebo or the active augmentation strategy is a very efficient way to determine efficacy. The yield of each study can be increased further by adding blinded crossover (from the ineffective placebo to the active augmentor) and discontinuation (from effective augmentor to a placebo) phases to the protocol.

Once the efficacy of the augmentation strategy is determined relative to placebo, it is important to document relative efficacy. Here the key question is: how effective is the novel augmentation strategy when compared with other relevant options? The augmentation strategy might be contrasted with switching patients to an antidepressant of the same class as the ineffective one, switching to an antidepressant of a dissimilar class, or using another augmentation strategy of proven efficacy. As published open-label treatment studies amply document,[2] the expected outcomes for these active comparators range from as low as 10% to as high as 60%. On average, response rates of 30% to 40% usually can be expected under double-blind conditions.[2] The investigator thus must ensure that the study has a sufficiently large sample size to ensure adequate statistical power to detect clinically meaningful differences in response rates (i.e., 60% vs. 40% or 40% vs. 20%). Sadly, most studies comparing two active strategies do not enroll enough patients to make such a differentiation reliably (i.e., up to 100 patients per group might be needed). Thus, "dead heats" are the rule, not the exception. Collaborative study groups are probably needed to correct this problem.

CONCLUSIONS

A wide variety of strategies are now available to treat depressed patients who do not respond to standard antidepressants. The augmentation strategies are intended to (1) accelerate response, (2) enhance clinical efficacy by treating comorbid conditions or complicating factors, (3) broaden the treatment's neurochemical profile by eliciting complementary pharmacodynamic action(s), and (4) altering the pharmacokinetic profile of the primary drug. The major liabilities of the augmentation strategies are (1) limited empirical evidence of effectiveness (vis-à-vis alternate SSRIs, TCAs, other newer antidepressants, MAOIs, or ECT); (2) greater complexity of the treatment regimen, with the resultant variably increased risk(s) of noncompliance, side effects, and drug-drug interactions; and (3) usually greater cost. These limitations are offset by the possibility of a faster onset of action, "sparing" the patient from going through a medication taper and washout, and the possibility that an augmentation strategy might specifically address or correct the underlying cause of the medication failure.

Both clinicians and their patients look forward to the day when strategies for treatment-resistant depression are selected on the basis of knowledge about illness pathophysiology and neuropharmacologic actions rather than regional and idiosyncratic factors. In the not too distant future, specific augmentation strategies hopefully will be selected to reverse, offset, or control the specific mechanisms that have prevented an adequate response to antidepressants.

Drug names: bupropion (Wellbutrin), buspirone (BuSpar), clomipramine (Anafranil), desipramine (Norpramin and others), dexamethasone (Decadron and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), ketoconazole (Nizoral), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), pindolol (Visken), sertraline (Zoloft), venlafaxine (Effexor).

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Disclosure of Off-Label Usage

None of the augmentation strategies listed in Tables 2 and 3 in this article have been approved by the Food and Drug Administration for the treatment of depression.