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Strategies for Treatment-Resistant Depression

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ABSTRACT ~ Approximately 30% of patients with major depression respond poorly to treatment with any given antidepressant regimen, and as many as 60% to 75% experience residual or recurrent symptoms. Strategies for improving response include extending the duration of each treatment beyond the usual 2-4 weeks, increasing the antidepressant dose, switching to another antidepressant, using two or more antidepressants together, and using adjunctive medications or other treatment modalities. Some of these strategies have strong support from clinical investigations while others are based more on clinical experience. This article reviews the risk factors for treatment resistance and provides strategies for improving treatment outcomes. Psychopharmacology Bulletin. 2002;36(suppl 3):39-62

INTRODUCTION

What is treatment-resistant depression? At what point in the treatment course does a physician determine that a patient's depression is treatment resistant? In order to answer these questions, it is necessary to examine the history and our own expectations of the available treatments for depression. Until recently, treatment response was determined by a reduction in depressive symptoms (ie, >50% reduction in symptoms), generally as measured on a standardized rating scale such as the Hamilton Rating Scale for Depression (HAM-D). This level of response can be expected in approximately 60% of patients on appropriately dosed monotherapy. However, over the last few years, remission rather than just symptom reduction has become the desired outcome. This change from earlier psychiatric treatment strategies recognizes the considerable burden that residual depressive symptoms may place on individual patients as well as the greater potential for relapse in those who are not treated to full remission.

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Longitudinal data demonstrate that as many as 50% to 70% of patients with major depression fail to achieve a sustained, complete remission.¹ Thus, three out of every four patients who develop a major depressive episode experience some level of residual or recurrent symptoms. With the myriad of treatments available, remission should be the expected goal. Furthermore, approximately 30% of patients will show treatment response with placebo alone. This suggests that approximately one third of the efficacy of antidepressants is due to placebo response, one third is an effect of the medication itself, and one third of patients will not benefit from monotherapy with an antidepressant (be it a placebo response or direct drug effect). For that 30% to 40% of patients, treatment resistance may be a problem.

Treatment resistance may come in many forms. Perhaps the most important distinction is between true treatment resistance and pseudoresistance. Too often, treatment resistance is less a result of the underlying depressive illness and more a function of indirect factors, including medication side effects, drug-drug interactions, poor therapeutic alliance, and poor adherence to treatment. Effective treatment should aim to not only control symptoms, but minimize side effects and improve overall function. Furthermore, effective treatment must maintain the early gains and minimize breakthrough episodes. Treatment resistance often refers to initial nonresponse, but it may occur later, during the continuation or maintenance phase of treatment. Long-term maintenance of remission is ultimately the desired outcome.

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TREATMENT RESISTANCE: DEFINITION AND RISK FACTORS

Treatment resistance is often defined as failure to respond to an adequate dose and duration of treatment with at least two antidepressants, each used alone. An adequate dose encompasses doses up to the maximally tolerated dose; for selective serotonin reuptake inhibitors (SSRIs), this may be a very high dose. An adequate duration is often considered to be 3–4 weeks, though some patients will take as long as 6–12 weeks to respond to treatment during an acute depressive episode. Such a delay in response is often impractical in general practice settings where patients are unlikely to stay with an ineffective regimen for such a long period of time.

Numerous studies have attempted to identify clinical variables that are associated with either a positive response or resistance to antidepressant treatment.^{2–4} Gender, age, age at onset of illness, duration of illness, number of previous episodes, presence of bipolar, anxious, agitated, endogenous, or melancholic features, alterations in self-worth, and co-occurring somatic complaints have been studied, along with

numerous other clinical variables. No clear pattern has emerged among these risk factors, except that prior treatment failure and comorbid medical or psychiatric illnesses are common among patients with treatment-resistant depression, while an early positive treatment response may suggest a favorable long-term outcome.

Prior Treatment Failure

In an early study of fluoxetine for patients with treatment-resistant depression, Amsterdam and colleagues² used a multivariate regression analysis to predict treatment response. As with other studies, they found that neither demographics nor clinical variables, such as duration of illness or depressive subtype, predicted outcome. However, the number of prior treatment trials had a significant negative effect on the response to fluoxetine. Specifically, the likelihood of remission with fluoxetine decreased by 20% for each previous, unsuccessful treatment trial. Most patients had failed to respond to tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs). Similar data are not available regarding treatment outcomes after failed trials of newer antidepressants. However, these results suggest that a certain percentage of patients with treatment-resistant depression may have a particularly virulent form of the illness that is unlikely to remit with typical antidepressant monotherapies.

Comorbid Personality Disorders

Several studies have found that comorbid personality disorders significantly increase the risk of antidepressant nonresponse.⁵⁻⁸ Borderline personality disorder is perhaps the best studied in this regard and appears to be a major contributor to treatment failure, especially early in the course of illness. Interestingly and perhaps counterintuitively, pharmacological maneuvers that may be useful in the treatment of symptoms associated with specific personality disorders have not always been shown to be efficacious in the treatment of comorbid depression in this population. For example, a recent pilot study⁹ observed that olanzapine significantly improved anxiety, paranoia, anger/hostility, and interpersonal sensitivity in women with borderline personality disorder but did not reduce depression. This is somewhat surprising given olanzapine's purported antidepressant effects.¹⁰ In addition, reasonable clinical data support the efficacy of typically used neuroleptics in the treatment of borderline personality disorder, but there are fewer studies of atypical antipsychotics or mood stabilizers. One double-blind study using lithium and one open-label study using valproate showed positive benefits for reducing impulsive aggression, but these investigations did not address affective symptoms.¹¹ This is not to imply that atypical

antipsychotics and mood stabilizers have no effect on depressive symptoms in patients with personality disorders (as they ultimately may be shown to be helpful), rather, current data indicate that patients with comorbid depressive and personality disorders may constitute a special subgroup of treatment-resistant depression, who may benefit less from the pharmacological maneuvers that are generally effective for the larger population, and who may require other or additional therapeutic interventions (eg, psychotherapy).

Comorbid Medical and Psychiatric Illnesses

In contrast to the situation with personality disorders, comorbid Axis I psychiatric disorders and Axis III medical conditions are not necessarily more frequent in patients with treatment-resistant depression than in those who respond favorably to antidepressants.¹² The major challenge in treating patients with major depression and coexisting Axis I or Axis III conditions is making an accurate diagnosis. An incomplete or inaccurate diagnostic assessment of depressive symptoms is likely to be a greater cause of apparent treatment failure than factors directly attributable to the co-occurring condition(s) themselves. Without an accurate diagnosis, it is difficult to target treatment interventions effectively. Furthermore, evaluations must be detailed and precise enough to detect subtle signs of comorbidity. For example, subsets of patients with treatment-resistant depression may have subtle thought or anxiety disorders at the core of their psychopathology. Longitudinal data and structured psychological tests may be needed to detect such symptoms.

Outcome studies have observed that antipsychotic medications are effective, even at low doses, when added to an antidepressant regimen in patients with low-grade psychotic symptoms.¹³ A similar argument may be made for the short-term use of anxiolytics in patients with depression and anxiety. The problems of co-occurring conditions are perhaps most difficult in younger patients with depression and substance-related disorders and in older individuals with depression and medical illnesses. Substance abuse can complicate the diagnosis and treatment of depression. Chronic medical illnesses (eg, congestive heart failure, chronic obstructive pulmonary disease) frequently cause problems such as anergia and sleep disturbance that closely resemble the neurovegetative symptoms of depression.¹⁴ Clinicians may dismiss low mood or reduced social activities as expected reactions to chronic illness and may not query patients about anhedonia or an altered sense of self, which may signify a treatable depressive disorder.¹⁵ The most effective approach to treating patients with coexisting depression and medical illness is to work closely with relevant medical specialists to ensure that medical treatments are optimized while pursuing an effective antidepressant regimen.

Another consideration in the management of patients with coexisting illnesses is the extent to which the treatments may interact. These interactions can be positive or negative. A common example is chronic pain in patients with depression. Opiates may either improve or exacerbate depressive symptoms. On the other hand, several neuropsychiatric medications (eg, TCAs, carbamazepine, venlafaxine, and gabapentin) can reduce pain. In these scenarios, multiple target symptoms must be tracked in order to determine which medications are necessary for the long term.

Hypothyroidism

Hypothyroidism is widely recognized as a medical cause of depression,¹⁶ but its importance in treatment-resistant depression versus non-resistant depression is not always recognized. Two large studies found low rates of thyroid disease in general adult psychiatric patient populations. One study examined 277 consecutive first-time psychiatric admissions.¹⁷ The second investigated 200 outpatients with major depression.¹⁸ No cases of overt (grade I) hypothyroidism were detected in either study, and only 3% of patients had evidence of subclinical (grade II) hypothyroidism (ie, elevated thyroid-stimulating hormone [TSH] with normal free thyroxine [T_4] levels). In contrast, several studies have reported a high prevalence of grade II hypothyroidism in patients with treatment-resistant depression, plus evidence that this condition may have an adverse effect on treatment outcome.

A review of six clinical studies found a particularly high average rate (52%) of grade II hypothyroidism in patients with treatment-resistant depression versus 8% to 17% among depressed patients in general.¹⁹ A study²⁰ from a specialized treatment-resistant depression unit in Australia found grade I or II hypothyroidism in 10 of 46 patients (22%) with treatment-resistant depression, compared with 1 of 47 individuals (2%) with nonresistant depression. In that study, patients with treatment-resistant depression who had the poorest response to treatment had higher rates of hypothyroidism than either patients with treatment-resistant depression who eventually responded to therapy or patients without treatment-resistant depression. Another investigation reported that depressed patients with grade II hypothyroidism were more likely to have comorbid panic disorder and a poorer antidepressant response than those with normal thyroid indices.²¹ Finally, a small study found a higher lifetime prevalence of depression in patients with grade II hypothyroidism (56%) than in healthy controls (20%).²² These data suggest that grade II hypothyroidism may be an important factor in the development of depression and resistance to its treatment. Of note, many internists and endocrinologists do not treat grade II

hypothyroidism without physical symptoms of the disease or the presence of goiter, hypercholesterolemia, pregnancy, or infertility.²³ For patients with treatment-resistant depression, this may result in medical recommendations that inhibit recovery from depression.

The specific mechanism by which thyroid replacement improves depression is not known, but one study²⁴ found an increase in central nervous system serotonin activity along with a reduction in depressive symptoms in hypothyroid patients treated with thyroxine. Bunevicius²⁵ and colleagues found that substituting triiodothyronine (T_3) for some of the usual dose of T_4 in a group of patients with hypothyroidism offered improvements in cognition and mood not seen in patients taking T_4 alone, despite both groups showing similar improvements in thyroid function. This suggests that T_3 has a specific mood effect beyond its direct thyroid effects.

Hypogonadism

Hormonal treatments for men and women with depressive symptoms have received anecdotal and theoretical support, but there are sparse data confirming their efficacy. Most research efforts have targeted hypogonadal patients—postmenopausal women, or men with low serum testosterone levels. An open-label study compared estrogen replacement therapy (ERT) with ERT plus fluoxetine in postmenopausal women. The data indicate that ERT alone may have antidepressant effects, and it may be an effective adjunct to fluoxetine.²⁶ A double-blind, placebo-controlled study of ERT alone in a group of perimenopausal women with major and minor depressive disorders found that remission rates were substantially superior to placebo (68% versus 20%).²⁷ The mechanisms by which estrogen may exert antidepressant effects are not known. It has multiple potential actions in the brain, including a possible role in the synthesis of monoamine neurotransmitters. For example, there is evidence from animal studies that estrogen increases dopamine decarboxylase gene expression in the locus caeruleus, which should logically modulate noradrenergic neurotransmission.²⁸

The use of testosterone in men with depression has much less support. Some researchers have suggested that testosterone may increase libido, energy, and even mood.²⁹⁻³¹ In one case series of five men with fluoxetine-resistant depression and low serum testosterone levels, four responded to testosterone replacement and three of the four had a relapse of depressive symptoms when testosterone was withdrawn.²⁹ On the other hand, a recent double-blind, placebo-controlled study found that testosterone was no different from placebo for treating depression in hypogonadal men.³⁰ Another double-blind, placebo-controlled study investigated the effects of testosterone on aggression using

supraphysiologic doses of the hormone. Depressive symptoms did not improve consistently, but a hypomanic state emerged in approximately 16% of patients.³¹ Thus, the available controlled data do not support the efficacy of testosterone in men with depression.

Postpartum Depression

Postpartum depression is another mood disorder in which sex hormones are posited to play a major role. Bloch and colleagues³² simulated the postpartum state by administering estrogen for 8 weeks to 16 women at doses that mimicked the third trimester of pregnancy, then withdrawing estrogen. This maneuver had minimal effect on eight women with no history of postpartum mood disturbance but induced depression in five of the eight women with histories of postpartum depression, even though they were not depressed at the start of the study. This suggests that some women have an inherent and persistent sensitivity to estrogen fluctuations, a possible explanation for the high recurrence rate of postpartum depression.

Two studies have found estradiol to be effective for postpartum psychiatric disorders. In one study, 10 women received sublingual estradiol for treatment of postpartum psychosis.³³ All improved over a 2-week period in concert with a gradual rise in their serum estradiol levels. In a 3-month, double-blind, placebo-controlled trial, 34 women with postpartum depression fared far better on an estradiol transdermal patch than 27 others receiving placebo.³⁴

Biological Determinants

True treatment resistance may be strongly influenced by biological factors. Smeraldi and colleagues³⁵ found a relationship between SSRI (fluvoxamine) response and a long variant of the promoter region of the serotonin transporter gene. Healy³⁶ showed that lower dopamine receptor sensitivity was predictive of a positive response to paroxetine. In an initial study, Cook³⁷ determined that quantitative electroencephalogram (EEG) cordance, which expresses perfusion and thus energy use of the brain, is predictive of fluoxetine response. A later investigation using placebo, venlafaxine, or fluoxetine found that despite there being no baseline differences among the three groups, both of the antidepressant groups (and not placebo) showed decreased EEG cordance in the prefrontal cortex both 48 hours and 1 week later.³⁸ Even more striking was the observation that the EEG cordance decreases preceded clinical response, which was not seen for up to 4 weeks, and those patients with the largest decrease in EEG cordance showed the most robust clinical response after week 8. These findings indicate that there are biological predispositions that are quantifiable to medication response.

OPTIMIZATION OF SINGLE-AGENT THERAPY

Dose and Duration of Antidepressant Treatment

It is generally accepted that antidepressants should be given for at least 6 weeks at maximally tolerated doses before failure can be pronounced. Clinicians and patients often give up on medications too early, generally when they sense no improvement during the first 1–2 weeks at the starting dose. There is a strong temptation to escalate doses rapidly or change quickly to one of the many other antidepressant medications that are now available. Experimental data suggest that neither of these approaches is particularly helpful early in the course of treatment. There is in fact no solid evidence to show that high doses of all antidepressants are more efficacious than doses in the usual therapeutic range. A major confounding factor is that the act of increasing a medication also extends the duration of treatment, making it difficult to determine what prompted the response, the higher dose or the extended duration of treatment. This concept was reinforced in a study by Schweizer and colleagues,³⁹ wherein patients who failed 3 weeks of fluoxetine at 20 mg/day were randomly assigned to either 60 mg/day or continuing on 20 mg/day for another 5 weeks. At the end of the study, both groups had significant rates of improvement. Others have found similar difficulties in predicting outcomes based on short-term results. In a placebo-controlled study by Quitkin and colleagues,⁴⁰ 32% of nonresponders at week 3 and 44% of patients with only minimal improvement by week 5 showed an adequate treatment response at week 6.

Nevertheless, some investigators have reported data showing that a poor early response predicts a low probability of significant benefit with continued treatment. Nierenberg and colleagues⁴¹ examined the likelihood of a positive response to fluoxetine after 8 weeks of treatment at 20 mg/day, based on the level of benefit observed at weeks 2, 4, and 6. Among 82 subjects, the overall response rate (>50% reduction in HAM-D score) was 57.3%. However, for patients with less than a 20% decrease in symptoms by weeks 2, 4, and 6, the success rate at week 8 was only 36.4%, 18.9%, and 6.5%, respectively. In a similar vein, Koran and colleagues⁴² examined risk factors in treatment response in a large (N=671) study of fluoxetine for geriatric patients with depression. They found that patients with a 20% or greater reduction in the HAM-D at weeks 1, 2, or 3 were more likely to experience marked improvement or full remission by week 6.

These contrasting findings suggest that symptomatic improvement within the first 2–4 weeks of medication interaction may be indicative of eventual success in achieving remission, but that 40% to 50% of patients who appear to be nonresponders at 2–4 weeks may in fact be

slow responders to their antidepressant. Unfortunately, in usual clinical practice, there are few patients who will agree to stay on a medication that they perceive to be ineffective for even 3 weeks, let alone for 8 weeks. From a practical standpoint, clinicians are faced with taking the next step if their patients have not substantially improved after about 3 weeks. Research data suggest that the easiest and most effective strategy for treating nonresponders is to increase the medication dose. Fava and colleagues⁴³ compared three different approaches to patients who had failed an 8-week trial of fluoxetine 20 mg/day: a dose increase of fluoxetine to 40–60 mg/day, augmentation with low-dose desipramine (25–50 mg/day), or augmentation with lithium (300–600 mg/day). Raising the fluoxetine dose was the most effective strategy for both partial responders and nonresponders. Adding lithium was also effective for nonresponders (even with the relatively low lithium levels employed), but adding desipramine was not. Serum concentrations of lithium and desipramine were not studied, and it is possible that higher doses of lithium and/or desipramine would have brought about a greater response. Nonetheless, this study demonstrates the benefits of raising the antidepressant dose.

In summary, optimization of monotherapy is the most appropriate first step for patients whose antidepressant response is less than adequate. This involves a therapeutic trial of 6–8 weeks, much longer than that typically undertaken in general clinical practice, accompanied by a gradual titration of the antidepressant to the maximum tolerated dose. This plan requires a strong therapeutic alliance, which can be maintained through a concerted effort at patient education and tight management of side effects. This approach may not be as captivating as the multiple switching and augmentation strategies that are in widespread use, but it is grounded in well-designed clinical investigations of treatment-resistant depression.

Many of the newer, non-SSRI antidepressants have reported a quicker onset of action, though this remains debatable.⁴⁴ A few studies have emerged to suggest other strategies for speeding up the initial antidepressant response.

Switching Antidepressants

What little work has been done in this area seems to demonstrate what is already common clinical practice—switching from one antidepressant class to another is an effective way of prompting response. Furthermore, class of drug at medication initiation or termination does not seem to make a difference. For example, a recent study showed that a switch from imipramine to sertraline had the same benefit as the opposite switch—sertraline to imipramine—for patients who had failed

the first drug. In both situations, more than half of the chronically depressed patients improved.⁴⁵

Overall, the available data suggest that switching antidepressants appears to be essentially as effective as augmentation. Furthermore, poor response after one maneuver (switch or augmentation) should be met simply by a second attempt.⁴⁶ Response rates of switching, augmentation, or a combination of both are based on open trials, and are about 50%,⁴⁷ but there have been very few investigations comparing the modalities against one another.

Intraclass switching had previously been thought to be ineffective, based on work showing that switching from one TCA to another rarely yields a positive outcome.⁴⁸ However, there are numerous studies that support switching from one SSRI to another, with positive response rates of 40% to 70%.⁴⁸ The SSRIs have quite different molecular structures, unlike the TCAs, which are more similar to one another in chemical structure. Thus, it may be appropriate to think of switching strategies as substituting one antidepressant molecule for a different one, rather than substituting with a different class, *per se*.

There has been considerable interest in venlafaxine for treatment-resistant depression. In contrast to the SSRIs, venlafaxine has a nearly linear dose-efficacy relationship,⁴⁹ most likely because it inhibits serotonin reuptake at low doses, and both serotonin and norepinephrine at higher doses.⁵⁰ In this sense, it may be a medication that possibly augments itself. There is also evidence that venlafaxine has a role in the opioid system. Opioid pharmacology has been used as a model of animal depression for quite some time, and a recent study found that the antidepressant response in animal models of depression may be related, in part, to serotonin-mediated β -endorphin release.⁵¹ Schreiber⁵² found that only venlafaxine and mirtazapine have effects on the opioid system, possibly explaining their role in neuropathic pain. Venlafaxine, like mirtazapine, has a low potential for drug-drug interactions because of its negligible effects on key cytochrome isoenzymes (2D6, 2C19, 1A2, 3A4)⁵³; venlafaxine also has low plasma-protein binding. Clinical data support the drug's possible superiority over SSRIs in treating patients to remission. For example, a pooled analysis⁵⁴ of eight double-blind, placebo-controlled trials of venlafaxine versus SSRIs and placebo found that remission rates were substantially higher for venlafaxine than for SSRIs (25% for placebo, 35% SSRIs, 45% venlafaxine). Others have found similar superiority over SSRIs (though not over TCAs).^{1,55} When tested specifically on patients with treatment-resistant depression, an open-label trial found that a positive response was seen in more than half of the previously treatment-resistant patients, and full remission occurred

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in almost one third.⁵⁶ Furthermore, response with venlafaxine appears to be long-lived, up to 10 months in one open-label trial.⁵⁷

AUGMENTATION

The vast majority of the work concerning augmentation of antidepressants in treatment-resistant depression has been done with TCAs. These findings often are applied to SSRIs as well, despite the fact that few comparable studies exist with SSRIs. However, a growing body of clinical and biochemical evidence indicates that more advanced pharmacotherapeutics are close at hand.

Enhancing Early Treatment Response

Numerous studies over many years have attempted to find a way to reduce the time lag for the response to antidepressant medications. No clearly superior strategies exist, but a number of maneuvers have been investigated with varying degrees of success. Benzodiazepines, especially clonazepam⁵⁸ and alprazolam,^{59,60} have been suggested to reduce depressive symptoms and improve compliance with standard antidepressant therapy. Clearly, issues of abuse and tolerance make these medications more difficult to use over longer time courses. Short-term prescription of benzodiazepines to patients with depression may bring about an immediate reduction in coexisting anxiety or agitation, which are exceedingly common in depression and are often employed by clinicians; however, we await controlled studies.

There has been considerable evidence that pindolol may enhance the onset of antidepressant response when added to an SSRI,⁶¹⁻⁶³ although the data are mixed. There is no consistent evidence that pindolol will reduce symptom severity over the long term, but it may speed up the early response by blocking the serotonin 5-HT_{1A} autoreceptor. Serotonin released by the nerve terminal binds to presynaptic 5-HT_{1A} autoreceptors, which function to modulate (ie, decrease) further serotonin release. Ultimately, this autoreceptor becomes desensitized, after which it has less effect on serotonergic output. Theoretically, pindolol could be used during the initial phase of treatment with an SSRI to block the 5-HT_{1A} autoreceptor. The evidence of any real benefit has been mixed, though a recent positron emission tomography (PET) study⁶⁴ suggested that some of the conflicting findings of pindolol's efficacy may be due to inadequate dosing in the clinical trials. The traditional study dose of 2.5 mg TID did not achieve significant occupancy of the 5-HT_{1A} autoreceptor, while doubling the dose achieved only a 19% occupancy rate. This suggests that pindolol may have to be taken in significantly higher doses to be effective, but this carries a risk of hypotension usually not seen at 2.5 mg BID to TID. The PET results

also suggest that pindolol acts by a mechanism entirely separate from 5-HT_{1A} antagonism, possibly via β -adrenergic receptor systems. Preliminary biochemical evidence also suggests that pindolol's efficacy may be related to a variant in the serotonin transporter gene.⁶⁵

T₃, a common adjunct for TCAs, may also accelerate antidepressant response. A recent review and meta-analysis⁶⁶ identified six double-blind, placebo-controlled studies of T₃ with TCAs. Five of six found T₃ to be significantly more effective than placebo in accelerating antidepressant response. The review suggested that women might be more likely to benefit from T₃ acceleration than men.

Combinations of Two Antidepressants

Since the introduction of the SSRIs, it has become an increasingly common clinical practice to combine antidepressants. Anecdotal reports and case series provide some evidence for the rationale of targeting two or more neurochemical pathways (eg, combining serotonergic and noradrenergic antidepressants), but there are only a handful of controlled clinical trials examining this practice.

SSRIs and TCAs. Case series⁶⁷ and one prospective⁶⁸ (but not controlled) trial suggest that the combination of a TCA and an SSRI may produce robust clinical response and improve remission rates. In the prospective trial, Nelson and colleagues⁶⁸ prescribed desipramine and fluoxetine simultaneously to 14 inpatients with major depression. Symptom reduction was greater at 1 and 2 weeks than in a historical comparison group prescribed desipramine alone. Ten of 14 patients (71%) on the combined treatment remitted completely (HAM-D <7) within 4 weeks. On the other hand, Fava and colleagues⁴³ found no benefit from adding desipramine 25-50 mg/day to fluoxetine 20 mg/day for 12 patients who had not responded to 8 weeks of fluoxetine alone. One difference between the two studies may be the dose of desipramine employed. Nelson and colleagues⁶⁸ used serum levels to adjust their desipramine dose while Fava and colleagues⁴³ used a fixed dose of 25-50 mg/day, which produced a low serum level averaging 100.3 ng/mL in the three patients for whom levels were obtained. No long-term data on TCA-SSRI combinations are available from these or any other studies. Care should be taken when using SSRIs with TCAs, as fluoxetine and paroxetine inhibit the cytochrome P450 (CYP) 2D6, and fluvoxamine inhibits 2D6 and 1A2, which substantially increases the serum levels of tricyclics. Sertraline and citalopram produce less P450 inhibition.

The difference in dosing strategies between the Nelson⁶⁸ and Fava⁴³ studies raises a potentially important issue when combining antidepressants. Prescribing low doses of two antidepressants may not be

particularly effective. Another arm of the study by Fava and colleagues⁴³ achieved a better outcome simply by increasing the fluoxetine dose. This suggests that it may be reasonable to optimize the dose of one antidepressant (ie, find the highest tolerated dose) before adding a second.

SSRIs and Bupropion. There are no controlled trials investigating bupropion augmentation for SSRIs. The only support for this maneuver comes from case series and reports. However, it is a particularly common approach that may have some biochemical logic backing it. Bupropion is a weak inhibitor of dopamine and norepinephrine transporters. This effect, in mesocorticolimbic areas, may be responsible for its antidepressant action.

Bupropion does not significantly affect serotonin concentrations. However, recent evidence indicates that serotonin potentiates dopamine and norepinephrine release in the brain. Based on this information, Li⁶⁹ tested bupropion augmentation with fluoxetine and found that fluoxetine substantially potentiated bupropion's increases of dopamine in rat hypothalamus, prefrontal cortex, and nucleus accumbens, and norepinephrine release in the hypothalamus. These findings suggest that SSRIs may potentiate bupropion response. Similarly, there is also biochemical evidence that bupropion can augment venlafaxine as well as SSRI response.⁷⁰ But care should be taken because bupropion can inhibit the metabolism of venlafaxine and SSRIs.

SSRIs and Mirtazapine. One small controlled trial⁷¹ investigated mirtazapine augmentation of antidepressant monotherapy in patients who did not improve on the SSRI alone. After 2 weeks of combined therapy, mirtazapine augmentation was superior to placebo augmentation (64% versus 20% remission). There is good biochemical evidence to support this treatment strategy, despite the paucity of clinical data. Mirtazapine is an antagonist of the presynaptic α_2 -noradrenergic autoreceptor. It enhances α_1 -mediated, noradrenergic transmission by releasing the presynaptic neuron from the braking action of the α_2 autoreceptor. In the raphe nuclei in the brainstem, the resultant increase in noradrenergic activity stimulates serotonergic neurons.⁷² This mechanism of action also bypasses the presynaptic, serotonergic autoreceptor 5-HT_{1A}, potentially allowing mirtazapine to both accelerate and improve response to SSRIs.

TCAs and MAOIs. There are many case reports and case series attesting to the efficacy of the combination of a TCA and an MAOI, but there are no randomized studies of this strategy. Historically, clinicians attempted this maneuver with clearly informed and reliable patients, but other options are now available that make this an infrequent therapeutic choice given the potential for adverse effects.

Augmentation of SSRIs With Other Agents

Atypical Antipsychotics. A recent review by Thase¹⁰ found support for using atypical antipsychotics in treatment-resistant depression, possibly because of their 5-HT_{2A} and 5-HT_{2C} antagonism (a mechanism that may complement the action of SSRIs). Unfortunately, this potential augmentation strategy has not been extensively studied.

Small, open-label studies have shown the utility of olanzapine, especially in melancholic depression. Not surprisingly, often the first symptom to respond is insomnia, with depression improving more slowly but steadily afterward.⁷³ Ghaemi's⁷⁴ retrospective chart review of both bipolar and unipolar patients found some moderate benefit from olanzapine, but with a high rate of side effects (usually weight gain). Shelton⁷⁵ determined that fluoxetine and olanzapine together were significantly better than either therapy alone. A possible explanation for this synergistic response is given by Zhang and colleagues,⁷⁶ who observed that the combination of olanzapine and fluoxetine, but not haloperidol and fluoxetine or clozapine and fluoxetine, increased dopamine, norepinephrine, and serotonin in the rat prefrontal cortex. The combination of haloperidol and fluoxetine did not increase any of the neurotransmitters above what was seen with fluoxetine alone. It is not certain that these animal results are related to the therapeutic benefits seen in humans, but they lend support to the hypothesis that augmentation strategies should be aimed at multiple receptor systems to achieve the greatest efficacy.

Risperidone also has been added to SSRIs in small, open-label studies with favorable improvement in depressive symptoms.⁷⁷ It is thought that risperidone may enhance the antidepressant's response by increasing serotonin in the frontal cortex via antagonism of presynaptic α_2 -adrenergic receptors⁷⁸ (similar to one of the mechanisms of action of mirtazapine).

Buspirone. Buspirone has been widely used as an adjunctive agent. However, as an augmenting agent for SSRIs, it has been suggested that it is no better than placebo in the treatment-resistant population, as demonstrated in a large double-blind study.⁷⁹

Antiepileptic Mood Stabilizers. While there is considerable investigation into the use of mood stabilizers (beyond lithium) for the treatment of bipolar depression, there is surprisingly little such research involving treatment-resistant unipolar depression. A review by Dietrich and Emrich⁸⁰ identify limited evidence for this practice, suggesting that antiepileptics are well tolerated and possibly efficacious.

Older Augmentation Strategies Revisited

Lithium. The addition of lithium to a TCA is the augmentation strategy with perhaps the most consistent and extensive experimental support in treatment-resistant depression.⁸¹ Some authors consider it

the first choice for monotherapy failures.⁸² Lithium alone may have an antidepressant action in unipolar depression, but the strongest data are for its use to augment TCAs. A recent retrospective study observed that severe depression was the best predictor of response to lithium augmentation of TCAs.⁸³ Other positive predictors included a shorter duration of depression and absence of a comorbid personality disorder.

It is often assumed that the benefits of lithium augmentation observed with TCAs apply to SSRIs as well, but this has not been studied extensively. Lithium may exert its antidepressant effects by increasing the synthesis or release of serotonin. Thus, the successful augmentation of TCAs by lithium is not overly surprising, as serotonergic transmission would be enhanced in the presence of medications that also improve norepinephrine systems (ie, the combination would affect two neurotransmitters). On the other hand, these same data might predict less benefit from lithium augmentation of SSRIs because the potential enhancement of serotonergic function by lithium may be modest in comparison to that already caused by SSRIs. To date, placebo-controlled trials of lithium augmentation have been conducted with only citalopram and fluoxetine.^{48,84,85}

As reported above, Fava and colleagues⁴³ found that patients who had no response to 20 mg/day of fluoxetine alone for 8 weeks showed the greatest improvement with lithium augmentation, but patients with a partial response to fluoxetine fared better with an increase in fluoxetine dose. No definitive conclusions can be drawn from any of this work, and further study—especially in the form of double-blind, placebo-controlled studies employing a broad range of serum-lithium concentrations—are needed to evaluate this potentially useful augmentation strategy more fully.

Lithium has also been used to augment venlafaxine. Two preliminary investigations found it to be effective and well tolerated, with rapid action.^{86,87} From a biochemical standpoint, venlafaxine may be a good candidate among the newer antidepressants for lithium augmentation. At moderate to high doses, its dual inhibition of serotonin and norepinephrine reuptake is similar to the mechanism of action of the TCAs. Unfortunately, there are no controlled clinical trials of this hypothesis.

Thyroid Hormones. The thyroid hormone T_3 can be an effective augmenting agent for TCAs. Most of the published data to support it, however, are anecdotal reports and uncontrolled trials, although there are a few placebo-controlled investigations. Joffe and colleagues⁸⁸ found T_3 to be as efficacious as lithium in TCA refractory depression. In addition, a recent review of the subject⁸⁹ reported that the overall success rate for T_3 augmentation of TCAs is about 50%. However, there are very limited data on T_3 augmentation of SSRIs.

Data supporting levothyroxine (synthetic T_4) as an augmenting strategy for SSRIs were recently presented. In a retrospective study, Clayton and Shen⁹⁰ found levothyroxine to be effective for inducing full remission of major depression in partial responders to an SSRI as long as the levothyroxine dose produced serum free T_4 levels at or slightly above the upper limit of the normal physiological range. T_3 has generally been found to be more effective than T_4 , and a recent study²⁵ found that T_3 was superior to T_4 in improving mood and cognition in patients with hypothyroidism.

Stimulants. Psychostimulants have been used in treatment-resistant depression, though they are somewhat controversial and not definitively proven. There are several possible reasons why these agents may be useful. First, several of the vegetative symptoms of depression, especially low energy and poor concentration, could be improved directly by a stimulant. Second, in keeping with the hypothesis that treatment resistance might be overcome by targeting multiple receptor systems, psychostimulants enhance dopamine neurotransmission, a pathway not substantially affected by other antidepressants, with the possible exception of sertraline and bupropion. An example of such a maneuver is the case series by Feighner,⁹¹ who added stimulants to MAOI and MAOI/TCA combinations, finding them efficacious for treatment resistance as well as fairly safe (ie, no hypertensive or hyperthermic crisis occurred). These findings were later supported by Fawcett⁹² in 1991. However, in reviewing the small amount of experimental data available, Thase^{10,93} found a limited role for psychostimulants and direct dopamine agonists such as bromocriptine in treatment-resistant depression.

OTHER OPTIONS FOR TREATMENT-RESISTANT DEPRESSION

Electroconvulsive Therapy

While it is generally accepted that electroconvulsive therapy (ECT) is effective for the treatment of depression,^{94,95} studies of ECT in treatment-resistant states suffer from the same problems as studies of other strategies—the majority of the work has been done in patients who failed TCAs. In this population, ECT is an accepted efficacious treatment alternative.⁹⁶ In a perhaps not surprising study,⁹⁷ patients who were resistant to medication treatment prior to receiving ECT had substantially higher rates of relapse after ECT, regardless of the adequacy of the post-ECT treatments. However, the high relapse rates found with ECT are likely due to selection bias, as it is usually a modality reserved for those who have not responded well to medications. Furthermore, ECT is rarely continued after the patient has shown response.⁹⁸ One effective step for managing relapse is the use of alternative pharmacotherapies rather than a return to the prior regimen. If no treatment is given, relapse

occurs in almost all (84%) patients; relapse rates were lowest with a combination of lithium and TCA (40%) versus TCA alone (60%).⁹⁹

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS), a relatively new modality, has been suggested to be efficacious for depression,¹⁰⁰ although it has not been thoroughly investigated for treatment-resistant states specifically. Some have found it to be as efficacious as ECT, even at 6-month follow-up.¹⁰¹ With the exception of seizures, the side effects are rare. Interestingly, TMS appears to elevate TSH as well as mood, though it is not clear if this is causal or coincident.¹⁰² The use of high (stimulatory) frequencies (>5 Hz) to stimulate the left dorsolateral prefrontal cortex was associated with the best outcome, though stimulation of the right dorsolateral prefrontal cortex using low (inhibitory) frequencies may also be efficacious.¹⁰³ A recent study suggested that the efficacy of left versus right prefrontal TMS is predictable by visual field response, with those responding to right visual field stimulation having a much higher response to left prefrontal TMS.¹⁰⁴ More work needs to be done in this promising area.

Psychotherapy

Many clinicians recommend psychotherapy for patients with medication-resistant depression. However, as is the case with medications, not all types of therapy have experimental evidence to support their efficacy for treatment-resistant depression. Thase¹⁰⁵ suggested that effective therapies for treatment-resistant depression share several characteristics, including a high level of structure, active involvement of the therapist, effective psychoeducation about treatment-resistant depression and its overall treatment, well-defined short-term treatment steps, and self-help homework activities. Interpersonal, cognitive, and behavioral therapies, all of which typically incorporate these elements, are the approaches most likely to benefit patients with treatment-resistant depression. Investigations of combined treatment with medications and psychotherapy are under way. The results of a large, multicenter trial of nefazodone plus a structured form of psychotherapy recently found that cognitive behavioral therapy or nefazodone both improved chronic depression, but the combination was significantly more efficacious.¹⁰⁶

Emerging Alternatives

Modafinil. Modafinil is a novel, wake-promoting agent currently approved for the treatment of narcolepsy but found in case reports to be useful in other disorders causing increased somnolence or anergy. One small study of major depressive and bipolar depressive patients with

poor responses to common treatment regimens found that modafinil prompted significant improvement in the majority of the patients.¹⁰⁷ Much more work has to be done to follow up on this preliminary result. However, the high tolerability and safety profile of modafinil and its low potential for abuse or drug-drug interactions make it a potentially promising intervention for treatment-resistant depression.

CONCLUSION

Treatment resistance is a common and frustrating complication of depression management. Few factors predict treatment resistance in advance, other than comorbid personality disorders and poor response to previous antidepressant trials. Coexisting medical illnesses and Axis I disorders, particularly substance-related disorders, present challenging diagnostic and treatment dilemmas. However, these conditions do not necessarily confer added treatment resistance if they are managed concomitantly with the depressive illness.

Experimental evidence indicates the need for longer treatment trials (as long as 6–8 weeks) than those currently employed in general clinical practice for patients with treatment-resistant depression. Additional data support the common management scheme of gradually increasing the doses of newer antidepressants, particularly SSRIs, in patients with a limited response to their initial intervention. Strong data favor switching strategies from one SSRI to another, from an SSRI to a TCA or vice versa, and from a TCA to an MAOI. More limited information suggests that switching from an SSRI to a newer medication with a different mechanism of action (eg, venlafaxine, mirtazapine, nefazodone, bupropion) is reasonable, but there are almost no data on switching between these agents. However, it is reasonable to switch to antidepressants that have dual receptor action, such as selective norepinephrine reuptake inhibitors (SNRIs).

The efficacy of augmenting TCAs with lithium is well established, and there is strong evidence that about 50% of patients will obtain substantial benefit from adding T_3 to a TCA. Smaller and less rigorous studies suggest that lithium and thyroid hormone T_3 augmentation may work for SSRIs as well. One study reported a favorable response from adding lithium to venlafaxine. Initial reports suggest that the atypical antipsychotics, particularly olanzapine and risperidone, may enhance treatment outcomes when combined with SSRIs. Buspirone does not appear useful for this purpose.

The data on combining antidepressants is quite sparse considering the frequency with which this strategy is used in clinical practice. Anecdotal data and a small number of preliminary controlled investigations have addressed the combination of an SSRI with a second antidepressant.

No definitive conclusions can be drawn from these reports, but current practice suggests adding an antidepressant of differing pharmacology. It is reasonable to expect that greater success will be achieved by optimizing the dose of the first antidepressant before adding a second, rather than using low- to midrange doses of both antidepressants, but there are few data that address this suggestion. Dual-action antidepressants, such as SNRIs, have preliminary evidence indicating particular usefulness in treatment resistance.

Psychotherapy is often recommended for patients with treatment-resistant depression, though well-constructed studies specifically addressing patients with treatment-resistant depression are not very numerous. Structured therapies with active therapist involvement, such as cognitive, behavioral, and interpersonal therapies, have the most support. ECT offers an additional, nonpharmacological intervention strategy, while TMS appears promising.

Hypothyroidism, including the often-overlooked grade II form of the illness, appears to predispose individuals to the development of depression and increase treatment resistance. The use of sex hormones to treat depression or to augment antidepressant medications has been advocated by a few authors. Recent studies found a favorable response to estrogen replacement therapy in women with perimenopausal or postpartum depression, but more work is needed in this area. Limited data on testosterone for treating depression in hypogonadal men are disappointing.

A few strategies that accelerate the therapeutic response to antidepressants have been reported. However, there are actually few formal data, and the data are mixed regarding the potential of pindolol to speed the response to SSRIs; the data are a bit stronger for T_3 and the speeding of response to TCAs. Larger and more controlled studies need to be conducted.

There is no single management strategy for treatment-resistant depression, so each case must be approached individually. Patients may, for various reasons, wish to take fewer (or more) medications, or they may hesitate to consider medicines with additional side effects. Drug-drug interactions must be considered, with special attention to the CYP enzyme system. A very systematic approach is essential, following research data where available. Finally, special attention to the physician-patient relationship may yield clues to the causes and possible remedies of treatment-resistant depression. ❖

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