

Treatment Options for Refractory Depression

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A significant proportion of patients with depressive disorders do not experience a full response with antidepressant treatment. Fortunately, most eventually remit, even though the time to response may be significantly delayed in many patients. A variety of options exist to deal with these difficult clinical situations. Established strategies include switching to an antidepressant of an alternative class (e.g., tricyclic to a monoamine oxidase inhibitor [MAOI] or selective serotonin reuptake inhibitor [SSRI]), electroconvulsive therapy (ECT), and augmentation with lithium or thyroid hormone. Promising alternatives include combined serotonin and norepinephrine enhancement strategies (e.g., SSRI plus serotonin norepinephrine reuptake inhibitor [NSRI] or higher doses of venlafaxine or fluoxetine), steroid suppression therapy, augmentation with atypical antipsychotics, and psychotherapy.

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Generally, depression is thought of as having a positive outcome. For example, antidepressant clinical trials show optimistic response rates from 60% to 80%. However, these favorable statistics belie some discouraging elements. Most pharmaceutical trials define response as a 50% or greater improvement in depression ratings, usually Hamilton Rating Scale for Depression (HAM-D) scores. Although scores on such measures clearly indicate improvement, they do not necessarily define a remission of the episode.¹ Rigorously defined remission appears to occur in a substantially smaller percentage of patients, particularly those who are more severely ill or who suffer from melancholia.² In fact, 20% to 40% of patients experience only minimal improvement with treatment. A substantial proportion of patients remain ill even after a rigorously applied pharmacotherapy regimen.

Fortunately, most persons with depression do appear to recover over time. For example, Mueller and colleagues³ recently reported that 93% of 431 depressed patients recovered over a 10-year period, with 67% recovering within 1 year. Of those who remained depressed for 5 years continuously, 38% recovered between years 5 and 10. McGrath et al.⁴ followed patients who had failed 6-week trials of both imipramine and phenelzine given singly and found that 55% eventually responded. These

studies indicate that most patients get better with time and support the need for vigorous, long-term intervention. However, initial response to treatment may be incomplete, and ultimate remission may be delayed by periods of months to years.

DEFINITION

The first step in determining refractoriness to treatment is to decide if the patient has had an adequate therapeutic trial. What dose and duration of drug therapy can be considered adequate? Many doses and time frames have been proposed,⁵ including some that might be considered impractical, however.¹ Data from Quitkin et al.⁶ may be helpful. This group evaluated the time to response of 693 depressed patients treated with a variety of antidepressants. In those patients rated as lacking minimal response by the end of week 3 of treatment, 32% who received drug therapy and 10% of placebo subjects went on to respond by the end of week 6, a significant difference. Alternatively, of those who showed essentially no response by the end of week 4, only 13% of drug-treated and 6% of placebo-treated patients responded by week 6. These data indicate that a substantial minority of persons who show no effect at week 3 will go on to respond by week 6 of treatment but that the rate of response for those showing no improvement by week 4 will be very low and no better than placebo. But of those subjects who were unimproved by week 4 but at least somewhat improved at a prior point, 39% of drug-treated patients versus only 8% who received placebo responded by week 6. The authors conclude that those patients tolerant of adequate doses but not at least minimally improved by week 4 should have their treatment regimen changed. However, those with some improvement by week 4 should have the therapy continued until week 6.

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Unfortunately, many patients receive multiple trials of medications at inadequate doses and durations.⁷ In practice, a careful history that documents prior trials of medications (including doses and durations at adequate dosing levels) is required before a patient can be defined as refractory. It may be necessary to revisit medications used in the past if the dose and duration were not optimized in those instances. The management of depression would be improved considerably if clinicians would exhaust each drug before moving to a new treatment. That is, if the patient demonstrates initial refractoriness to conventional doses of medication, the dose should be titrated to the maximum tolerable within the recommended range and continued for 4 weeks in face of complete nonresponse or 6 weeks in partial responders before abandoning therapy.⁸

TREATMENT APPROACHES

Monotherapies

A common clinical practice is to switch from 1 antidepressant to another after an initial failure. Switching from 1 tricyclic to an alternative heterocyclic appears to yield low rates of response,^{9–11} while a switch to a monoamine oxidase inhibitor (MAOI) is considerably more successful.¹¹ Thase and Rush,¹¹ summarizing 10 studies, showed that 138 (62%) of 221 patients refractory to tricyclics had a positive response to a subsequent trial of MAOI treatment. Similarly, a switch from a tricyclic to a selective serotonin reuptake inhibitor (SSRI) also has proved more successful (with the possible exception of fluvoxamine^{12,13}). Response rates for a TCA to SSRI switch have ranged from 43% to 75% in outpatient studies.¹¹ These data would indicate that either MAOIs or SSRIs are appropriate alternatives in tricyclic-resistant patients.

However, tricyclics are no longer first-line antidepressants, having been supplanted by newer drugs because of safety, side effect, and compliance considerations. However, Peselow et al.¹⁴ found that 11 (65%) of 17 paroxetine nonresponders improved with a subsequent 6-week trial of imipramine. Although this is only a single study, the results do support the use of tricyclics as alternatives in SSRI nonresponders.

Even more common in practice is switching from one SSRI to another. Brown and Harrison¹⁵ examined the effectiveness of sertraline in depressed patients who had previously discontinued fluoxetine due to side effects. Eighty-five (91%) of 93 patients intolerant to fluoxetine were able to complete a trial of sertraline (minimum dose 50 mg/day). Of this number, 76% responded positively. These data indicate that patients *intolerant* of one SSRI may well tolerate another but do not support the practice of switching to an alternative SSRI in patients who fail an adequate trial of one SSRI.

Supratherapeutic dosing strategies could represent an alternative approach. Most TCAs have reasonably well-

established plasma level–response relationships. However, the same is not true for newer agents. Early clinical trial work has indicated that most SSRIs have a relatively flat dose-response relationship, with approximately equivalent effect in lower and higher dose ranges.^{16–18} However, these data are in unselected depressed patients and do not indicate whether higher doses might benefit a subset of patients who fail to respond to lower doses. Fava and colleagues have examined the effectiveness of using high-dose fluoxetine in patients not responsive to 20 mg/day.^{19,20} The first study was an open-label evaluation of 15 patients who had failed to respond to a trial of fluoxetine at 20 mg/day for 8 to 12 weeks.¹⁹ This study, in which the dose of fluoxetine was advanced to 60–80 mg/day for 4 weeks, demonstrated small but statistically significant improvements in HAM-D scores. In a subsequent project,²⁰ 41 patients who had failed to respond to 8 weeks of 20 mg/day of fluoxetine were randomly assigned to 1 of 3 treatment conditions for 4 weeks: fluoxetine, 40–60 mg/day; fluoxetine, 20 mg/day, plus desipramine, 25–50 mg/day; or fluoxetine, 20 mg/day, plus lithium, 300–600 mg/day. HAM-D scores showed the greatest reduction in the high-dose fluoxetine groups (mean \pm SD = 14.1 \pm 7.3) versus fluoxetine plus desipramine (mean \pm SD = 16.1 \pm 13.9) or fluoxetine plus lithium (mean \pm SD = 13.6 \pm 10.6). Unfortunately, the doses of desipramine and lithium used to augment fluoxetine cannot be considered adequate. Therefore, this study cannot be considered an appropriate test of the effectiveness of these agents for augmentation. However, the data do pose the possibility that higher doses of fluoxetine (40–60 mg/day) might be helpful in patients who have failed a trial of 20 mg/day.

A single open trial has examined the effectiveness of venlafaxine, an antidepressant with mixed norepinephrine and serotonin uptake activity, in refractory depression. Nierenberg and associates²¹ conducted an open trial of venlafaxine in 84 patients with major depression with a very rigorously defined refractoriness: failure of at least 3 adequate trials of antidepressants from at least 2 different antidepressant classes or electroconvulsive therapy (ECT), plus at least 1 attempt at augmentation. About one third of patients were considered partial or full responders. Of this group, 46% were able to maintain a positive effect over a 3-month follow-up period. These results, if confirmed, indicate that venlafaxine may be helpful in a small but significant group of core refractory patients and raise the possibility of a future trial in less severely refractory patients as well.

Augmentation

De Montigny's earliest clinical observations of the beneficial effect of lithium augmentation of tricyclics^{22,23} has been confirmed in many open but few placebo-controlled studies,¹¹ with 44% to 83% showing partial to complete

effect. For example, Price et al.²⁴ conducted a placebo-controlled evaluation of the effectiveness of lithium augmentation of a variety of antidepressants in a mixed group of 84 delusionally depressed in- and outpatients. Forty-eight percent were defined as responders, with only 31% showing "marked" response. Although the effect with lithium was initially reported by de Montigny to occur rapidly in many subjects,²² response in others may require up to 6 weeks.²⁵

Alternatively, little research has supported the effectiveness of lithium augmentation of MAOIs¹¹ or SSRIs. Delgado et al.²⁶ conducted an open trial of lithium augmentation in 18 patients with depression (16 unipolar, 2 bipolar) who had failed fluvoxamine treatment, with half responding. Clearly, much more study is needed.

Early open trials supported the usefulness of adding triiodothyronine (T₃) to tricyclics in refractory patients.²⁷ Subsequent controlled trials have produced somewhat mixed results.²⁸ However, overall, the results are supportive. For example, Joffe et al.²⁹ studied 51 patients who were refractory to tricyclics. Patients were randomly assigned to 3 groups: T₃, 37.5 µg/day; lithium carbonate, 900 mg/day; or placebo. T₃ (59% response) was as effective as lithium (53% response), and both were much more effective than placebo (19% response). This rigorous study supports the effectiveness of both T₃ and lithium augmentation of tricyclics. However, studies of thyroid hormone augmentation of MAOIs, SSRIs, or other antidepressants are lacking.

Baron and colleagues³⁰ reported in 1988 that the combination of desipramine and fluoxetine produced a more rapid down-regulation of central β-receptors than either drug given singly. This was followed by case series reports of combined heterocyclic-SSRI combinations in refractory patients.³¹⁻³⁵ These reports suggest that the combination of a noradrenergic heterocyclic agent (like desipramine or bupropion) and an SSRI may be an effective combination in some refractory patients. However, controlled studies are needed in order to confirm these results.

Several early anecdotal reports and open series recounted the beneficial effect of a combination of a tricyclic and an MAOI antidepressant in depressed patients refractory to either agent alone.^{11,28,36} There were no subsequent controlled studies of the combination. However, Davidson and coworkers³⁷ demonstrated that a combination of amitriptyline and phenelzine was less effective than ECT.

A variety of other combination treatments have been reported with varying success. These include combining anticonvulsants, particularly carbamazepine, with antidepressants. Uncontrolled trials have yielded success rates ranging from 20% to 40%.^{11,38,39} Other combination treatments include the coadministration of psychostimulants such as dextroamphetamine or methylphenidate with tricyclics or MAOIs,^{14,28,40} estrogen supplementation in

women with refractory depression,⁴¹ buspirone augmentation of tricyclics or SSRIs,^{42,43} or pindolol augmentation of SSRIs.⁴⁴

There are 2 other promising possibilities, the first being steroid suppressive therapies. In an open trial, Murphy et al.⁴⁵ found that monotherapy with steroid suppressive drugs such as aminoglutethimide, ketoconazole, or metyrapone produced significant remission of depressive symptoms in 6 of 8 patients with refractory depression, with partial response in the other 2. These results are somewhat supported by the findings of Amsterdam et al.⁴⁶ This group treated 6 depressed patients who had elevated 24-hour urinary free cortisol with ketoconazole. Four of the 6 experienced a partial response. These groups have speculated that any improvement in depression in this population may be a readjustment or normalization of the abnormalities of the hypothalamic-pituitary-adrenal axis in depression. Steroid suppression either as a monotherapy or augmentation approach may emerge as a new adjunct in refractory depression.

A second, largely untested, area is the effectiveness of atypical antipsychotics. For example, Dassa and colleagues⁴⁷ have reported on a 40-year-old woman with refractory major depression with psychotic features who had failed a series of drug treatments and ECT. She experienced resolution of her psychotic symptoms and improvement in depression with clozapine. In a later publication, Jacobsen⁴⁸ reported that 17 of 20 patients with affective disorders (including 4 with unipolar major depression) experienced improvement in symptoms with the addition of risperidone. These data suggest that atypical antipsychotics may be beneficial in some refractory depressives, although much more research is needed to establish efficacy.

Electroconvulsive Therapy

For patients who have failed to respond to a single antidepressant, either a tricyclic or MAOI, response rates with ECT have ranged from 50% to 89%.¹¹ However, no studies have adequately evaluated patients who have failed multiple courses and combinations of drug therapies or those who have failed to respond to other types of antidepressants. Unfortunately, even if response occurs, the problem is only partly solved. Continuation pharmacotherapy usually is effective in nonrefractory patients following ECT.^{49,50} However, a significant percentage of patients treated with ECT will relapse following acute response.^{51,52} Continuation ECT remains somewhat undesirable because of cost, convenience, and safety issues. However, it may be the only hope for certain patients who experience acute response to ECT. Petrides and colleagues⁵³ followed 21 patients receiving continuation ECT after initial positive response. Relapse occurred in one third, including 42% of delusional depressives. These rates may be lower than would be expected without continuation treatment.

Psychotherapy

Psychotherapy is commonly used in the management of refractory depression.⁵⁴ However, the effectiveness of psychotherapy, either alone or in combination with medications, in the management of pharmacologically nonresponsive patients with depression is largely unresearched. Several case series¹¹ have shown modest success with cognitive-behavioral psychotherapy, but controlled research is needed.

CONCLUSION

A significant proportion of patients with depression will experience an incomplete response to antidepressant drug therapy. There are several important elements in dealing with this population. All drug trials should be rigorously applied. That is, in the face of nonresponse to standard doses, each drug should be taken to the maximum tolerable level within the recommended range for at least 4 weeks. Those who have shown essentially no improvement should then be treated with an antidepressant of an alternative class. For example, this could involve switching an SSRI to either a mixed serotonin norepinephrine reuptake inhibitor (i.e., venlafaxine, mirtazapine, or imipramine) or a predominantly noradrenergic agent (desipramine or bupropion).

Partial responders to an initial monotherapy trial or those who fail a second drug should receive augmentation. Lithium augmentation remains the most rigorously tested strategy and, generally, should be taken as a first-line approach. Augmentation alternatives, including T₃, heterocyclic-SSRI combinations, and others outlined earlier, may then be tried. ECT can be held as an approach of last resort, with continuation treatment used if early relapse occurs in face of adequate maintenance pharmacotherapy. Therapeutic nihilism is not justified for most patients. In fact, a key element in the successful management of refractory depression is countering hopelessness in both the patient and the pharmacotherapist. Aggressive and systematic pharmacotherapy is helpful in the majority of depressed patients.

Drug names: aminoglutethimide (Cytadren), amitriptyline (Elavil and others), bupropion (Wellbutrin), bupropion (BuSpar), carbamazepine (Tegretol and others), clozapine (Clozaril), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), ketoconazole (Nizoral), methylphenidate (Ritalin), metyrapone (Metopirone), mirtazapine (Remeron), norepinephrine (Levophed), paroxetine (Paxil), phenelzine (Nardil), pindolol (Visken), risperidone (Risperdal), sertraline (Zoloft), triiodothyronine (Cytomel and others), venlafaxine (Effexor).

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DISCLOSURE OF OFF-LABEL USAGE

The following agents mentioned in this article are *not* indicated for augmentation of antidepressants: buspirone, carbamazepine, lithium, pindolol, psychostimulants, triiodothyronine.

The following agents mentioned in this article are *not* indicated for steroid suppressive therapies: aminoglutethimide, ketoconazole, metyrapone.

The following agents mentioned in this article are *not* indicated for refractory depression: atypical antipsychotics.