Issues in Treatment-Resistant Depression

Martin B. Keller, M.D.

Major depressive disorder is a debilitating disease that imposes significant social and economic burdens not only on patients but also on society. Although various treatment options are available, treatment-resistant depression is common. Determining the exact prevalence of treatment-resistant depression is difficult because definitions vary, as do definitions of antidepressant response. Operational definitions of antidepressant response, nonresponse, partial response, and remission will be discussed in this article. Pharmacotherapy options for patients with treatment-resistant depression include augmentation, combination, and switching therapies; however, data from controlled clinical trials supporting these therapies are limited. Electroconvulsive therapy and psychotherapy offer additional treatment strategies. New nonpharmacologic therapies are under investigation. Remission is the goal of treatment. *(J Clin Psychiatry 2005;66[suppl 8]:5–12)*

Major depressive disorder is a debilitating disease that imposes significant social and economic burdens on both patients and society. Depression affects more than 18 million people in the United States and 340 million people worldwide.[1] The lifetime risk of major depressive disorder is estimated at more than 15%, with women affected almost twice as often as men.[2] Although numerous treatment options are available for depression, many patients do not respond to initial therapy.

TREATMENT-RESISTANT DEPRESSION

Determining the number of people who are resistant to treatment is difficult because of the use of varying definitions of treatment resistance, treatment response, and remission in the published literature. Treatment-resistant depression has been variously defined as failure to respond to 1 trial of antidepressant monotherapy, failure to respond to 2 or more trials of monotherapy with different antidepressants, and failure to respond to 4 or more trials of different antidepressant therapies, including augmentation, combination, and electroconvulsive therapy (ECT). Thase and Rush[3] designed a model that describes 5 stages of treatment-resistant depression; this model can be used as a guide for choosing treatment strategies (Figure 1). Patients in stages III, IV, and V are considered treatment refractory.

Defining treatment-resistant depression is further complicated by the use of varying definitions of antidepressant response. Operational definitions of treatment response generally refer to percentage improvement on standardized rating scales, including the Clinical Global Impressions scale (CGI),[4] Montgomery-Asberg Depression Rating Scale (MADRS),[5] and Hamilton Rating Scale for Depression (HAM-D).[6] The HAM-D is considered the gold standard of assessment tools for depression and is often used as a comparator for newer test instruments. Comparable sensitivity of these scales was recently demonstrated in a retrospective chart review of 208 patients who participated in 8 randomized placebo-controlled trials of antidepressants.[7] Effect sizes were similar for the HAM-D, MADRS, and 2 CGI scales (CGI-Severity of Illness and CGI-Improvement) for all antidepressants studied.

Operational definitions of antidepressant response are classified into 4 categories: nonresponse, partial response, treatment response, and remission.[8] Partial response is typically defined as a greater than 25% but less than 50% decrease in depression assessment scale scores; treatment response is defined as a 50% or greater decrease in scores with a final HAM-D score of 15 or less. Patients who have no clinically meaningful response to treatment are considered nonresponders.[8]

Although the definition of remission is still evolving, it can be summarized as the absence of depressive symptoms or the presence of minimal residual symptoms.[8,9] A debate exists regarding whether assessment at a single time point (e.g., at the end of a clinical trial) is acceptable in defining remission or whether remission should be defined as no or few symptoms sustained over a predefined length of time.[9] Naturalistic data from a recent study demonstrated that remission at 4 weeks was predictive of remission at 8, 12,

From the Department of Psychiatry and Human Behavior, Brown University, Providence, R.I.

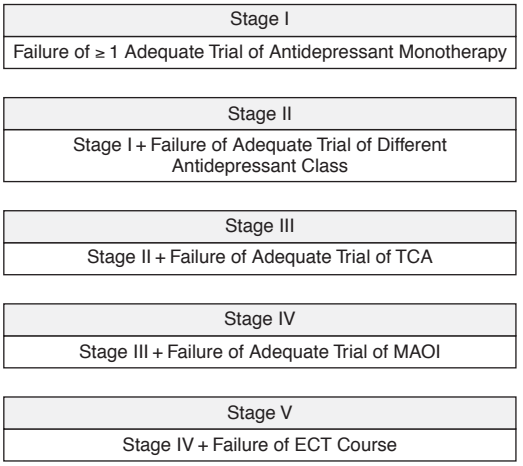
This article is derived from the planning roundtable "New Therapies for Treatment-Resistant Depression and Anxiety," which was held September 28–29, 2003, in Atlanta, Ga., and supported by an educational grant from Janssen Medical Affairs, L.L.C.

Corresponding author and reprints: Martin B. Keller, M.D., Box G-BH, Brown University, Providence, RI 02912 (e-mail: martin_keller@brown.edu).

© COPYRIGHT 2005 PHYSICIANS POSTGRADUATE PRESS, INC.

© COPYRIGHT 2005 PHYSICIANS POSTGRADUATE PRESS, INC.

Figure 1. Staging Criteria for Treatment-Resistant Depression[a]



[a]Adapted with permission from Thase and Rush.[3]
Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, TCA = tricyclic antidepressant.

and 26 weeks (Judd et al., unpublished data, 2003); further studies may be warranted to determine a clinically relevant time frame for defining remission. Return to full psychosocial functioning is an important component of remission, and separate evaluation may be necessary to identify patients who have achieved remission.[10] Recovery, which is distinct from remission, has been defined as failure to meet syndromal criteria for major depressive disorder for at least 8 weeks.[11]

Risk Factors

Approximately 30% to 45% of patients diagnosed with depression do not have an adequate response to a first trial of antidepressant therapy.[12] Among these patients, 12% to 15% exhibit partial response, and 19% to 34% are considered nonresponders.[12] Several patient-related and treatment-related risk factors have been identified that increase the likelihood of nonresponse to antidepressant treatment.[13] Patient-related risk factors include disease severity[13] and concomitant medical or psychiatric disorders, such as alcohol abuse[14] or anxiety disorders.[15] Limited data also suggest that there may be a familial predisposition to poor response to antidepressants in which serotonin transporter gene polymorphisms may play a role.[16–18] Treatment-related risk factors include inadequate antidepressant drug dose and duration, inaccurate diagnosis, and treatment noncompliance.[13,19]

Patients with chronic subtypes of depression (chronic major depressive disorder, double depression, and recurrent major depressive disorder) may take longer to respond to treatment, which may contribute to treatment failure by causing clinicians to discontinue treatment prematurely.[13]

Economic Impact

Patients with treatment-resistant depression are generally considered the most disabled of those with major depressive disorder.[1,8] In 2001, an update of the World Health Organization and World Bank Global Burden of Disease Study,[1] which assessed the global burden of more than 100 diseases, reported that neuropsychiatric disorders combined accounted for the greatest percentage of the total years of life with disability (YLDs) of all diseases (31%), and unipolar major depressive disorder alone accounted for 12% of global YLDs. Major depressive disorder ranked first as a cause of disability-adjusted life years in developed countries throughout the world.[20]

In a retrospective analysis of medical claims data, Crown et al.[19] assessed the economic impact of treatment-resistant depression. The study included data from 3370 patients with treatment-resistant depression (483 inpatients; 2887 outpatients) and 7335 patients with non–treatment-resistant depression. Depression-related costs, general medical costs, and total health care costs were compared among treatment groups. Total annual depression-related costs over a 5-year period were significantly higher for patients with treatment-resistant depression ($28,001 for inpatients; $3699 for outpatients) compared with those who were not treatment resistant ($1455; $p < .001$, treatment-resistant vs. non–treatment-resistant depression). Total general medical costs were highest for treatment-resistant inpatients ($14,343), followed by treatment-resistant outpatients ($6542) and non–treatment-resistant patients ($5057; $p < .001$). The treatment-resistant inpatients had the highest total annualized health care costs ($42,344) compared with both the treatment-resistant outpatients ($10,241) and the non–treatment-resistant patients ($6512). Because Crown et al.[19] did not measure lost productivity of patients or family members, these findings may underestimate the true costs of treatment-resistant depression.

USE OF NEXT-STEP TREATMENT STRATEGIES IN CLINICAL PRACTICE

Several treatment options are available for patients with depression who do not respond to first-line therapy. In clinical practice, the choice of next-step therapy depends on the first-line treatment used, the clinician's recent treatment successes, and institutional and regional preferences. Surveys have been conducted to identify the strategies most commonly used by clinicians.[21,22]

The Psychopharmacology Working Group and the Research Committee of the Royal College of Psychiatrists in the United Kingdom conducted a survey of 300 psychiatrists to determine preferences for treating patients who did not respond to first-line treatment with a tricyclic antidepressant.[21] A total of 175 clinicians answered questions about a 1-page clinical vignette. The most common next-

© Copyright 2005 Physicians Postgraduate Press, Inc. © Copyright 2005 Physicians Postgraduate Press, Inc.

step treatment choice was to increase the dose of the tricyclic antidepressant (45%), followed by switching to a selective serotonin reuptake inhibitor (SSRI) (32%). Electroconvulsive therapy (20%), lithium augmentation (12%), and continuing the original treatment for another 4 weeks (4%) were less commonly used.[21] This U.K. study was based on a previous study[23] in which the same clinical vignette was presented to 118 psychiatrists in the northeastern United States. Among these clinicians, lithium augmentation was the most common next-step option for treatment-resistant depression (34%). Continuing treatment with the same tricyclic antidepressant for another 2 weeks (18%) and switching to an SSRI (16%) were the next most frequent selections, followed by ECT (11%). In contrast to the U.K. study,[21] few psychiatrists in the United States suggested increasing the tricyclic dose.[23]

Vignettes used in these studies were expanded for a survey by Fredman et al.[22] about choice of therapy for nonresponders to initial treatment with an SSRI. Among the 432 clinicians who completed the survey, 44% indicated that switching to a non-SSRI drug was the preferred next-step treatment for patients who do not respond after 8 weeks of adequate SSRI treatment. The next most popular treatments were increasing the SSRI dose (27%), switching to another SSRI (17%), and augmenting with another agent (12%).

In treating patients who partially respond to an SSRI, 2 U.S. surveys[22,24] indicated that increasing the SSRI dose is the most common treatment choice among clinicians. This is an interesting finding, considering that some SSRIs appear to have flat dose-response curves.[25–27] Although a clear dose-response relationship has been demonstrated with venlafaxine,[28] results of studies of increasing doses of SSRIs other than venlafaxine have not been consistent in showing a dose-response relationship.[29–32]

TREATMENT OPTIONS FOR TREATMENT-RESISTANT DEPRESSION

Both nonpharmacologic and pharmacologic therapies are available for patients with treatment-resistant depression. Pharmacotherapy strategies include augmenting an antidepressant with a drug of another class, such as an antipsychotic or antiepileptic; combining antidepressants; and switching from one antidepressant to another. However, few controlled clinical trials have been conducted to assess the efficacy of these options. In addition, no drug therapy has been approved by the U.S. Food and Drug Administration for treatment-resistant depression. Therefore, specific mention of any treatment for treatment-resistant depression is off label.

Augmentation Therapy

Treatment augmentation is the addition of a non-antidepressant drug to boost or enhance the effect of a currently prescribed antidepressant. The most commonly studied augmenting agent is lithium.[33–36] Other agents for which small studies have been published include buspirone,[37,38] lamotrigine,[39,40] bupropion,[41] pindolol,[42] and triiodothyronine[35] (Table 1). Benefits of augmentation therapy include rapid onset of action, no withdrawal symptoms, and continued use of the antidepressant that produced an initial, although inadequate, response. Disadvantages include possible drug-drug interactions, increased costs, and additional medication, which may affect patient compliance.

Table 1. Response Rates From Selected Augmentation Studies[a]

Antidepressant	Augmenting Agent	Response Rate (%) Active Drug	Placebo	p
Amitriptyline, dothiepin, imipramine	Lithium	44	22	< .01
Citalopram	Lithium	60	14	< .05
Desipramine, imipramine	Lithium	53	19	.038
Desipramine, imipramine	Triiodothyronine	59	19	.018
Citalopram, fluoxetine, paroxetine	Buspirone	59	…	…
Clomipramine	Buspirone	63	…	…
Citalopram, paroxetine	Buspirone	51	47	NS
Fluoxetine	Pindolol	75	59	.04
Nortriptyline	Lithium	13	20	NS
Fluoxetine	Lamotrigine	85	30	.013
Various	Lamotrigine	41	…	…
SSRIs, venlafaxine	Bupropion	54	…	…

[a]Data from Stein and Bernadt,[33] Baumann et al.,[34] Joffe et al.,[35] Nierenberg et al.,[36] Dimitriou and Dimitriou,[37] Landen et al.,[38] Barbosa et al.,[39] Barbee and Jamhour,[40] DeBattista et al.,[41] and Perez et al.[42]

Abbreviations: NS = not significant, SSRI = selective serotonin reuptake inhibitor. Symbol: … = no data.

Placebo-controlled studies from the early 1990s demonstrated that adding lithium had significant antidepressant effects in treatment-resistant patients originally treated with tricyclic antidepressants.[33,35] Stein and Bernadt[33] conducted a study of 34 patients treated with a tricyclic antidepressant augmented with lithium for 9 weeks. In addition to the tricyclic antidepressant, patients were treated with lithium 250 mg/day for 3 weeks followed by lithium 750 mg/day for the remaining 6 weeks (N = 16) or were treated with placebo for the first 3 weeks, lithium 250 mg/day for weeks 3 to 6, and lithium 750 mg/day for weeks 6 to 9 (N = 18). Mean ± SD plasma lithium levels in the group treated with lithium for 9 weeks were 0.76 ± 0.45 mmol/L at week 4 and 0.78 ± 0.35 mmol/L at week 7. In the group that received placebo for the first 3 weeks and then received lithium for the remaining 6 weeks, mean ± SD plasma lithium levels were 0.25 ± 0.15 mmol/L at week 4 and 0.65 ± 0.21 mmol/L at week 7. During weeks 3 to 6, patients receiving lithium 750 mg/day had significant improvement in MADRS scores compared with those receiving lithium 250 mg/day ($p < .01$). Treatment response, defined as a 50% or greater decrease in HAM-D scores (the

© Copyright 2005 Physicians Postgraduate Press, Inc. © Copyright 2005 Physicians Postgraduate Press, Inc.

authors did not define response as a HAM-D score of 15 or less), was seen in 44%, 18%, and 22% of patients treated with lithium 750 mg/day, lithium 250 mg/day, and placebo, respectively.[33]

Joffe et al.[35] conducted a similar study of 50 patients with unipolar depression who did not respond to a tricyclic antidepressant. Patients were randomly assigned to receive liothyronine 37.5 μg/day (N = 17), lithium 900 to 1200 mg/day (N = 17), or placebo (N = 16), in addition to their tricyclic antidepressant for 2 weeks. Response rates, defined as a greater than 50% decrease in HAM-D scores and a final HAM-D score of less than 10, were 59%, 53%, and 19% for patients treated with liothyronine, lithium, and placebo, respectively.

In a randomized placebo-controlled trial, 23 patients who did not respond to an adequate antidepressant trial were treated with fluoxetine 20 mg/day and had lamotrigine 25 to 100 mg/day (N = 13) or placebo (N = 10) added to their treatment regimen for 6 weeks.[39] Patients had previously been treated with a tricyclic antidepressant (N = 17), citalopram (N = 5), or venlafaxine (N = 3). Response rates, defined as a CGI-Improvement score of 2 or less, were significantly greater in the lamotrigine group than in the placebo group (85% and 30%, respectively; p = .013).

In a small 8-week double-blind study of augmentation with an atypical antipsychotic,[43] patients with a partial response to fluoxetine had significantly greater improvement in MADRS scores when treated with olanzapine 5 to 20 mg/day plus fluoxetine 20 to 60 mg/day (N = 10) than when they continued on fluoxetine alone (N = 10) (p < .05). Additional studies of augmentation of antidepressants with olanzapine and with risperidone are reviewed by Nemeroff[44] in this supplement.

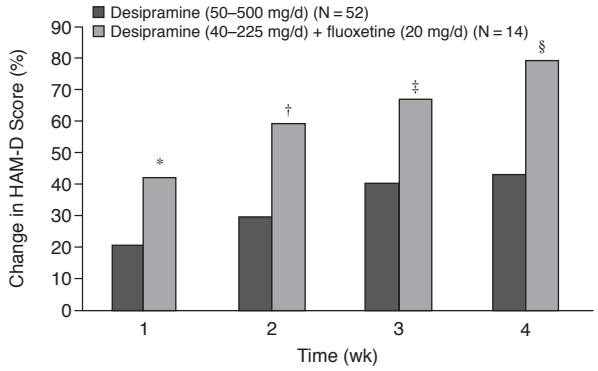
Although lithium has been the most rigorously studied augmentation agent, data are limited by the short treatment duration of most of these trials. There is also no evidence that certain commonly used agents, such as clonazepam and valproic acid, are effective as augmenting agents.

Combination Therapy

Combination therapy is the use of at least 2 antidepressants that have well-established efficacy.[45] Advantages of this treatment option include avoiding withdrawal symptoms, rapid onset of action, and continuation of the drug that produced a partial response. Disadvantages include increased costs, poorer patient compliance, and the risk of drug-drug interactions.

In 1991, Nelson et al.[46] conducted a 4-week open-label study of combination therapy with fluoxetine and desipramine in 14 patients with major depression who had not responded to 1 week of hospitalization without antidepressant treatment. Results were compared with 52 inpatients treated with desipramine alone. Patients treated with both drugs had a 42% decrease in HAM-D scores after 1 week compared with a 20% decrease for patients treated with desipramine alone (p = .007) (Figure 2). Patients who received combination therapy continued to have a greater improvement in HAM-D scores over 4 weeks compared with those who received monotherapy.

Figure 2. Percentage Change in HAM-D Scores With Desipramine Alone and in Combination With Fluoxetine[a]



[a]Reprinted with permission from Nelson et al.[46]
*p = .007 vs. desipramine.
†p = .001 vs. desipramine.
‡p = .004 vs. desipramine.
§p = .0001 vs. desipramine.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

In a subsequent 6-week, randomized, double-blind study, Nelson et al.[47] compared the efficacy of fluoxetine 20 mg/day plus flexible-dose desipramine (N = 13) with that of either fluoxetine (N = 14) or desipramine (N = 21) alone. Remission rates, defined as a 75% improvement in MADRS scores and a final score of 9 or less, were significantly higher in the combined treatment group than in either the fluoxetine or desipramine monotherapy groups (54%, 7%, and 0%, respectively; p = .001). Unlike the earlier study by Nelson et al.,[46] there were no significant between-group differences in mean scores on the MADRS at weeks 1 or 2.

Maes et al.[48] conducted a 4-week, double-blind, placebo-controlled study of trazodone in combination with fluoxetine or pindolol in 33 patients with major depression, 26 of whom were treatment resistant. Patients were randomly assigned to receive trazodone 100 mg/day in combination with placebo (N = 10), fluoxetine 20 mg/day (N = 12), or pindolol 7.5 mg/day (N = 11). In the subset of patients with treatment-resistant depression, mean ± SD improvements in HAM-D scores from baseline to endpoint were significantly greater in the trazodone plus pindolol (14.5 ± 4.0) or trazodone plus fluoxetine (14.9 ± 5.9) groups than in the placebo group (5.5 ± 5.5; p = .002).

Switching Therapy

The third pharmacotherapy option for patients who do not respond to initial antidepressant therapy is switching

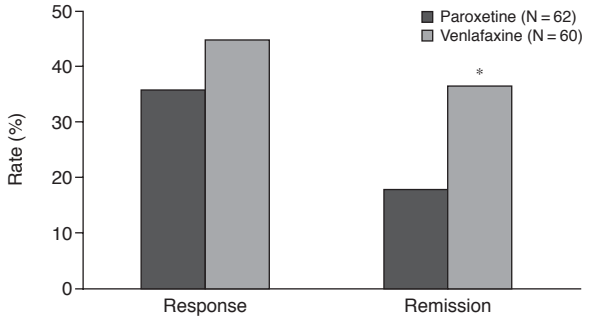
© Copyright 2005 Physicians Postgraduate Press, Inc. © Copyright 2005 Physicians Postgraduate Press, Inc.

drugs. The advantages of switching to a different drug include improved patient compliance, fewer adverse effects, and improved response. Further, because the patient continues to take only 1 medication, switching may be more cost-effective than augmentation or combination therapies. Disadvantages include the possibility of withdrawal symptoms, patient reluctance to take a new drug, and time lag between initiation of the new drug and treatment response. Therapy may involve different antidepressants with distinct pharmacologic profiles or switching to an antidepressant within the same class.

Thase et al.[49] investigated the efficacy of fluoxetine in 106 patients with major depressive disorder who did not respond to (N = 72) or were intolerant of (N = 34) treatment with sertraline 50 to 300 mg/day. Response was defined as a 50% or greater decrease in total HAM-D scores compared with baseline scores. At the end of the 6-week open-label trial, 63% of patients had a 50% or greater improvement in HAM-D scores after treatment with fluoxetine at a maximum dosage of 60 mg/day. In a double-blind study by Thase et al.,[50] patients who did not respond to 12 weeks of treatment with either sertraline (N = 117) or imipramine (N = 51) were switched to the alternate drug for 12 additional weeks. Response rates according to predefined HAM-D and CGI score criteria (at least a 50% decrease in total HAM-D score to a final score of ≤ 15 and a CGI-Severity of Illness score of ≤ 3) were 60% and 44% for sertraline and imipramine, respectively, for the intent-to-treat analysis (p = .03); between-drug differences in response and remission rates were not significant for patients who completed the trial.

Poirier and Boyer[51] conducted a double-blind trial of venlafaxine and paroxetine in patients who had not responded to 2 prior antidepressant trials. Patients were randomly assigned to receive venlafaxine 200 to 300 mg/day (N = 60) or paroxetine 30 to 40 mg/day (N = 62) for 4 weeks. Response was defined as a greater than 50% decrease in HAM-D scores, and remission was defined as a HAM-D score of less than 10 on day 28 of treatment. In the observed case analysis, patients treated with venlafaxine had a response rate of 52% and a remission rate of 42%; patients treated with paroxetine had a 33% response rate and a 20% remission rate (p = .01). Last observation carried forward response and remission rates are shown in Figure 3.

Figure 3. Response and Remission Rates for Patients Treated With Venlafaxine or Paroxetine (last observation carried forward)[a,b]



[a] Reprinted with permission from Poirier and Boyer.[51]
[b]Patients with history of resistance to 2 previous antidepressant trials and a 17-item Hamilton Rating Scale for Depression score of ≥ 18; randomly assigned to receive venlafaxine (mean dose = 269 mg/d) or paroxetine (mean dose = 36.3 mg/d) for 28 days.
*p < .05 vs. paroxetine.

Nonpharmacologic Strategies

Although pharmacotherapy is generally the first-line option for treatment-resistant depression, ECT and psychotherapy offer additional treatment strategies. Also, new nonpharmacologic therapies are being investigated.

Electroconvulsive therapy was considered an effective treatment option for depression before the era of antidepressant medication.[52] Today, few clinicians surveyed would choose ECT as a first-line option after failure to respond to treatment with 1 antidepressant[21,23]; however, studies show ECT is effective.[52,53]

Folkerts et al.[52] compared the effects of ECT with those of paroxetine in 39 patients with major depression who had not responded to at least 2 antidepressant trials. Patients were randomly assigned to treatment with paroxetine 20 to 50 mg/day for 4 weeks (N = 18) or right unilateral ECT (mean = 7.2 treatments over 2–3 weeks) (N = 21) followed by paroxetine or another antidepressant for 4 weeks. Patients in the paroxetine group who had a less than 50% decrease in HAM-D scores at 4 weeks were treated with ECT or another antidepressant for 2 weeks. After 2 to 3 weeks of ECT, 71% of patients had responded to treatment, defined as a decrease of at least 50% in the baseline HAM-D score, compared with 28% of patients treated with paroxetine for 4 weeks (p < .006). Baseline HAM-D scores were decreased by 60% in the ECT group and 30% in the paroxetine group at study endpoint (p < .001).

A retrospective study investigated combination treatment with ECT and venlafaxine in 13 patients with major depression who had failed 2 prior antidepressant trials.[53] The venlafaxine dosage was 150 to 375 mg/day, and the number of ECT sessions was 6 to 12 per patient. At day 28, 10 (77%) of 13 patients had responded to treatment, defined as a greater than 50% decrease in HAM-D scores and a CGI-Improvement score of 1 or 2.

Cognitive, behavioral, or interpersonal psychotherapy, conducted individually or in group settings, can also be helpful in patients with treatment-resistant depression.[54] Psychotherapy typically lasts from 10 to 16 weeks. Although limited data support the efficacy of psychotherapy in treatment-resistant depression, clinicians must consider all options when choosing among treatment modalities.

© Copyright 2005 Physicians Postgraduate Press, Inc.

© Copyright 2005 Physicians Postgraduate Press, Inc.

Transcranial magnetic stimulation or repetitive transcranial magnetic stimulation,[55,56] vagus nerve stimulation,[57,58] and deep brain stimulation (B. Greenberg, M.D., Ph.D., oral communications, 2002–2004) are new nonpharmacologic therapies for treatment-resistant depression; however, study results have been mixed. Further studies that include investigation of long-term outcomes are needed.

TREATMENT RECOMMENDATIONS

Many approaches are used to treat treatment-resistant depression, none of which are approved by the U.S. Food and Drug Administration. Based on available published evidence and clinical experience, the following suggestions should be considered. If a patient does not respond to monotherapy with an SSRI, switching to another SSRI is the preferred option. If response is limited but treatment is well tolerated, augmentation should follow. If treatment with an SSRI is not well tolerated, switching to venlafaxine is the preferred treatment option. If the patient does not respond to venlafaxine, bupropion would be used as augmentation therapy, followed by a mood stabilizer. Treatment with a monoamine oxidase inhibitor, either alone or in combination with lithium, should be considered before ECT. Also, assessing the degree of prior response can aid in determining whether treatment should be augmented or switched.

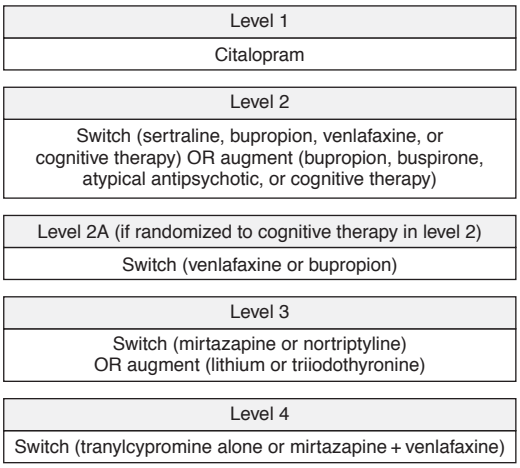
SEQUENCED TREATMENT ALTERNATIVES TO RELIEVE DEPRESSION

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study currently being conducted by the National Institute of Mental Health is designed to identify optimal treatment after failure of initial antidepressant monotherapy.[59] This multisite, prospective, sequentially randomized study has a target accrual of 4000 adults aged 18 to 75 with nonpsychotic major depressive disorder. The primary study outcome is the 17-item HAM-D score, and secondary measures include the Inventory of Depressive Symptomatology-Clinician score, self-reported depressive symptoms, physical and mental function, adverse event burden, patient satisfaction, and health care use.[59] Patients nonresponsive to treatment at each of 4 sequential treatment levels will proceed to the next treatment option (Figure 4). Results from this study[59] should provide additional outcomes information regarding symptoms, function, adverse events, health care use, and cost estimates related to treatment-resistant depression that will be useful in clinical practice.

CONCLUSION

Treatment-resistant depression is common and associated with considerable personal and societal burdens. A trial of an antidepressant agent is the first step in treating patients with treatment-resistant depression. The next steps are not well defined, given a lack of controlled trials. The goal of treatment is remission. To help reach this goal, studies of biological predictors of response are needed, as is a randomized trial of predictors of nonresponse in treatment-naive patients.

Figure 4. Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Schema[a,b]



[a]Adapted with permission from Fava et al.[59]
[b]Twelve-month continuation/follow-up after achieving adequate response.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lamotrigine (Lamictal), liothyronine (Triostat and Cytomel), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), pindolol (Visken and others), risperidone (Risperdal), sertraline (Zoloft), trazodone (Desyrel and others), valproic acid (Depakene and others), venlafaxine (Effexor).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, bupropion, buspirone, citalopram, clomipramine, clonazepam, desipramine, fluoxetine, imipramine, lamotrigine, liothyronine, lithium, mirtazapine, nortriptyline, olanzapine, paroxetine, pindolol, risperidone, sertraline, trazodone, valproic acid, and venlafaxine are not approved by the U.S. Food and Drug Administration for treatment-resistant depression.

REFERENCES

1. Murray C, Lopez AD. The Global Burden of Disease. Cambridge, Mass: Harvard University Press; 1996
2. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289:3095–3105
3. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. J Clin Psychiatry 1997;58(suppl 13): 23–29
4. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222

© Copyright 2005 Physicians Postgraduate Press, Inc. © Copyright 2005 Physicians Postgraduate Press, Inc.

5. Montgomery SA, Asberg MC. A new depression rating scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
6. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
7. Khan A, Khan SR, Shankles EB, et al. Relative sensitivity of the Montgomery-Asberg Depression Rating Scale, the Hamilton Depression Rating Scale and the Clinical Global Impressions rating scale in antidepressant clinical trials. Int Clin Psychopharmacol 2002;17:281–285
8. Greden JF. The burden of disease for treatment-resistant depression. J Clin Psychiatry 2001;62(suppl 16):26–31
9. Nierenberg AA, DeCecco LM. Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: a focus on treatment-resistant depression. J Clin Psychiatry 2001;62(suppl 16):5–9
10. Keller MB. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. JAMA 2003;289: 3152–3160
11. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 1991;48:851–855
12. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am 1996;19:179–200
13. Kornstein SG, Schneider RK. Clinical features of treatment-resistant depression. J Clin Psychiatry 2001;62(suppl 16):18–25
14. Castaneda R, Sussman N, Westreich L, et al. A review of the effects of moderate alcohol intake on the treatment of anxiety and mood disorders. J Clin Psychiatry 1996;57:207–212
15. McLeod JD, Kessler RC, Landis KR. Speed of recovery from major depressive episodes in a community sample of married men and women. J Abnorm Psychol 1992;101:277–286
16. Arias B, Catalan R, Gasto C, et al. 5-HTTLPR polymorphism of the serotonin transporter gene predicts non-remission in major depression patients treated with citalopram in a 12-week follow up study. J Clin Psychopharmacol 2003;23:563–567
17. Wetter TC, Ising M. Association between polymorphism within the promoter region of the serotonin transporter gene and treatment response in depression: further evidence but still controversial issues. Sleep Med 2004;5:93–95
18. Rausch JL, Johnson ME, Fei YJ, et al. Initial conditions of serotonin transporter kinetics and genotype: influence on SSRI treatment trial outcome. Biol Psychiatry 2002;51:723–732
19. Crown WH, Finkelstein S, Berndt ER, et al. The impact of treatment-resistant depression on health care utilization and costs. J Clin Psychiatry 2002;63:963–971
20. World Health Organization. Mental health: new understanding, new hope. Available at: http://www.who.int/whr2001/2001/main/en/pdf/chapter2.en.pdf. Accessed June 21, 2004
21. Shergill SS, Katona CL. Pharmacological choices after one antidepressant fails: a survey of UK psychiatrists. J Affect Disord 1997;43:19–25
22. Fredman SJ, Fava M, Kienke AS, et al. Partial response, nonresponse, and relapse with selective serotonin reuptake inhibitors in major depression: a survey of current "next-step" practices. J Clin Psychiatry 2000;61: 403–408
23. Nierenberg AA. Treatment choice after one antidepressant fails: a survey of northeastern psychiatrists. J Clin Psychiatry 1991;52:383–385
24. Mischoulon D, Nierenberg AA, Kizilbash L, et al. Strategies for managing depression refractory to selective serotonin reuptake inhibitor treatment: a survey of clinicians. Can J Psychiatry 2000;45:476–481
25. Benkert O, Szegedi A, Wetzel H, et al. Dose escalation vs continued doses of paroxetine and maprotiline: a prospective study in depressed outpatients with inadequate treatment response. Acta Psychiatr Scand 1997;95:288–296
26. Reynaert C, Parent M, Mirel J, et al. Moclobemide versus fluoxetine for a major depressive episode. Psychopharmacology (Berl) 1995;118: 183–187
27. Fabre LF, Abuzzahab FS, Amin M, et al. Sertraline safety and efficacy in major depression: a double-blind fixed-dose comparison with placebo. Biol Psychiatry 1995;38:592–602
28. Kelsey JE. Dose-response relationship with venlafaxine. J Clin Psychopharmacol 1996;16:21S–26S
29. Franchini L, Gasperini M, Perez J, et al. Dose-response efficacy of paroxetine in preventing depressive recurrences: a randomized, double-blind study. J Clin Psychiatry 1998;59:229–232
30. Fava M, Rosenbaum JF, Cohen L, et al. High-dose fluoxetine in the treatment of depressed patients not responsive to a standard dose of fluoxetine. J Affect Disord 1992;25:229–234
31. Fava M, Rosenbaum JF, McGrath PJ, et al. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. Am J Psychiatry 1994;151:1372–1374
32. Fava M, Alpert J, Nierenberg A, et al. Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and nonresponders to fluoxetine. J Clin Psychopharmacol 2002;22:379–387
33. Stein G, Bernadt M. Lithium augmentation therapy in tricyclic-resistant depression: a controlled trial using lithium in low and normal doses. Br J Psychiatry 1993;162:634–640
34. Baumann P, Nil R, Souche A, et al. A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. J Clin Psychopharmacol 1996; 16:307–314
35. Joffe RT, Singer W, Levitt AJ, et al. A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. Arch Gen Psychiatry 1993;50:387–393
36. Nierenberg AA, Papakostas GI, Petersen T, et al. Lithium augmentation of nortriptyline for subjects resistant to multiple antidepressants. J Clin Psychopharmacol 2003;23:92–95
37. Dimitriou EC, Dimitriou CE. Buspirone augmentation of antidepressant therapy. J Clin Psychopharmacol 1998;18:465–469
38. Landen M, Bjorling G, Agren H, et al. A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. J Clin Psychiatry 1998; 59:664–668
39. Barbosa L, Berk M, Vorster M. A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes. J Clin Psychiatry 2003;64:403–407
40. Barbee JG, Jamhour NJ. Lamotrigine as an augmentation agent in treatment-resistant depression. J Clin Psychiatry 2002;63:737–741
41. DeBattista C, Solvason HB, Poirier J, et al. A prospective trial of bupropion SR augmentation of partial and non-responders to serotonergic antidepressants. J Clin Psychopharmacol 2003;23:27–30
42. Perez V, Gilaberte I, Faries D, et al. Randomised, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. Lancet 1997;349:1594–1597
43. Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. Am J Psychiatry 2001;158:131–134
44. Nemeroff CB. Use of atypical antipsychotics in refractory depression and anxiety. J Clin Psychiatry 2005;66(suppl 8):13–21
45. Lam RW, Wan DD, Cohen NL, et al. Combining antidepressants for treatment-resistant depression: a review. J Clin Psychiatry 2002;63: 685–693
46. Nelson JC, Mazure CM, Bowers MB Jr, et al. A preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. Arch Gen Psychiatry 1991;48:303–307
47. Nelson JC, Mazure CM, Jatlow PI, et al. Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. Biol Psychiatry 2004;55:296–300
48. Maes M, Vandoolaeghe E, Desnyder R. Efficacy of treatment with trazodone in combination with pindolol or fluoxetine in major depression. J Affect Disord 1996;41:201–210
49. Thase ME, Blomgren SL, Birkett MA, et al. Fluoxetine treatment of patients with major depressive disorder who failed initial treatment with sertraline. J Clin Psychiatry 1997;58:16–21
50. Thase ME, Rush AJ, Howland RH, et al. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. Arch Gen Psychiatry 2002;59:233–239
51. Poirier MF, Boyer P. Venlafaxine and paroxetine in treatment-resistant depression: double-blind, randomised comparison. Br J Psychiatry 1999;175:12–16
52. Folkerts HW, Michael N, Tolle R, et al. Electroconvulsive therapy vs paroxetine in treatment-resistant depression: a randomized study. Acta Psychiatr Scand 1997;96:334–342
53. Gonzalez-Pinto A, Gutierrez M, Gonzalez N, et al. Efficacy and safety of venlafaxine-ECT combination in treatment-resistant depression.

© COPYRIGHT 2005 PHYSICIANS POSTGRADUATE PRESS, INC. © COPYRIGHT 2005 PHYSICIANS POSTGRADUATE PRESS, INC.

J Neuropsychiatry Clin Neurosci 2002;14:206–209
54. Thase ME, Friedman ES, Howland RH. Management of treatment-resistant depression: psychotherapeutic perspectives. J Clin Psychiatry 2001;62(suppl 18):18–24
55. Boutros NN, Gueorguieva R, Hoffman RE, et al. Lack of a therapeutic effect of a 2-week sub-threshold transcranial magnetic stimulation course for treatment-resistant depression. Psychiatry Res 2002;113: 245–254
56. Martis B, Alam D, Dowd SM, et al. Neurocognitive effects of repetitive transcranial magnetic stimulation in severe major depression. Clin Neurophysiol 2003;114:1125–1132
57. Marangell LB, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. Biol Psychiatry 2002;51:280–287
58. Sackeim HA, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. Neuropsychopharmacology 2001;25:713–728
59. Fava M, Rush AJ, Trivedi MH, et al. Background and rationale for the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Psychiatr Clin North Am 2003;26:457–494

© COPYRIGHT 2005 PHYSICIANS POSTGRADUATE PRESS, INC. © COPYRIGHT 2005 PHYSICIANS POSTGRADUATE PRESS, INC.