Using Treatment Algorithms to Bring Patients to Remission

Madhukar H. Trivedi, M.D.

Many patients treated with antidepressants fail to achieve full remission, and the costs, both social and economic, of response without remission as well as residual symptoms are high. Patients who experience incomplete remission to antidepressant treatment are candidates for a sequential treatment approach involving treatment options such as switching, augmentation, or combination of antidepressants. Recently, the number of alternatives for treatment has increased substantially. Algorithms and treatment guidelines that synthesize current data and research provide clinicians with a structure when changes in treatment strategy are necessary. Guidelines and algorithms are not designed to take away the clinician's autonomy but instead are intended to provide support for treatment decisions, and effective ones allow for a wide degree of flexibility. It can be easily argued that the use of algorithms with the associated decision support tools increases the role of the clinician in assessment of the clinical status and subsequent treatment choices. *(J Clin Psychiatry 2003;64[suppl 2]:8–13)*

Many patients treated with antidepressants fail to achieve full remission. In fact, a review of the definition and epidemiology of treatment-resistant depression[1] found that between 29% and 46% of depressed patients will respond only partially to antidepressant treatment and 19% to 34% will not respond at all. In the Medical Outcomes Study,[2] 523 depressed patients were identified, screened, and followed up 2 years later. Patients with dysthymia at baseline were most likely to have a major depressive episode during the follow-up period (24%), but even those patients with subthreshold symptoms at baseline had a 25% incidence of a major depressive episode during follow-up.

The costs, both social and economic, of incomplete remission and residual symptoms are high. In a large study[3] on imipramine and sertraline in chronic depression, almost 90% of remitted patients were rated by interviewers as having high levels of adjustment and quality of life, but the other side of that statistic is that over 10% of remitted patients still experienced difficulty at work and at home. At endpoint, 16% of remitted patients rated their own psychosocial adjustment as merely "fair," and 4% rated their adjustment as "poor." Over one third of patients in that study were nonresponders (299/635). Those patients continued to have significant problems in psychosocial adjustment, high levels of work and social impairment, and low levels of quality of life and satisfaction. This impairment has a staggering economic effect: in 1993, the annual cost of depression in the United States was reported to be $43 billion, 72% of which was due to indirect costs of functional impairment.[4]

Patients who experience partial or no response to antidepressant treatment are candidates for second- or third-line treatment options, including augmentation with a second agent, combination of 2 agents or an antidepressant plus psychotherapy, and switching to a different agent. Recently, the number of alternatives for treatment has increased substantially, and many of the antidepressants currently available have different mechanisms and spectrums of action as well as different levels of tolerability and safety that can vary widely by individual patient. However, there remains a significant inconsistency in how treatments are applied. Algorithms and treatment guidelines that synthesize current data and research provide clinicians with a structure when changes in treatment strategy are necessary. Guidelines and algorithms are not designed to take away the clinician's autonomy but instead are intended to provide support for treatment decisions, and effective ones allow for a wide degree of flexibility.

DEVELOPMENT OF TREATMENT ALGORITHMS

Treatment algorithms are typically presented as decision trees for medication management, and they provide information regarding medications appropriate for the primary disorder, applicable doses, and strategies for aug-

From St. Paul Hospital, University of Texas Southwest Medical School, Dallas, Tex.

This article is derived from the teleconference "Treating Depression and Anxiety to Remission: Use of Algorithms," which was held April 17, 2002, and supported by an unrestricted educational grant from Wyeth Pharmaceuticals.

Corresponding author and reprints: Madhukar H. Trivedi, M.D., St. Paul Hospital, University of Texas Southwest Medical School, P.O. Box B-1, Suite 520, Dallas, TX 75235-9101 (e-mail: madhukar.trivedi@utsouthwestern.edu).

menting or changing medications. Critical decision points are identified that ensure proper evaluation at timely intervals. Information is also provided regarding evaluations for adjusting doses and treatment of associated symptoms and side effects. In a treatment algorithm, the emphasis is on long-term efficacy, safety, and tolerability; the "best-practice" treatment sequence is determined by evaluating the relative safety and efficacy of each agent.[5,6] Proven treatments that are well-tolerated are often recommended first. The goal of treatment in any algorithm should always be sustained remission—complete recovery—and not just the alleviation of symptoms or adequate response.

Current treatment algorithms have been developed using an evidence-based method, in which each treatment option is scrutinized from the perspective of the current scientific literature. Evidence is divided into 3 levels: Level A is solid, research-based evidence derived from multiple randomized controlled trials and strong consensus support; Level B consists of evidence from some research studies, including at least one randomized controlled trial, and some consensus support; and Level C is anecdotal clinical reports.[7] At the first stage of treatment, a patient will typically receive monotherapy with an agent supported by Level A evidence. When the research data are not clear, expert consensus is needed to determine the best "next-step" options for patients who do not respond to monotherapy.

Treatment algorithms such as the Texas Medication Algorithm Project (TMAP) are organized into a series of evidence-based stages that guide clinicians in making treatment decisions. Monotherapy with medications that are associated with few side effects and safety concerns is usually the first level,[6,8] and treatment becomes increasingly complex as the patient moves through the algorithm. As the treatment becomes more complex, the patient's risk for adverse events increases as well. In an algorithm such as TMAP, the clinician is required to evaluate the patient's progress periodically to determine the level of response. The clinician may then decide to continue the dose, increase the dose, add a medication, switch a medication, or move to another part of the algorithm.[6,9] Additionally, patients may enter the algorithm at any stage or skip a stage if clinically appropriate. Although some physicians may be concerned that algorithms are constraining and eliminate the need for decision making, algorithms do not treat patients on their own; the expertise and decision-making ability of clinicians are still needed.

In fact, algorithms such as TMAP typically have a number of critical decision points, at which the expertise of the clinician or physician is crucial.[8,9] These decision points establish time frames for the evaluation of patient response, function, and side effects. Once a treatment is started, critical decision points in the algorithm prompt the clinician to assess the patient at certain intervals; in TMAP, these intervals are weeks 4, 6, 8, 10, and 12. At each critical decision point, the clinician must decide whether the optimal outcome—remission—has been achieved. If remission has not been achieved, the clinician must then determine what path will improve the patient response, i.e., whether to continue with the current treatment, adjust the dose, augment the treatment with another agent, or switch to a different agent.

The recently completed TMAP and the currently underway Sequenced Treatment Alternatives to Relieve Depression (STAR*D)[10] are both algorithm projects, yet they have approached the development of a treatment algorithm differently. TMAP developed a series of treatment algorithms for individual disorders and implemented them with complementary components such as patient education and physician support.[6,9,11,12] STAR*D is a National Institute of Mental Health–funded project at 14 research centers across the United States that is studying prospectively which potential next-step treatments are appropriate for patients with nonpsychotic major depressive disorder who do not achieve remission on their current antidepressant regimen.

Texas Medication Algorithm Project

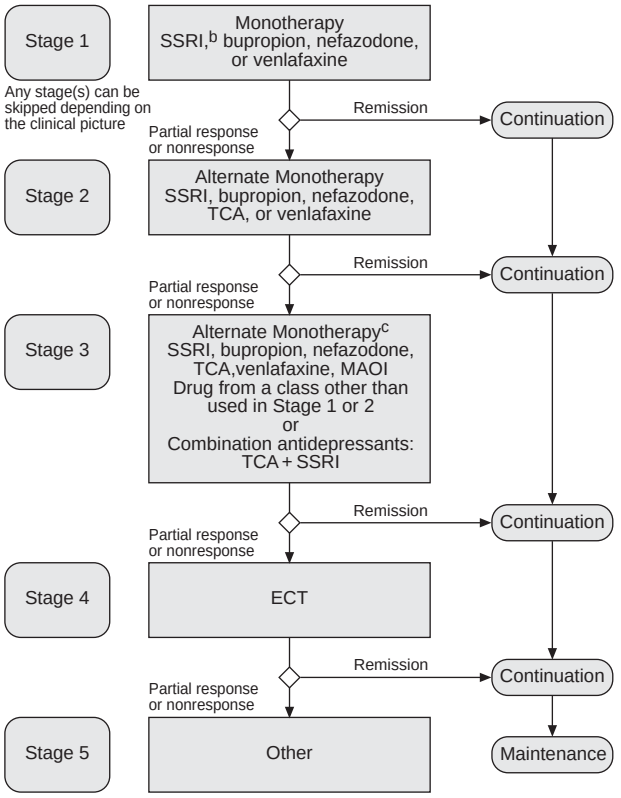
The TMAP algorithms were developed during a series of consensus conferences at which experts reviewed the data from randomized controlled trials and other sources to determine the best treatment options. Algorithms have been developed for major depressive disorder,[9] bipolar disorder,[13] and schizophrenia.[13] The TMAP algorithms for major depressive disorder were developed from a consensus conference that included academic psychiatrists, psychopharmacology specialists, physicians and administrators from the Texas Department of Mental Health and retardation, and mental health consumers and family members.[9] Figure 1 presents the algorithm for major depressive disorder without psychotic features. These algorithms are arranged into 3 major phases: acute (stage 1), continuation (stages 2–4), and maintenance treatment (stage 5). Patients are moved from stage to stage because of inadequate symptom improvement or intolerable side effects.

After the algorithm was drafted, over 1400 patients at 19 sites were assigned to 1 of 3 groups: treatment as usual, algorithm for depression, or treatment as usual at a site using algorithms for other disorders. Patients were enrolled for up to 2 years, and patients and their families received education about depression and medications. The patient education materials as well as a list of publications and updated versions of the algorithms are available at the TMAP Web site.[13]

Sequenced Treatment Alternatives to Relieve Depression

The STAR*D project is approaching the development of a treatment algorithm from a different direction. It is a prospective study that will randomly assign patients who have not achieved remission to treatment with a selective

Figure 1. Texas Medication Algorithm Project (TMAP): Major Depressive Disorder Without Psychotic Features[a]



[a]Adapted from Crismon et al.[9] The TMAP algorithms are in the public domain, and this figure may be reproduced without permission, but with the appropriate citation. Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.
[b]SSRIs preferred.
[c]Consider TCA or venlafaxine if not tried.

serotonin reuptake inhibitor (SSRI) to 1 of 6 treatment options (Table 1).[10] Patients may go through 3 such steps subsequently if necessary to achieve remission. After indicating which options are or are not acceptable, patients are randomly assigned to a treatment strategy, and after at least 12 weeks of acute treatment, patients are followed for 12 months. The protocol includes patient and family education. Periodic assessments, including symptom severity, level of functioning, side effect burden, patient satisfaction/quality of life, and health care utilization and cost, are conducted by evaluators who are blind to level of treatment and treatment strategy. STAR*D will also attempt to offer a system of quick evaluation of new treatments and determine how they fit into the treatment sequence. More information about the study is available on the STAR*D Web site.[10]

CURRENT EVIDENCE FOR TREATMENT OPTIONS

Several treatment options should be considered after a failed monotherapy trial, including switching medications within or across antidepressant classes, augmenting with a medication that is not an antidepressant, and combining treatment with 2 antidepressants or an antidepressant plus psychotherapy.

Table 1. Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Treatment Options[a]

Those who do not respond to monotherapy with an antidepressant will be assigned to 1 of 6 treatment options:
1. Augmenting the first antidepressant with other medications or psychotherapy
2. Changing to a different antidepressant or psychotherapy
3. Adding psychotherapy or discontinuing the first antidepressant medication while switching to psychotherapy
4. Switching to another antidepressant
5. Augmenting the first antidepressant with other medications
6. Augmenting the first antidepressant with other medications or switching to another antidepressant

[a]Data from STAR*D.[10]

Switching to Another Antidepressant

Depressed patients are switched from one antidepressant to another to either obtain a different neurochemical effect or resolve intolerable side effects. A survey of 402 psychiatrists from across the United States queried what steps would be taken for patients who fail to respond to at least 8 weeks of treatment with an SSRI.[14] After raising the dose of the SSRI (80%), switching to a non-SSRI was the most popular choice (44%). Several factors make switching an attractive option. Switching can be more acceptable to patients than polypharmacy, because it is usually easier for the patient to remember, thereby enhancing compliance, and it is typically less costly. If the patient is experiencing severe side effects, switching to an agent with a different side effect profile will be an appealing option for the patient as well.[15]

Switching from one SSRI to another has many benefits. Patients intolerant to one SSRI may tolerate another very well, and nonresponders to one may respond to another. In addition, the pharmacokinetic profiles of the SSRIs vary, and each has its own side effect and drug-drug interaction profile.[16,17] In one study,[16] 106 depressed patients who could not tolerate (N = 34) or did not respond to (N = 72) sertraline were switched to fluoxetine treatment for 6 weeks. Response was defined as at least a 50% reduction on the 28-item Hamilton Rating Scale for Depression (HAM-D). Sixty-seven patients (63%) responded to fluoxetine, and significant improvements were reported on secondary measures of depression and functioning.

Some clinicians and patients may favor switching to an antidepressant in a different class. Thase and colleagues[18] conducted a multisite study on patients with chronic depression who failed to respond to 12 weeks of treatment with either sertraline, an SSRI, or imipramine, a tricyclic antidepressant (TCA). Patients were switched to the other study drug for an additional 12 weeks of treatment. Both

groups experienced a statistically significant degree of improvement—more than 50% of patients in each group responded to the new drug, although the sertraline group experienced fewer side effects and less dropout due to adverse effects. However, care must be taken when switching patients to TCAs, because they have more serious side effects and are more dangerous in overdose than the SSRIs.

Another strategy for patients who do not respond to a selective agent such as the SSRIs is to switch them to a dual-mechanism drug such as venlafaxine, a serotonin-norepinephrine reuptake inhibitor, or mirtazapine, a noradrenergic and specific serotonergic antidepressant. Venlafaxine has been shown to be associated with higher rates of remission than either SSRIs or placebo.[19] In a pooled analysis[19] of 8 double-blind studies on major depressive disorder, Thase and coworkers found that venlafaxine had an overall remission rate of 45%, the SSRIs, 35%, and placebo, 25%. In recent reports of a study on venlafaxine in treatment-resistant depression,[20,21] patients were included in the study if they met criteria for absolute treatment resistance (treatment ≥ 6 weeks with an antidepressant, ≥ 3 weeks at an adequate dose) or relative treatment resistance (treatment ≥ 4 weeks with an antidepressant, ≥ 2 weeks at an adequate dose). Previous antidepressant treatment included TCAs, SSRIs, and monoamine oxidase inhibitors. After the initial 8 weeks of treatment, 149 patients were followed for up to 10 months.[21] At the end of 8 weeks, 69% of the patients were classified as responders (≥ 50% decrease in Montgomery-Asberg Depression Rating Scale score), and by the final visit, 73% of the patients had responded to venlafaxine treatment. Mirtazapine was studied in patients for whom the SSRIs fluoxetine, paroxetine, or sertraline failed to work.[22] One hundred and three patients with major depressive disorder received mirtazapine for 8 weeks. Response was defined as ≥ 50% reduction in the 17-item HAM-D score, and 48% of patients had responded by the endpoint. Both these agents are strong candidates for switching.

Switching antidepressants has its disadvantages, however. Side effects associated with the new medication may be different but just as intolerable as those with the original agent. If the patient is a partial responder to the original agent, that benefit will be lost in a switch. Some antidepressants are associated with discontinuation-emergent adverse events. In addition, patients may feel a sense of personal failure if asked to abandon a treatment altogether.[15]

Augmentation With a Different Type of Medication

Like switching, augmentation of antidepressant treatment with another kind of medication has its advantages and disadvantages. Among the advantages are a potentially rapid response and maintenance of any partial response to the initial treatment. In addition, it is usually not necessary when augmenting to taper the dose of the first agent down while increasing the dose of the second, so no treatment time is lost. On the other hand, combination treatment is more complicated than monotherapy—drug interactions may occur, new side effects may emerge, and the regimen is more expensive.

A number of agents have been used as augmentation medications to antidepressants, with varying degrees of success and support in the literature. For example, placebo-controlled studies have shown thyroid hormones, both triiodothyronine (T_3) and thyroxine (T_4), to be effective augmenting agents to TCAs, but the evidence for their use with SSRIs is much more limited. (See Nelson[23] and Thase[24] for reviews). Lithium is also a commonly prescribed augmentation agent, one reason being that it has been associated with a quicker response, sometimes within 48 hours.[23] In double-blind, placebo-controlled studies[25–27] of lithium plus an SSRI, lithium augmentation was found to be both safe and effective. Buspirone augmentation is another often-used strategy for nonresponse or partial response to antidepressant treatment. A placebo-controlled trial[28] found that while buspirone was well tolerated among depressed patients taking citalopram, it was not significantly more effective than placebo. The role of atypical antipsychotics as augmenting agents for depression has yet to be determined,[24] although a well-designed double-blind study of olanzapine added to fluoxetine therapy had positive results.[29]

Combination With Another Antidepressant or Psychotherapy

Combination treatment has many of the same advantages and disadvantages as augmentation. However, combination treatment with another antidepressant can offer a synergistic antidepressant effect if the second antidepressant has a mechanism of action different from the first. According to a recent review of combining antidepressants for treatment-resistant depression,[30] the evidence for combination therapy is lacking—the authors found only 5 randomized controlled trials and 22 open-label studies. Three of 5 randomized trials used mianserin, which is not available in the United States. In the studies reporting a response rate (24 studies, overall N = 601), the mean response rate was 62%. Clearly, more randomized, placebo-controlled studies are needed.

The evidence also suggests that the combination of antidepressant treatment plus psychotherapy may be an effective treatment for depression partially responsive or nonresponsive to monotherapy. Keller and coworkers[31] analyzed nefazodone, cognitive-behavioral therapy, and their combination in 681 patients with chronic, nonpsychotic major depressive disorder. Patients were randomly assigned to treatment with nefazodone, psychotherapy, or the combination for 12 weeks. The goal of treatment was remission, which was defined as a score of 8 or below on the HAM-D at weeks 10 and 12, whereas satisfactory response was defined as at least a 50% decrease in the

HAM-D score. Five hundred nineteen subjects completed the study; the rates of response (remission plus satisfactory response) were 55% in the nefazodone group, 52% in the psychotherapy group, and 85% in the combination group ($p < .001$ for both comparisons). Psychotherapy, then, seems to be an effective add-on to antidepressant treatment.

MEASUREMENT OF OUTCOMES

Measures of symptom severity and functional outcome, both clinician rated and patient rated, can be useful in determining whether full remission or merely a significant response has been obtained. Assessment of symptom reduction and functional improvement can also assist physicians in making clinical decisions about appropriate treatment. Subjectively, a clinician and patient may agree that the patient is much improved and has achieved remission, but residual symptoms may be present. Residual symptoms may put the patient at a higher risk of relapse compared with a patient who has achieved remission confirmed by objective measures.

Patient self-reports can also give patients a way to communicate with their physicians about issues, symptoms, or side effects that may be difficult to broach otherwise. Sexual dysfunction, for example, is not only a symptom of depression but can also be a side effect of drug treatment. However, many patients may feel shy about discussing such a personal topic with their physician, and a self-report measure offers them a way to report those symptoms more discreetly. In addition, patients may feel more involved in their treatment when self-report instruments are used.

Numerous rating scales are available. The HAM-D[32] is a clinician-rated scale that has been thought of as the gold standard in depression research. The Inventory for Depressive Symptomatology[33] is another clinician-rated scale, but it has the advantage of including a mirror-image, self-rated version. For functional measures, the Medical Outcomes Study 36-item Short Form,[34] the Social Adjustment Scale,[35] and the Quality of Life Enjoyment and Satisfaction Questionnaire[36] are useful in research, but can be difficult to use in practice. However, monitoring symptoms, side effects, and quality of life are important in routine practice, and treatment algorithms are designed so that measuring outcome is essential when evaluating whether to continue treatment or move a patient to another part of the algorithm.

IMPLEMENTATION OF ALGORITHMS

Implementing algorithms into clinical practice requires behavioral change on the part of the physicians, their staff, and their patients. Remission must be kept in mind as the ultimate goal of treatment. Physician training on the use of algorithms is necessary, but simply exposing physicians to treatment guidelines is not enough. The algorithm must be practical to use in everyday clinical situations, and not so unwieldy that it will simply sit on the physician's bookshelf. Patient education is also important and must be provided as part of the algorithm since patient education can improve compliance with treatment.[6,11]

Consistent use of rating scales can help clinicians assess treatment response accurately and decide where in an algorithm a patient should be. Movement through an algorithm like TMAP is based on these critical decision points at which the clinician determines the patient's degree of improvement, side effect burden, and absolute level of symptom severity.

CONCLUSION

One would expect treatment algorithms to reduce the cost of treatment, increase remission rates, and improve patient adherence,[9,37] and research in those areas continues. Another exciting area of research is that of the development and practicality of computerized algorithms.[38] A computerized algorithm will allow a physician to fill in a patient's assessment and offer treatment options that can be accepted or rejected instantly. This type of software in a handheld computer will be highly practical for busy clinicians because it will bring the algorithm directly into the treatment setting.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa), fluoxetine (Prozac and others), imipramine (Surmontil, Tofranil, and others), levothyroxine (Synthroid, Novothyrox, and others), liothyronine (Triostat, Cytomel), mirtazapine (Remeron), nefazodone (Serzone), olanzapine (Zyprexa), sertraline (Zoloft), venlafaxine (Effexor).

Disclosure of off-label usage: Dr. Trivedi has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration labeling.

REFERENCES

1. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am 1996;19:179–200
2. Wells KB, Burnam MA, Rogers W, et al. The course of depression in adult outpatients: results from the Medical Outcomes Study. Arch Gen Psychiatry 1992;49:788–794
3. Miller IW, Keitner GI, Schatzberg AF, et al. The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. J Clin Psychiatry 1998;59:608–619
4. Greenberg PE, Stiglin LE, Finkelstein SN, et al. The economic burden of depression in 1990. J Clin Psychiatry 1993;54:405–418
5. Shulberg HC, Katon WJ, Simon GE, et al. Best clinical practice: guidelines for managing major depression in primary medical care. J Clin Psychiatry 1999;60(suppl 7):19–26
6. Rush AJ, Crismon ML, Toprac MG, et al. Implementing guidelines and systems of care: experiences with the Texas Medication Algorithm Project (TMAP). J Pract Psychiatry Behav Health 1999;5:75–86
7. Trivedi MH, Rush AJ, Crismon ML, et al. Treatment guidelines and algorithms. Psychiatr Clin North Am Annu Drug Ther 2000;7:1–22
8. Trivedi MH, Kleiber BA. Algorithm for the treatment of chronic depression. J Clin Psychiatry 2001;62(suppl 6):22–29
9. Crismon ML, Trivedi MH, Pigott TA, et al. The Texas Medication

Algorithm Project: report of the Texas Consensus Conference Panel on Medication Treatment of Major Depressive Disorder. J Clin Psychiatry 1999;60:142–156
10. STAR*D: Sequenced Treatment Alternatives to Relieve Depression. Available at: http://www.edc.gsph.pitt.edu/stard. Accessed Aug 12, 2002
11. Toprac MG, Rush AJ, Conner TM, et al. The Texas Medication Algorithm Project patient and family education program: a consumer-guided initiative. J Clin Psychiatry 2000;61:477–486
12. Rush AJ, Rago WV, Crismon ML, et al. Medication of the severely and persistently mentally ill: the Texas Medication Algorithm Project. J Clin Psychiatry 1999;60:284–291
13. Texas Medication Algorithm Project. TMAP Table of Contents. Aug 6, 2001. Available at: http://www.mhmr.state.tx.us/centraloffice/medicaldirector/tmaptoc.html. Accessed Aug 12, 2002
14. Fredman SJ, Rosenbaum JF, Fava M, et al. How often do psychiatrists raise the dose when SSRIs do not work? In: New Research Program and Abstracts of the 152nd Annual Meeting of the American Psychiatric Association; May 17, 1999; Washington, DC. Abstract NR128:97
15. Fava M. Management of nonresponse and intolerance: switching strategies. J Clin Psychiatry 2000;61(suppl 2):10–12
16. 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
17. Brown WA, Harrison W. Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? J Clin Psychiatry 1995; 56:30–34
18. 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
19. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 2001;178:234–241
20. Mitchell PB, Schweitzer I, Burrows G, et al. Efficacy of venlafaxine and predictors of response in a prospective open-label study of patients with treatment-resistant major depression. J Clin Psychopharmacol 2000;20: 483–487
21. Schweitzer I, Burrows G, Tuckwell V, et al. Sustained response to open-label venlafaxine in drug-resistant major depression. J Clin Psychopharmacol 2001;21:185–189
22. Fava M, Dunner DL, Greist JH, et al. Efficacy and safety of mirtazapine in major depressive disorder patients after SSRI treatment failure: an open-label trial. J Clin Psychiatry 2001;62:413–420
23. Nelson JC. Augmentation strategies in depression 2000. J Clin Psychiatry 2000;61(suppl 2):13–19
24. Thase ME. What role do atypical antipsychotic drugs have in treatment-resistant depression? J Clin Psychiatry 2002;63:95–103
25. 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
26. Katona CL, Abou-Saleh MT, Harrison DA, et al. Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. Br J Psychiatry 1995; 166:80–86
27. 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, pharmacogenetic investigation. J Clin Psychopharmacol 1996;16:307–314
28. 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
29. Tohen M, Shelton R, Tollefson GD, et al. Olanzapine plus fluoxetine: double-blind and open-label results in treatment-resistant major depressive disorder. Presented at the 12th annual meeting of the European College of Psychopharmacology; Sept 21–25, 1999; London, England
30. Lam RW, Wan DDC, Cohen NL, et al. Combining antidepressants for treatment-resistant depression: a review. J Clin Psychiatry 2002;63: 685–693
31. Keller MB, McCullough JP, Klein DN, et al. Comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000; 342:1462–1470
32. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
33. Rush AJ, Giles DE, Schlesser MA, et al. The Inventory for Depressive Symptomatology (IDS): preliminary findings. Psychiatry Res 1986;18: 65–87
34. Stewart AL, Hays RD, Ware JE. The MOS Short Form general health survey: reliability and validity in a patient population. Med Care 1988;26: 724–735
35. Weissman MM, Paykel ES, Prusoff BA. Social Adjustment Scale Handbook. New York, NY: College of Physicians and Surgeons of Columbia University; 1972
36. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol Bull 1993;29: 321–326
37. Trivedi MH, DeBattista C, Fawcett J, et al. Developing treatment algorithms for unipolar depression in cyberspace: International Psychopharmacology Algorithm Project (IPAP). Psychopharmacol Bull 1998;34: 355–359
38. Trivedi MH, Kern JK, Baker SM, et al. Computerized medical algorithms and decision support systems for major psychiatric disorders. J Psychiatr Pract 2000;6:237–246