# Using Treatment Algorithms for the Effective Management of Treatment-Resistant Depression

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Increasingly, clinicians are looking to evidence-based medicine for information about treatment options. Treatment algorithms have been used with a variety of psychiatric disorders to assist physicians in making treatment decisions. The direct, prescriptive nature of algorithms also makes them suitable for use in treatment-resistant depression. Two major projects, the Texas Medication Algorithm Project and Sequenced Treatment Alternatives to Relieve Depression, have begun to address the questions of sequenced treatment options. Future directions for algorithm development and implementation are discussed. *(J Clin Psychiatry 2001;62[suppl 18]:25–29)*



Little agreement exists about either the definition of treatment-resistant depression or evidence-based options for treatment. Once it is determined that a patient has treatment-resistant depression, the next question is how to approach treatment. It is no longer acceptable to attain only a symptomatic response to treatment, generally described as 50% improvement in symptoms. Complete remission of symptoms with full recovery of psychosocial functioning is the current treatment standard.[1] In fact, most disease management approaches, such as the Texas Medication Algorithm Project (TMAP) and Sequenced Treatment Alternatives to Relieve Depression (STAR*D), recommend achieving full symptom remission and return of psychosocial function with minimal side effect burden as an optimal goal of treatment.[2,3] This goal is especially important for those patients who are at risk for developing resistance to treatment or present with a chronic course of illness.[4] The best strategy for addressing treatment-resistant depression appears to be early detection and vigorous treatment, with aggressive treatment of residual symptoms followed by continued maintenance treatment.[5]

New medications, evidence from psychotherapy, and treatment combinations continue to appear. The question becomes how to select appropriate treatments using good clinical judgment, taking into account the risks and benefits of each option. Evidence-based medicine has moved to the forefront in the making of treatment decisions.[6] Various methods have been used to provide structure for treatment decisions, such as treatment guidelines, critical pathways, disease management protocols, and algorithms. Treatment guidelines, such as those developed by the Agency for Health Care Policy and Research (AHCPR),[1,7] are based on general principles of patient care and present a range of acceptable treatments. Guidelines are considered to be one of the most justifiable, cost-effective methods of treatment. In addition, guidelines provide physicians with a structured synthesis of relevant data, and their use may result in more stable and predictable treatments and procedures. However, these guidelines do not provide specific treatment information for use in clinical settings. Treatment algorithms are more explicit and prescriptive, providing specific information regarding clinical care.

Present treatment algorithms have been developed using an evidence-based method, in which initial recommendations are derived from a rigorous scientific literature review. Evidence for a particular treatment may be divided into 3 levels: Level A, solid research-based evidence such as multiple randomized, controlled trials and strong group endorsement; Level B, some research-based evidence, including at least 1 randomized, controlled trial and some consensus support; or Level C, anecdotal clinical reports.[6]

For example, clinicians tend to use selective serotonin reuptake inhibitors (SSRIs) as the first level of treatment. There are strong research data to support this decision (Level A evidence). However, where the research data are not clear, expert consensus is needed to determine the best options for those patients who do not respond at the first treatment stage. Many times, the algorithm will provide more than one option, such as augmenting or switching medications.[2,8]

The lack of Level A evidence in some cases has influenced the way in which treatment options are presented in

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an algorithm.[5] The use of combination treatments is one example. There is not extensive evidence for increased efficacy with combinations; therefore, they are presented at a later stage of treatment. Electroconvulsive therapy is presented in later treatment stages, not due to efficacy or safety concerns but due to patient acceptability.[2,6]

## TREATMENT ALGORITHMS

Algorithms provide a framework for evidence-based treatment decisions. Presented as decision trees for medication management, treatment algorithms offer a range of medications to be used for the primary syndrome, applicable doses, and strategies for augmenting or changing medications. In addition, information is provided regarding critical decision points in time, requisite evaluations for modifying dosages, and subroutines for treatment of associated symptoms and side effects. Used in this way, algorithms allow researchers and clinicians to uniformly apply or test treatment options, thereby assimilating evidence into practice.

The development of the TMAP algorithms was based on the philosophy that patients should receive the most efficacious and safe treatments first, as well as the simplest intervention possible. As necessary, subsequent interventions would graduate toward increased complexity and/or risk. In addition, treatment algorithms emphasize the role of patient preference in treatment and providing multiple treatment options for physicians.

As a result, treatment algorithms are intended to be individually tailored and easy to use by physicians and patients. Emphasis is placed upon long-term safety and tolerability, and proven treatments are to be used first. Finally, the goal of treatment should be symptom remission rather than adequate response.

The algorithms are organized into a series of stages or steps that guide clinicians in making appropriate treatment decisions. The determination of the "best-practice" treatment sequence is based on the relative efficacy and safety of a medication.[8,9] Medications presented at the first level of treatment are monotherapies, with the fewest side effects or safety concerns.[5,9] As a patient moves through the stages of the algorithm, treatment becomes increasingly complex and often has a less favorable side effect profile or is associated with greater risk.

Treatment selections at the first stage of the algorithm include the newer antidepressant medications, such as SSRIs, bupropion, nefazodone, venlafaxine, or mirtazapine. Stage 2 medications would include tricyclic antidepressants, as well as the above mentioned medications. At stage 3, monoamine oxidase inhibitors may also be considered. It is recommended that physicians change class of medications by stage 3. In addition to switching medications, it may be necessary to augment the antidepressant with another medication or use a combination of antidepressants to attain complete symptom remission.

Periodically, the clinician is required to evaluate a patient's progress after an adequate trial to determine the level of response. On the basis of that evaluation, the clinician may continue the dose, increase the dose, add a medication, switch medications, or move to another stage.[2,5] Patients may enter the algorithm at any stage or skip a stage as clinically appropriate.[2,9]

When there is more than one option at a particular step or stage, it is important to include the patient in discussions of specific treatment issues relative to those options.[6,9–11] Examples of these issues are acceptability of possible side effects or the patient's willingness to take more than one medication when augmenting. Clinician concerns at later stages may include the increased degree of side effects or higher potential for suicidality or overdose.

## TREATMENT SWITCHING, AUGMENTATION, OR COMBINATIONS

There are times when monotherapy is not adequate to attain remission of symptoms, and it may be necessary to modify treatment. The decision may be made to switch the patient to another antidepressant (same or different class) or to combine or augment the prescribed antidepressant with another agent.[2,5] Augmentation also may involve 2 medications indicated for different disorders, such as the combined use of an antidepressant and an antipsychotic.[2,5,8] Combination using 2 antidepressants may be useful if the individual medications differ in the targeted neurotransmitter system, mechanism of action, or a combination of the two.[8] There is growing evidence that combination treatment with an antidepressant and psychotherapy is significantly more efficacious than either treatment alone.[12]

There are a number of factors to consider when determining whether switching to another monotherapy or augmentation of the current treatment is most appropriate. Arguments for switching treatments include lower medication costs, fewer potential side effects, and better patient adherence.[2,8] Alternatively, in dealing with treatment-resistant depression, the benefits of maintaining a positive patient attitude toward symptom improvement, retaining the partial response achieved with a given medication, and possibly attaining full response from nonresponders or partial responders may warrant augmentation as an optimal treatment.[8,13] In addressing these difficult issues, treatment algorithms may provide a strong evidence-based guide to selecting appropriate "next-step" treatments when used in conjunction with CDPs.

## CRITICAL DECISION POINTS

There has been growing concern that patients may not be treated soon enough, or, if treated, with an inadequate dose or trial.[14–17] This is of special concern in the management of treatment-resistant depression. It has been shown

that early intervention and treatment to full remission are critical in reducing the frequency of treatment-resistant or chronic depression.[4,18] The innate structure of treatment algorithms guards against a shotgun approach to treatment. As medications are shown to be ineffective or intolerable to the patient, a structured approach may help the clinician and patient to persevere in seeking full remission of symptoms.

In order to attain full symptom remission in treatment-resistant depression, specific strategies may be needed. It is suggested that physicians allow for a longer trial and higher dosages during initial treatment.[2,19] Once it is determined that the initial treatment medication lacks efficacy for that patient, another trial within the same class or across classes is recommended. Subsequent steps would include switching to another class of antidepressants or augmentation with another medication. Failing that treatment, combination treatments with 2 antidepressants is suggested. Another option for treatment would be a combination of an antidepressant and psychotherapy.[19]

Critical decision points (CDPs) are integral to the design of treatment algorithms, establishing time frames for evaluation of patient response. Proper evaluation at timely intervals may assist clinicians in achieving full remission in the first stage of treatment.[2,5] Once a treatment is initiated, CDPs prompt reassessment at weeks 4, 6, 8, 10, and 12. At each CDP, it is determined whether the optimal outcome has been achieved at the present stage. If a patient has not achieved full remission of symptoms, options such as augmentation are provided in the algorithm to improve patient response.

CDPs do not dictate treatment decisions, but provide a framework to cue physicians to reevaluate the patient regarding treatment response and tolerability. The final decision to make changes to treatment strategies is left up to the physician's clinical judgment and the patient's preferences based on appropriateness for that individual. One goal in the use of CDPs is that when provided with such guidelines, physicians will be more likely to make changes to treatment in a more timely manner.

## MODELING TREATMENT ALGORITHMS: TMAP AND STAR*D

Two large, multisite research projects, the recently completed TMAP[2,9,20] and the ongoing STAR*D,[3] have utilized treatment algorithms in their design. These studies approach treatment algorithms differently. TMAP developed treatment algorithms for individual disorders and implemented each algorithm with complementary components, such as patient education and physician support staff.[2,9,10,20] STAR*D examines potential best "next-step" treatments for nonpsychotic major depressive disorder patients who do not have a satisfactory response to initial treatment.[3]

### Texas Medication Algorithm Project

Treatment algorithms used in TMAP were developed during a series of consensus conferences, at which experts gathered to determine the best treatment options based on available research data from randomized controlled trials and other evidence-based sources.[2] Algorithms were developed for 3 primary disorders (major depressive disorder, bipolar disorder, and schizophrenia). The order in which treatments were presented in the algorithms was in large part dependent on medication efficacy, side effect profile, and acceptability by patients.

Over 1400 patients at 17 public sector mental health clinics were enrolled in 1 of 3 conditions (algorithm, treatment as usual, and treatment as usual within a site utilizing algorithms for another disorder). Patients were enrolled for up to 2 years, during which time a number of clinical and outcome assessments were completed. Patient and family education was provided, as well as clinical support personnel for physicians.[2,10]

Results of this study are currently being analyzed and interpreted. Patient education materials, a list of publications related to this project, and graphic representations of the algorithms used may be found at the following Web site: http://www.mhmr.state.tx.us/centraloffice/medicaldirector/tmaptoc.html.

### Sequenced Treatment Alternatives to Relieve Depression

STAR*D focuses on treatment of patients with nonpsychotic major depressive disorder who do not have a satisfactory response to an initial adequate trial of the SSRI citalopram. Patients may progress through as many as 3 additional levels of treatment to achieve remission. Assignment to various treatment options at each level will be randomly generated, following exclusion of certain options based on patient acceptability.[3]

It is estimated that over 4000 patients from specialty and primary care clinics within 14 regional centers will be enrolled in this 5-year study. After a minimum of 12 weeks of acute treatment, patients will be followed for 2 months. Independent evaluators, blinded to level and treatment, will conduct periodic outcome evaluations. Measures will include symptom severity, level of functioning, side effect burden, patient satisfaction/quality of life, and health care utilization and cost. The protocols do include patient and family education. During follow-up, the degree and timing of relapse will be assessed.[3] Information on the study can be accessed through the STAR*D Web site.[3]

### Project Comparison

Both projects seek to compare efficacy and patient acceptance of various treatment options, including long-term benefits, side effect burdens, and economic costs. In addition, they have evaluated outcome measures for use in clinical practice. One difference between the TMAP and

STAR*D protocols is the random assignment of treatments within the algorithm. TMAP treatment selections within the algorithm were based on patient preference and clinical judgment whenever possible. While TMAP offered treatment algorithms to guide physicians in treatment decisions, how those algorithms were applied varied greatly. Because STAR*D focuses upon nonresponders to initial treatment, a major objective of the study is to determine what is the best "next step" in treatment.[3] When initial treatment fails, subjects will be randomly assigned to another treatment option (somewhat guided by patient acceptability). Randomization allows for blinded results and a more even distribution of treatment options used in the study. STAR*D will also attempt to provide a system of rapid evaluation of newly approved treatments and determination of how they fit into the treatment sequence.[3]

## IMPLEMENTATION OF TREATMENT ALGORITHMS

There are a number of ways to facilitate algorithm implementation in a clinical setting. Thorough physician training on the use of algorithms is critical to successful implementation.[9] Exposure to guidelines through medical education or publications is not effective in promoting their use by physicians.[6] Consistent use of symptom rating scales, as well as more frequent patient visits, assists clinicians in accurately assessing treatment response. In addition, patient adherence is improved when patient education is provided.[9,10]

It is important to note that movement through the algorithm is determined by clinical evaluation at the CDPs and that treatment decisions should be determined by the degree of improvement based on patient outcome assessments, the absolute level of symptom severity, and side effect burden.

Routine use of clinician-rated scales or patient self-report scales provides ongoing information about patient response to treatment. Response information is important in management of treatment-resistant depression.[9,11] Subjectively, the patient may feel better and the physician may believe the patient is in remission when, in fact, residual symptoms continue to be present. As a result, the patient may have a higher rate of relapse than if treated to full remission of symptoms.

In addition, self-reports allow patients to focus on specific issues with the physician by offering another medium to report symptoms. As a result, patients often feel they are actively participating in their treatment. The use of the patient as collaborator enhances the chances of successful treatment, especially in treatment-resistant depression for which a patient may have had a number of treatments that were only partially effective or stopped working over time.[6,9,11] When engaged in making treatment decisions, the patient may be more willing to tolerate the sometimes laborious process of finding an effective treatment.

## DO ALGORITHMS WORK?

There has been a good deal of support for the use of algorithms in treating depression with the expectation that the use of such guidelines would reduce the cost of treatment, increase remission rates, and improve patient adherence.[2,21] Algorithms have been shown to be effective in treating general medical disorders, leading researchers to examine their use in psychiatry.[6] The potential benefits and preliminary results are exciting, but research is continuing to evaluate their effectiveness.

## FUTURE DIRECTIONS IN THE USE OF ALGORITHMS TO TREAT DEPRESSION

This is an exciting time in psychiatry, not only because of the emergence of new medications with improved effectiveness and lower side effect burdens, but also because research continues to be done that provides answers to the questions of what is "best practice." It is not practical to study all possible sequences or therapies. One major question facing researchers is what sequence of treatment is best or most effective. STAR*D has started to address that issue, and future research will continue to define this approach to treatment.

Future research is expected to build upon the efforts of TMAP and STAR*D so that appropriate content and sequencing of treatment may be further understood and utilized in clinical practice. Evaluation of other tools, such as CDPs and patient education materials or prompts, continues and will promote faster and fuller treatment response. A computerized decision support system utilizing treatment algorithms has been developed and will soon become available to clinicians.[22] It is expected that algorithms will continue to be a valuable tool in the treatment of depression and will also continue to define cutting-edge information. Even as there is a risk that formularies will become restricted and limit physician/patient choices, the overall quality of treatment is enhanced with the advancement of evidence-based medicine.

*Drug names:* bupropion (Wellbutrin), citalopram (Celexa), mirtazapine (Remeron), nefazodone (Serzone), venlafaxine (Effexor).

*Disclosure of off-label usage:* The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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