STAR*D: Lessons Learned for Primary Care

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Needs Assessment: Treatment of major depressive disorder often occurs in primary care settings. Yet, many questions remain regarding the nature of depression in primary care and its optimal treatment. The Sequenced Treatment Alternatives to Relieve Depression study provides much-needed guidance on how to optimize depression management.

Learning Objectives:
• Describe the rationale and design of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study
• Relate key findings of STAR*D with respect to remission and relapse rates
• Apply STAR*D findings to primary care
• Explain the importance of measurement-based care and disease-management strategies

Target Audience: Primary care physicians and psychiatrists.

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This activity has been peer-reviewed and approved by Eric Hollander, MD, chair at the Mount Sinai School of Medicine, and Norman Sussman, MD, editor of Primary Psychiatry and professor of psychiatry at New York University School of Medicine. Review Date: December 13, 2006.

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To receive credit for this activity: Read this article and the two CME-designated accompanying articles, reflect on the information presented, and then complete the CME quiz. To obtain credits, you should score 70% or better. Release date: January 2007. Termination date: January 2009. The estimated time to complete all three articles and the quiz is 3 hours.

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Abstract

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the largest prospective treatment study of depression ever conducted, addresses the question of how to proceed when a depressed patient does not adequately respond to one or more treatment attempts. The study enrolled 4,041 patients with major depressive disorder in 18 primary care and 23 psychiatric care clinics, with no difference in depression severity seen between psychiatric and primary care sites. Approximately 33% of depressed patients who were initially treated with the selective serotonin reuptake inhibitor citalopram attained clinical remission. For nonremitters, subsequent medication switch and augmentation strategies produced modest remission rates. Patients whose depressions fully remitted were less likely to relapse than those who experienced only response without remission. Using measurement-based care strategies, remission rates were similar for patients seen in psychiatric and primary care settings.

Introduction

Despite advances in the understanding of major depressive disorder (MDD), there remain many unanswered questions regarding its optimal management. The National Institute of Mental Health-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the largest prospective treatment study of MDD ever conducted, attempts to fill in these gaps. In particular, it attempts to answer the question of how to proceed when a depressed patient does not adequately respond to one or more treatment attempts—a problem for which there have not been solid, empirically-based guidelines.

The results from STAR*D are particularly relevant to primary care physicians (PCPs), as the majority of depressed patients receive their depression treatment in primary care settings.1 Despite this fact, for various reasons many of these depressed patients do not receive adequate treatment.2-6 With 38% of STAR*D’s patients enrolled in primary care settings, the study provides the most extensive characterization of patients in primary care settings to date and has the potential to provide PCPs much-needed guidance as to how to optimize depression management.

Overview of STAR*D

Conducted by 14 regional centers across the United States, STAR*D enrolled >4,000 patients in public and private practice settings over a 3-year period. The study was unique in identifying patients within 18 primary care and 23 psychiatric clinics. This is in marked contrast to most industry-sponsored trials in which subjects are actively recruited by advertising and other means, thus reflecting symptomatic volunteers versus “real-world” patients actually receiving care in community settings.

Greatly enhancing the generalizability of findings to the realities of PCPs’ actual practices was the inclusion of patients with MDD with most commonly occurring medical and substance use disorders. Exclusion criteria were minimal (eg, bipolar disorder, psychoses). This differs from most clinical trials where subjects are routinely excluded due to comorbid conditions or greater levels of severity, including the presence of suicidality.

Full details on the design and implementation of STAR*D can be found elsewhere.7-9 In brief, there were four “levels”
of care through which patients could proceed. Patients whose depression did not sufficiently improve at a given level, as well as those who did not tolerate the given treatment, were encouraged to move on to the next level. Treatment at each level of care lasted up to 14 weeks. All patients began at Level 1 with treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram, representing the common use of SSRIs in general practice. Table 1 lists the available treatment options for each level.

The study design employed a unique randomization scheme known as equipoise stratified randomization, whereby patients could opt out of particular treatment arms (but not individual medications), thus being randomized only to those arms they found acceptable. This also was done to replicate real-life practice, as it acknowledges that patients’ treatment preferences play an important role in clinical decision making.

Patients received high-quality care that included frequent clinic visits and close coordination of care. At each treatment level, patients were seen at 2, 4, 6, 9, and 12 weeks after entry. During each visit, data on symptom severity, side-effect burden, and other important clinical information were gathered via standardized rating scales. This use of formal rating scales to monitor progress and guide medication dosing illustrated a concept known as measurement-based care.

Baseline ratings at study entry were compared with subsequent scores to assess level of clinical improvement. The treatment goal in STAR*D was remission, a complete or near-complete resolution of depressive symptoms. This is in contrast with most studies of depression, which tend to use response—generally defined as a 50% reduction in symptoms—as the target outcome. Remission was defined by scores on two standardized instruments that assess depressive symptoms, the 17-item Hamilton Rating Scale for Depression (HAM-D<sub>17</sub>) and the 16-item self-report form of the Quick Inventory of Depressive Symptomatology (QIDS-SR<sub>16</sub>). Remission was indicated by a score of ≤7 on the HAM-D<sub>17</sub> (the primary outcome measure) or ≤5 on the QIDS-SR<sub>16</sub> (the secondary outcome measure). In prior studies, remission has been correlated with better daily functioning, lower rates of relapse, and decreased risk of suicide and substance abuse.

The STAR*D Patients

A total of 4,041 patients were enrolled, having met initial eligibility criteria, which included being 18–75 years of age and having a nonpsychotic depression with a baseline HAM-D<sub>17</sub> score of ≥14. However, 1,165 of those patients were subsequently excluded from the treatment outcome analysis for a variety of reasons. These reasons included having a confirmatory baseline HAM-D<sub>17</sub> score of <14, missing HAM-D<sub>17</sub> data, and failure to return. There were no substantial differences between those included in the Level 1 analysis and those excluded.

This left 2,876 patients with analyzable data for Level 1 outcomes. Of those patients, 37.9% were treated in primary care settings. Their average age was 40.8 years. Twenty-four percent were ethnic minorities and 63.7% were female. A little more than 50% had private medical insurance; 14.2% had public insurance, and the remaining 34.7% were...
The Figure shows the flow of patients through all four stages of the study.¹¹

**Primary Care Patients and Medical Comorbidity**

Using baseline data gathered at time of enrollment into STAR*D, several analyses have been published regarding patient demographic and clinical characteristics that are particularly relevant to PCPs. One analysis found that patients enrolled in primary care settings had depressions that were as severe as those seen in specialty care settings.¹² Similarly, there were no substantial differences in the symptomatic presentations. Approximately 50% of patients in both settings (45% in primary care, 50.8% in specialty care) endorsed having had some suicidal ideation within the preceding week. This challenged long-standing beliefs that depression in primary care is less severe and presents with a markedly different constellation of symptoms.

Concurrent general medical conditions were common among patients seen in both the primary and specialty care settings.¹³ The overall prevalence of significant medical comorbidity was 52.8%. Not surprisingly, a greater proportion of patients seen in primary care settings had comorbid medical conditions than those in psychiatric clinics. Sixty-five percent of the primary care patients had medical comorbidity, compared with 46% of specialty care patients. The study found no differences in reports of fatigue, appetite disturbances, or sleep disturbances—all core diagnostic criteria—when comparing those with general medical conditions and those without. It was thus concluded that those with medical comorbidity can be evaluated for depression by the same diagnostic criteria used to assess the medically well.¹³

There were several patient subpopulations in which general medical conditions were more prevalent. For example, patients with greater psychiatric comorbidity¹⁴ and those with chronic episodes¹⁵ (current episode duration of at least 2 years at enrollment) had greater medical comorbidity. These patients were more likely to be seen in primary care settings. Patients with recurrent depression (lifetime history of two or more episodes) were also found to have higher amounts of medical comorbidity,¹⁶ though the prevalence of recurrent depression was similar in both treatment settings.
Outcomes Data

Level 1 Outcome

Remission rates with citalopram treatment were only modest, despite the quality of care, optimized dosing (up to 60 mg/day), and close follow-up. Specifically, the rates of remission were 28% per HAM-D\_17 scores and 33% per QIDS-SR\_16 scores.\textsuperscript{10} These rates were similar to those observed in randomized, controlled trials with SSRIs. The rate of response (≥50% reduction in depression ratings) was 47%, notably lower than in many industry-sponsored antidepressant trials. There were no differences in remission or response rates when comparing those in primary care versus specialty care.

The mean dose upon exit from Level 1 was 41.8 mg/day, a dose higher than often used in primary care; this mean dosage includes those individuals who did not complete the entire 12–14 weeks of treatment, often exiting at lower doses. In addition, of those patients who did achieve remission (per QIDS-SR\_16 score), 40% did so after only 8 weeks of treatment. These results support the importance of optimized dosage and are a reminder that full remission does not occur as quickly as clinicians often suggest to patients.

Specific demographic groups who experienced greater rates of remission included Caucasians, females, those employed, and those with higher levels of education or income. Conversely, certain factors were associated with decreased rates of remission. These included lower baseline function and quality of life, the presence of more concurrent psychiatric disorders (in particular, anxiety disorder and substance abuse), and longer duration of the current depressive episode at time of enrollment. Notably, the presence of more concurrent general medical conditions was also associated with not attaining remission. Thus even closer attention and follow-up may be warranted for those patients who have many characteristics associated with a less favorable outcome.

Level 2 Outcome

Patients randomized within the switch arm of Level 2 obtained the following remission rates on the HAM-D\_17: 17.6% for sertraline (doses up to 200 mg/day), 24.8% for venlafaxine extended release (XR; up to 375 mg/day), and 21.3% for bupropion sustained release (SR; up to 400 mg/day). These differences were not statistically significant. Though the nature of side effects varied to some expectable degree, there were no statistically significant differences in overall side-effect burden or serious adverse events (AEs).\textsuperscript{17}

Patients randomized to receive augmentation of their citalopram had the following remission rates on the HAM-D\_17: 29.7% for those receiving augmentation with bupropion SR (up to 400 mg/day) and 30.1% for buspirone (up to 60 mg/day); this difference was not statistically significant. However patients in the bupropion SR augmentation group did have a greater percentage decrease in QIDS-SR\_16 scores and a lower QIDS-SR\_16 score at the end of the study as compared to the buspirone group, secondary outcomes that were statistically significant. Finally, in the buspirone group there were higher rates of discontinuation due to intolerance. These findings led to the conclusion that bupropion SR has some advantages over buspirone, though both medications can be useful for augmentation purposes.\textsuperscript{18}

Of note, outcomes data on those patients who participated in cognitive therapy treatment arms have not yet been published but are forthcoming.

Level 3 Outcome

As with Level 2, both switch and augmentation strategies were used in Level 3. Among those who switched from their previous treatments to the atypical antidepressant mirtazapine (up to 60 mg/day) or the tricyclic antidepressant (TCA) nortriptyline (up to 200 mg/day), the remission rates were quite low. Specifically, the rates of remission per the HAM-D\_17 were 12.3% for mirtazapine and 19.8% for nortriptyline. This difference was not statistically significant. There were also no significant differences with respect to tolerability or serious AEs.\textsuperscript{19}

Remission rates for patients receiving augmentation of their previous antidepressants were 15.9% for patients receiving
lithium (up to 900 mg/day) and 24.7% for those given triiodothyronine (T₃; up to 50 μg/day). Though there was no statistical difference in efficacy, patients who took lithium did report more frequent side effects, and as a result lower doses were used than would generally be required for optimal augmentation. It was concluded that for augmentation purposes T₃ has slight advantages over lithium based on tolerability and ease of use.

**Level 4 Outcome**

Patients who entered Level 4 could be considered to be highly treatment-resistant, having had inadequate outcomes with three previous treatment approaches. Patients were switched from their previous medication and treated with either the monoamine oxidase inhibitor (MAOI) tranylcypromine (up to 60 mg/day) or a combination of venlafaxine (up to 375 mg/day) and mirtazapine (up to 60 mg/day.) As in Level 3, the rates of remission were quite low. Remission rates per the HAM-D₁₇ were 6.9% with tranylcypromine and 13.7% with the venlafaxine-mirtazapine combination. The difference between the two was not statistically significant. However, the tranylcypromine was thought to be a less preferable option, given greater side-effect burden and the dietary restrictions required with MAOIs.

**Naturalistic Follow-up and Relapse Outcomes**

Patients who reached full remission continued their treatment for another year as part of a naturalistic follow-up. Although remission was the target goal of treatment, some patients whose depressions responded but did not remit chose to go into the follow-up phase instead of moving onto the next randomization level. A recent STAR*D report reiterated the importance of aiming for complete remission by analyzing the relapse rates of those who had entered the naturalistic 1-year follow-up phase. For all four levels of treatment, the relapse rate was lower for those who were in remission at the time of entering follow-up compared with those not in remission. For example, of those moving on to the 1-year follow-up directly from Level 1, 33.5% in remission had relapsed within the year as opposed to 58.6% of those who had not achieved remission.

Relapse rates were also higher for patients who had gone through more treatment steps prior to entering follow-up, regardless of whether or not they had achieved remission. The total relapse rates were 40.1%, 55.3%, 64.6%, and 71.1% for those moving on to the follow-up phase following Levels 1, 2, 3, and 4, respectively. Those who required more than two treatment steps relapsed more quickly than those entering follow-up at Levels 1 or 2.

**Discussion**

A major strength of STAR*D is the generalizability of its findings to “real-world” practice. Several design elements—such as the inclusion of primary care settings, the diversity of patients enrolled with minimal exclusion criteria, and the use of equipoise stratified randomization—make the STAR*D results directly applicable to most primary care practices. Key learning points from the study are listed in Table 2.
Pharmacotherpay Outcomes

The overall results from STAR*D remind us of the modest effectiveness of our currently available antidepressant treatments. With just under 33% of Level 1 patients achieving remission—despite optimal dosing, symptom-based monitoring and frequent clinic visits, and patient education with the assistance of clinical research coordinators—the results indicate that most patients will not have an optimal outcome with initial SSRI treatment. Furthermore, 40% of patients whose depression remitted (per QIDS-SR16) required at least 8 weeks of treatment to achieve remission. Clearly, physicians should not be afraid to dose vigorously and to allow an adequate treatment period before considering a trial of an antidepressant as having failed.

Given that at least 66% of patients will not achieve remission after initially being treated with an SSRI, the question of what to do next is critical. Level 2 of STAR*D attempts to provide some direction. As with Level 1, the remission rate in Level 2 was modest, with approximately 25% of patients switched to another antidepressant remitting and approximately 30% of patients in the augmentation groups remitting. The switch and augmentation arms cannot be directly compared, due to patient differences in each arm related to patient self-selection.

Among the three different switch options (bupropion SR, sertraline, and venlafaxine XR) in Level 2, there were no statistically significant differences in remission rates. Given popular assumptions about differing antidepressant efficacy, these results may be surprising to some. It has often been thought that lack of response to or intolerance of one SSRI predicts the same with a second SSRI; these data contradict this belief. It is also commonly believed that if an initial SSRI is not helpful, switching to an antidepressant with a different mechanism of action is preferred. This too is not substantiated by the STAR*D data, as the three switch options had different pharmacologic mechanisms. The data suggest that if a patient has an inadequate response to an initial trial of an SSRI, either another SSRI or a non-SSRI would be a reasonable choice. However, these findings should not be interpreted as supporting continued SSRI trials following two failed attempts with SSRIs.

Level 2 results demonstrated that either bupropion SR or buspirone is a reasonable option for augmenting an SSRI, as they produced similar rates of remission. However, bupropion SR’s superiority on some secondary efficacy measures, as well as better tolerability, indicate that bupropion might have some advantages over buspirone. Bupropion also has the benefit of proven monotherapy antidepressant efficacy, which can be useful if titration off the SSRI is desired at some future time.

Affirming clinical experience, patients did have strong preferences regarding treatment selection. Those who were tolerating and experienced some benefit from citalopram were more open to continuing it and augmenting with a second agent. Meanwhile, those who had little improvement on citalopram or had intolerable side effects generally preferred to move on to a different antidepressant. The message for physicians is that patients often have strong preferences that should be elicited and considered when making treatment decisions.

Levels 3 and 4 results are even more sobering, indicating that physicians should anticipate even lower remission rates when patients have two or more unsuccessful medication trials. The treatments used in these advanced levels were
medications and medication combinations with which some PCPs might be less familiar. Lithium, the TCA nortriptyline, and the MAOI tranylcypromine can be challenging to prescribe due to less favorable side-effect profiles, toxicity risks, the need for laboratory monitoring, and the potential for drug interactions. PCPs who are not comfortable prescribing these treatments may choose to seek psychiatric consultation when a patient’s depression requires these or other complicated psychopharmacologic regimens. Table 3 lists other situations in which it may be useful to obtain a consultation.

<table>
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<tr>
<th>TABLE 3</th>
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<tr>
<td><strong>WHEN TO CONSIDER PSYCHIATRIC CONSULTATION</strong></td>
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<tr>
<td>- Significant suicide risk</td>
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<td>- Severe hopelessness or scheme feelings of guilt/suicide</td>
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<tr>
<td>- Significant decline in social or occupational functioning</td>
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<tr>
<td>- Precordation symptoms or severity</td>
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<tr>
<td>- Suspected for bipolar disorder</td>
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<tr>
<td><strong>Psychiatric symptoms</strong></td>
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<tr>
<td>- Comorbid psychiatric comorbidity (e.g., obsessive-compulsive disorder, posttraumatic stress disorder)</td>
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<tr>
<td>- Significant substance abuse</td>
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<td>- Complex psychopharmacologic regimens</td>
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<td>- Inadequate response to three or more antidepressant medications</td>
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Importance of Achieving Remission

STAR*D confirmed the importance of making remission, as opposed to mere response, the target goal of treatment. The difference between remission and response goes beyond the sheer number or severity of symptoms, as response without full remission has previously been associated with higher rates of relapse and recurrence, decreased work productivity, and higher levels of healthcare use.\(^\text{10}\)

At all four levels in STAR*D, relapse rates were higher for those who responded but did not remit.\(^\text{11}\) Whereas most previous conclusions about risk of relapse have been based on observations of depressed patients following just one treatment, the STAR*D data suggest that even if several treatments are required to reach remission, it is associated with a better outcome.

The study also documented the highly recurrent nature of MDD, even with adequate treatment. In the best-case scenario—patients who had achieved full remission with the initial treatment with citalopram—approximately 33% relapsed within the year; among those who remitted only at Level 4, 50% relapsed in the follow-up period.

The Disease Management Model and Measurement-Based Care

High quality patient care was delivered in STAR*D using techniques derived from a disease management model, a concept involving the collaborative efforts of physicians, nurses, and clinical support staff working together to make assessments, determine appropriate treatments, provide disease-state education, and maintain regular patient contact. Studies of disease-management programs for depression suggest that they can improve patient care and have good cost effectiveness.\(^\text{6}\)

A component of disease management models successfully implemented in both primary and specialty care settings was the use of measurement-based care with the QIDS-SR\(_{16}\),\(^\text{22}\) an easily administered self-report in which patients rate the severity of core depressive symptoms.\(^\text{23}\) QIDS-SR\(_{16}\) scores obtained at each visit were used by the clinicians to monitor progress and helped to inform the dosage schedule.

An additional benefit of utilizing self-report measures is that patients become much better observers of their own symptomatology and thus can facilitate more complete but expedient review of their symptoms. It also provides patients and clinicians a clearer sense of the patient’s progress, thereby reassuring the patient of the clinician’s thoroughness in monitoring their status. Use of the QIDS-SR\(_{16}\) or other assessment tools should be continued even during the remission phase of follow-up, with the goal of identifying relapse before a patient becomes fully syndromal.

Another disease-management strategy employed in STAR*D was the scheduling of frequent clinic visits. Patients were seen every 2–3 weeks, with the option for additional visits if clinically indicated. In addition, aggressive outreach was made toward those who missed scheduled visits. The use of frequent visits allows for close monitoring of response, facilitates more rapid titration of medication, enhances patient safety, and helps prevent dropout from treatment. Available data suggest that primary care patients may not be seen for regular follow-up visits after being started on antidepressants, as adequate visit frequency is often a challenge in a busy primary care setting. STAR*D demonstrates that frequent patient visits are feasible in primary care settings, provided that necessary resources are devoted to depression management.

Successful use of disease-management strategies in STAR*D provides further support for their use on a wider scale, especially given the significant personal, medical, and financial costs of inadequately treated depression. In particular, the identical outcomes in psychiatric clinics and primary care clinics when using disease management techniques argues for the effectiveness of these strategies in primary care, as well as for recognition by insurers of the value of these services.

Issues Specific to Primary Care

Depressions seen in primary care settings were just as severe as those seen in specialty care. This finding firmly contradicts the common belief that PCPs see milder forms of depression than those treated by mental health specialists. Furthermore, other depression treatment challenges faced in primary care include greater amounts of chronic depression and more general medical illnesses, which appear to make depression more difficult to treat successfully.

Table 4 summarizes observations about STAR*D patients seen in primary care settings in comparison with those seen in specialty care.

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<th>TABLE 4</th>
<th>COMPARISON OF PRIMARY VS. PSYCHIATRIC CARE IN STAR*D</th>
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<tr>
<td>No difference in severity of depressive illness</td>
<td></td>
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<tr>
<td>Minimal differences in depressive symptom presentation</td>
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<tr>
<td>Approximately 60% of patients had recent suicidal ideation in both</td>
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<tr>
<td>More medical comorbidities in primary care</td>
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<tr>
<td>More psychiatric comorbidity in primary care</td>
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<tr>
<td>Chronic depressions more prevalent in primary care</td>
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<td>No differences in measures with optimised SSR treatment</td>
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Future research efforts are needed to identify specific but cost-effective interventions to target those patients at risk for poorer prognosis. Useful strategies that are currently available include knowledge of community resources, including low-cost community mental health centers; use of non-promotional educational materials appropriate to patients’ educational level; assistance by other office personnel in obtaining self-assessments; and referral to groups such as the Depression and Bipolar Support Alliance (DBSA), which are generally free of charge and present in communities throughout the country. Participation in DBSA provides useful peer-support and education for patients, and has been shown to improve treatment adherence.

The Role of Psychotherapy

While STAR*D outcomes for the cognitive therapy components are not yet available, previous studies of chronic depressions have demonstrated the clear advantage of combining some forms of psychotherapy with antidepressant treatment versus either treatment alone. Referrals to psychotherapy should be considered whenever depressed patients present with more chronic forms of the illness or greater life adversity. Psychotherapy can enhance patients’ coping, antidepressant efficacy, and adherence to pharmacotherapy, as well as provide useful mental health consultation for the treating PCP. Coordination of care through communication between the physician’s office and the therapist can further improve outcome and is highly recommended whenever referrals to therapy are made.
Conclusion

The wealth of data obtained through STAR*D demonstrates the importance of large-scale effectiveness trials. The ability to follow thousands of patients over an extended length of time has enabled a thorough characterization of depression and its treatment that has not been available (and likely would not be available) through smaller industry-sponsored trials. Nevertheless, STAR*D has raised just as many questions as it has answered, demonstrating the complexity of depression, especially in primary care.

Further analyses of STAR*D data are still forthcoming. Future studies will examine whether particular patient characteristics correlate with their treatment choices (ie, proceeding to the next treatment level versus moving into the year-long follow-up versus exiting the study). Additional reports on longer-term outcomes are also anticipated. Results of these studies will shed light on which treatment choices are most common, what may motivate these choices, and the clinical consequences of these decisions.

Also of interest will be investigation of specific biomarkers that may be used to predict response to antidepressant treatment, analyses made possible through the collection of blood samples from 1,952 consenting STAR*D patients. Additional STAR*D reports on use of biomarkers may assist in the development of more individualized depression treatments, which in turn may help physicians improve upon the modest remission rates observed. Clinicians and patients are able to follow emerging STAR*D findings at www.star-d.org and www.nimh.nih.gov.

While there are still no clear-cut “winners” in terms of what to do when an initial treatment fails, the critical need to treat until remission and to continue diligent monitoring even after remission is attained is clear. Treatment success rates in primary care can approach those seen for depression treatment in psychiatric practices with the provision of adequate management. Clearly, further advances are necessary in the development of new treatments for depression. However, more studies of other strategies and combinations utilizing currently available treatments and of effective means of predicting treatment responses are needed. In the meantime, we physicians will all continue to strive to bring our patients the best chance of getting and staying well.

References


11/18/2012


