What Are the Implications of the STAR*D Trial for Primary Care? A Review and Synthesis

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Background: Although results of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial have been widely disseminated to mental health care providers, hitherto, primary care providers, who diagnose and manage most individuals with depressive syndromes, have had minimal exposure to the study's key findings.

Objective: We aim to provide translational implications of the STAR*D trial for primary care practitioners as well as for future research vistas.

Data Sources: A PubMed search was carried out with key search terms *STAR*D* and *treatment-resistant depression* found in articles published from 2001 through 2007.

Study Selection: Articles reporting on the STAR*D outcomes at each sequence of treatment were the primary sources for review.

Data Extraction: Results from the primary outcome measures at each sequential treatment were extracted and reviewed. Articles reporting variables affecting the probability of achieving remission were also selected.

Results: The STAR*D trial is the largest effectiveness study evaluating next-step therapies in real-world patients with major depressive disorder. The ecological validity of the study results are burnished by several methodological factors, including the enrollment of both publicly and privately insured patients, the recruitment of patients in primary and specialty care settings, the broad inclusion criteria, the use of pharmacologic and psychosocial (i.e., cognitive-behavioral therapy) treatment options, the use of measurement-based care, and the randomized clinical equipoise design. Taken together, remission rates of approximately 50% to 55% were reported after 2 sequential treatment interventions. A substantial percentage of individuals achieving remission do so after 6 weeks of treatment. The probabilities of achieving remission with third- and fourth-step therapy were considerably lower, i.e., ≤ 25%. The probabilities of relapse during continuation therapy increased as a function of number of treatment trials required to achieve remission. There is no evidence that individuals failing to achieve remission with a selective serotonin reuptake inhibitor (SSRI) have a greater probability of remitting with a separate class antidepressant versus an alternative SSRI.

Conclusion: A window of therapeutic opportunity appears to exist insofar as acute remission rates in major depressive disorder are greatest with the first 2 sequential treatments. Taken together, measurement-based care affords the greatest probability that an individual will achieve remission. Despite optimal continuation treatment, relapse rates remain significant, underscoring the chronicity of depressive disorders.

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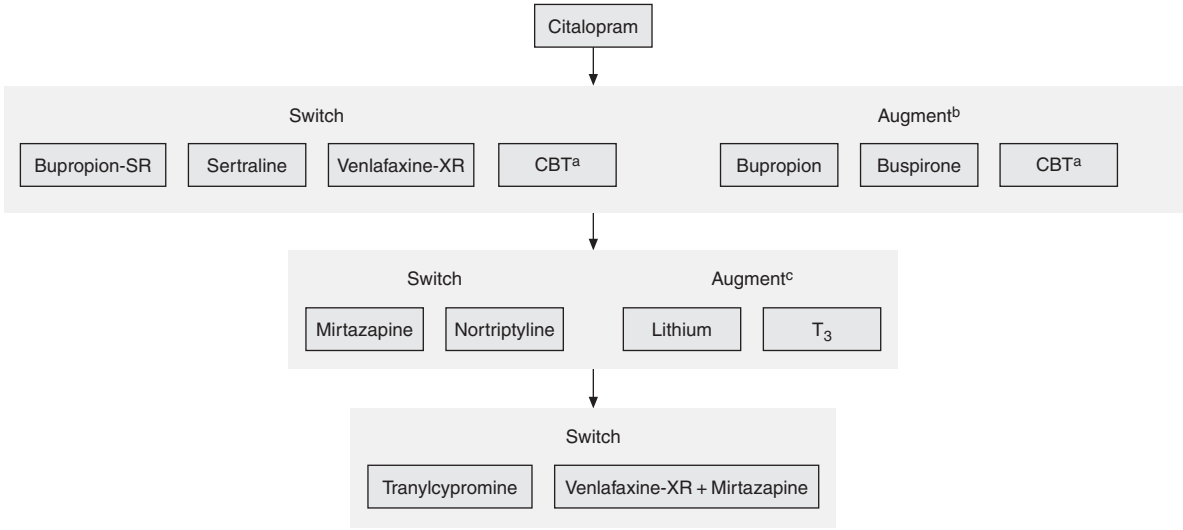
The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial was the largest study (N = 4041) ever conducted evaluating and comparing algorithmic treatment effectiveness in real-world patients experiencing a depressive episode as part of major depressive disorder.[1–7] The STAR*D trial was supported by the National Institute of Mental Health and was implemented over a 5-year period. Although results of this landmark trial have been widely disseminated to mental health care providers, hitherto, primary care providers, who diagnose and manage most individuals with depressive syndromes, have had minimal exposure to the study's key findings.

The composite of depression in primary care is similar to specialty care settings with reports of an overrepresentation of somatic symptoms in individuals utilizing primary care services. Subgroup analyses evaluating individuals recruited from specialty and primary care sectors

Figure 1. Sequential Therapies Evaluated in the STAR*D Trial



[a]Individuals who received CBT at step 2 were advanced to step 2a (not shown) in which they received either venlafaxine-XR or bupropion to ensure that all participants who entered step 3 had unsatisfactory responses to 2 different antidepressants.
[b]These augmentation therapies (bupropion, buspirone, or CBT) were added to citalopram.
[c]The 2 medication augmentation options at level 2 (bupropion and buspirone) were discontinued without tapering, while citalopram therapy was continued with the addition of lithium or T_3. Step 2 medication switch options (bupropion-SR, sertraline, or venlafaxine-XR) were continued with the addition of lithium or T_3.
Abbreviations: CBT = cognitve-behavioral therapy, SR = sustained release, STAR*D = Sequenced Treatment Alternatives to Relieve Depression, T_3 = triiodothyronine, XR = extended release.

participating in the STAR*D trial revealed minimal differences in symptom severity, course of illness variables, and/or patterns of comorbidity.[1] These findings are not commensurate with previously published smaller studies comparing between-group differences as well as opinion that depression in primary care is less severe and associated with less harmful dysfunction. Moreover, symptomatic outcome, presented as a continuous or categorical (i.e., remission/response) outcome variable, was not different in the specialty and primary care STAR*D patients.

The encompassing aim of the STAR*D trial was to address the pragmatic and fundamental question: What is the treatment of next choice in individuals failing to achieve remission with index antidepressant therapy? Toward that aim, the STAR*D trial evaluated disparate pharmacologic treatment options as well as cognitive-behavioral therapy (CBT) administered as augmentation/combination or switching strategies (Figure 1). The primary outcome measure in the STAR*D trial was remission, operationalized as a total 17-item Hamilton Rating Scale for Depression[8] score of ≤ 7. Subjects who failed to achieve remission after a 12 to 14 week index trial with the selective serotonin reuptake inhibitor (SSRI) citalopram were given the opportunity to proceed to the next step of treatment. Individuals who achieved remission after index therapy were offered enrollment into a 12-month follow-up observation period to evaluate for relapse of illness.

Treatment options in the STAR*D trial were selected on the basis of extant literature and clinical experience with patients who have treatment-resistant major depression. In keeping with the view that decision support (e.g., evidence-based guidelines, clinimetrics) is a critical component of chronic disease management capable of enhancing patient outcome, all participating centers adopted measurement-based care. *Measurement-based care* refers to the routine use of rating scales, systematic monitoring of treatment adverse events, guideline-informed antidepressant dosing, and other decision support to guide treatment.

The STAR*D trial is bandied as a real-world study, which implies that the study participants were highly representative of patients commonly encountered in the treatment arena. Participants were not recruited by media announcements as is typical in pivotal registration efficacy trials conducted at academic centers. Other methodological factors that contribute to the ecological validity and generalizability of the study results are the enrollment of both publicly and privately insured patients, the recruitment in primary and specialty care settings, the broad inclusion criteria, the use of pharmacologic and psychosocial (i.e., CBT) treatment options, and the randomized clinical equipoise design.

A novel aspect of the STAR*D trial design is the use of equipoise-stratified randomization. This approach allows participants to eliminate the possibility of being randomly assigned to treatments that they deem to be unacceptable.

For example, individuals may elect to be randomly assigned to switch or augmentation therapies only. Moreover, subjects who preferred CBT versus a pharmacologic treatment strategy were offered only the psychosocial treatment. The shared decision making regarding treatment assignment resembles real-world primary care practice.

In this article, we aim to provide translational implications of the STAR*D trial for primary care practitioners as well as for future research vistas.

DATA SOURCES

A PubMed search was carried out with key search terms *STAR*D* and *treatment-resistant depression* found in articles published from 2001 through 2007. Articles reporting on the STAR*D outcomes at each sequence of treatment were the primary sources for review. Results from the primary outcome measures at each sequential treatment were extracted and reviewed. Articles reporting variables affecting the probability of achieving remission were also selected.

RESULTS

Upon completion of the first step of therapy, the remission rate with citalopram monotherapy (mean ± SD exit dose, 41.8 ± 16.9 mg/d) was 28%.[1] Although the majority of individuals who remitted (or responded) did so after 6 weeks of treatment, a substantial proportion achieved the primary outcome (remission) between treatment weeks 6 and 12. Factors associated with a higher probability of remission included being white, female, employed, and better educated as well as earning higher levels of income. In contrast, those individuals with a lengthy index episode of depression and presenting with psychiatric or medical comorbidity exhibited a lower probability of achieving remission.

Upon completion of the second step of therapy, subjects who elected to switch medications exhibited a remission rate of 21% with sustained-released bupropion (mean ± SD exit dose, 282.7 ± 104.4 mg/d), 18% with sertraline (135.5 ± 57.4 mg/d), and 25% with extended-release venlafaxine (193.6 ± 106.2 mg/d) treatment.[2] There were no statistically significant differences between groups in rates of remission and overall tolerability burden. These outcomes do not provide evidence that switching to a between-class antidepressant (e.g., SSRIs switched to venlafaxine) provides a higher probability of remission than switching to a within-class option (e.g., SSRI switched to an alternative SSRI).

Subjects who preferred an augmentation strategy after an insufficient index citalopram trial were augmented with either sustained-release bupropion or buspirone. Similar remission rates were observed with sustained-release bupropion (29.7%; mean ± SD exit dose, 267.5 ± 99.8 mg/d) and buspirone (30.1%, 40.9 ± 16.7 mg/d).[3] Sustained-release bupropion was associated with a greater reduction in secondary depression measures (Quick Inventory of Depressive Symptomatology-Self-Report[9] [QIDS-SR]) and a lower dropout rate due to intolerance when compared to buspirone.

Taken together, remission rates with next-step treatment are approximately 25%, resulting in an aggregate remission rate of approximately 50% to 55% after 2 sequential treatment interventions.

Individuals who received CBT as either a switch or augmentation strategy had similar remission rates to those who received pharmacotherapy.[4] Augmentation with pharmacotherapy resulted in a faster onset of remission when compared to adjuvant CBT. The between-group outcome differences (i.e., medication versus CBT) may be in part attributed to differences in sample characteristics. For example, subjects choosing CBT were required to co-pay for services and commute to separate locations to receive therapies. Unsurprisingly, individuals switched to an alternative antidepressant reported more treatment-emergent adverse events when compared to those receiving CBT alone.

In third-step therapy, 2 switch strategies (i.e., mirtazapine and nortriptyline) and 2 frequently employed augmentation strategies in primary care (i.e., lithium and triiodothyronine [T_3]) were compared. There were no statistically significant differences between the switch groups in efficacy and overall tolerability or reported adverse events.[5] For example, remission rates for mirtazapine (mean ± SD exit dose, 42.1 ± 15.7 mg/d) and nortriptyline (96.8 ± 41.1 mg/d) were 12% and 20%, respectively. Among individuals assigned to augmentation, remission rates for lithium (mean ± SD exit dose, 859.8 ± 373.1 mg/d) and T_3 (45.2 ± 11.4 μg/d) were also similar at 16% and 25%, respectively.[6] Lithium treatment, however, was associated with a higher frequency of adverse events when compared to T_3 therapy ($p = .045$), and more participants left treatment because of side effects in the lithium group (23.2%) compared to the T_3 group (9.6%). This finding suggests a relative advantage for T_3 in terms of overall therapeutic index.

The fourth step of therapy compared tranylcypromine monotherapy to venlafaxine/mirtazapine combination. The remission rates with tranylcypromine (7%; mean ± SD exit dose, 36.9 ± 18.5 mg/d) were numerically lower than venlafaxine/mirtazapine combination therapy (14%, 210.3 ± 95.2 mg/d and 35.7 ± 17.6 mg/d, respectively).[7] Although both treatment groups were similar in effectiveness, tranylcypromine was associated with higher discontinuation rates due to intolerability. This observation as well as the lack of dietary restrictions for venlafaxine/mirtazapine indicates it is the preferred fourth-line antidepressant strategy.

Table 1. Thase-Rush Treatment-Resistant Depression (TRD) Staging Method[a]

TRD Stage	Criterion
Stage 1	Failure of at least one adequate trial of one major class of antidepressant
Stage 2	Stage 1 resistance plus failure of an adequate trial of an antidepressant in a distinctly different class from that used in stage 1
Stage 3	Stage 2 resistance plus failure of an adequate trial of a tricyclic antidepressant
Stage 4	Stage 3 resistance plus failure of an adequate trial of a monoamine oxidase inhibitor
Stage 5	Stage 4 resistance plus failure of a course of bilateral electroconvulsive therapy

[a]Adapted with permission from Thase and Rush.[11]

Table 2. Drugs Used for Augmentation in Treatment-Resistant Depression (TRD)[a,b]

Drug	Strength of Evidence of Efficacy in TRD
Lithium	A (with TCA) C (with SSRI)
Bupropion or mirtazapine combination therapy	B
Anticonvulsants (lamotrigine, divalproex sodium, carbamazepine)	B
Thyroid hormone (T_3)	B (with TCA) C (with SSRI)
Atypical antipsychotics (e.g., risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole)	A (olanzapine, quetiapine) C (other atypicals)
Dopamine agonists (pramipexole)	C
Pindolol	C
Stimulants	C
Buspirone	B
Modafinil	C
Testosterone, estrogen	B (testosterone)
Miscellaneous (buprenorphine, SAMe, inositol)	C

[a]Data from Thase.[12]
[b]Table adapted with permission from Nemeroff.[13]
A: ≥ 2 adequately powered, double-blind, placebo-controlled trials.
B: ≥ 1 adequately powered, double-blind, placebo-controlled trial (or an equivalent weight of evidence from multiple smaller trials).
C: positive evidence from open-label trials and case series.
Abbreviations: SSRI = selective serotonin reuptake inhibitor, T_3 = triiodothyronine, TCA = tricyclic antidepressant.

DISCUSSION

The STAR*D trial provides an empirical basis for informing clinical decisions in the management of depression in primary care settings. The overarching question addressed by the STAR*D trial, (i.e., what is the most effective treatment of next choice?) is a common scenario in real-world clinical practice. Several algorithms for the selection and sequencing of antidepressant treatment, staging of treatment resistance in major depression, and hierarchies of evidence supporting treatment options have been published elsewhere[10–13] (Tables 1 and 2). Guiding therapeutic principles include clarification of the principle diagnosis, identifying comorbidities or medications that possibly exacerbate depressive symptoms, ensuring adherence to treatment, and optimization of the index trial. Subsequent options include combining/augmenting with or switching to alternative medications or CBT.

Most depressed patients in the primary care setting who are labeled as treatment resistant are in fact "pseudoresistant" (i.e., they have not received sufficient guideline-concordant treatment).[14] Before a strong pronouncement of treatment resistance is made, index trial optimization should be implemented by ensuring maximally recommended dosing for a sufficient period of time. Most available evidence-/consensus-based guidelines for the treatment of depression recommend index trial duration of approximately 4 to 6 weeks.[15–18] Results from the STAR*D trial indicate that longer index trials may be required for treated patients to realize the full therapeutic potential of the intervention. For example, of all participants who eventually remitted to index therapy, up to one half did so between weeks 6 and 12.[1] Consequently, discontinuing antidepressant treatment prior to 6 weeks of therapy due to ineffectiveness may be premature in some cases. The suggestion for a longer index trial needs to be considered in the context of patient acceptance of ongoing treatment despite the lack of a meaningful therapeutic benefit. An interesting implication of the observed late response to index therapy is the possibility that many individuals previously labeled as augmentation/combination responders may in fact be simply responding to the index trial.

Converging with clinical experience, STAR*D results indicate that the probability of achieving remission decreased in the STAR*D trial as a function of number of treatment interventions.[19] Similarly, the probability of relapse was higher in individuals requiring multiple steps to achieve acute remission. For example, the overall remission rates for the medication options were 28%, 25%, 18%, and 10% at steps 1, 2, 3, and 4, respectively.[1–7] Taken together, 53% and 81% of patients can be expected to achieve remission after 2 and 4 sequential pharmacotherapies, respectively. Given that higher relapse rates were observed among those who are treatment resistant, patients requiring multiple treatment interventions need to be carefully observed for recrudescence of depressive symptomatology. Primary care providers may be less comfortable prescribing later-step treatments (e.g., tranylcypromine), inviting the need for specialist consultation, when available, after 2 or more failed adequate antidepressant trials.[20] It should be noted that the STAR*D trial did not evaluate the potential role of electroconvulsive therapy, which remains an effective treatment option for select patients suboptimally responding to pharmacotherapy and/or manual-based psychosocial intervention.

In an attempt to individualize treatment selection, several factors associated with remission have been identified. These include being white, female, and married as well as having higher educational attainment, higher economic status, private insurance, fewer concurrent general medical and psychiatric conditions, better overall physical and mental function, greater life satisfaction, and a shorter index episode.[1] In contrast, being unmarried or living alone and having longer index episodes, a greater number of general medical and concurrent psychiatric disorders, lower baseline function, and lower quality of life were associated with lower remission rates.[1]

Evidence from the STAR*D trial supports expert consensus that symptomatic remission should be the goal of acute treatment.[17,21–23] *Remission*, an outcome that transcends response, is defined as the resolution of disease activity. Individuals who achieved remission had a lower probability of relapse (i.e., level 1 [34%], level 2 [47%], level 3 [43%], and level 4 [50%]) compared to those who did not attain remission at entry into the follow-up phase (i.e., level 1 [59%], level 2 [68%], level 3 [76%], and level 4 [83%]).[19] These observations suggest that residual depressive symptoms predispose and portend subsequent relapse in depression.

Remission is associated with a better prognosis even if multiple treatment interventions are required. For example, individuals achieving acute remission in the STAR*D trial evinced a longer time to relapse when compared to individuals not achieving remission (i.e., level 1 [4.4 months], level 2 [4.5 months], level 3 [3.9 months], and level 4 [2.5 months] versus level 1 [3.6 months], level 2 [3.2 months], level 3 [3.0 months], and level 4 [3.5 months]).[19] A further analysis of the STAR*D data set revealed that female patients of reproductive age achieving remission were less likely to have a child with a mental disorder when compared to women whose depression was nonremitting.[24]

An important clinical question pertains to the relative effectiveness of switching to an alternative monotherapy versus augmentation/combination with pharmacotherapy or CBT. Unfortunately, this question cannot be addressed by the STAR*D trial due to the clinical equipoise randomization design.

It is worth noting that overall symptomatic outcomes in the first and subsequent steps of the STAR*D trial may exceed outcomes typically encountered in routine clinical care. The use of measurement-based care, which includes measuring patient symptoms, using critical decision points for dose adjustments, and training clinicians, likely accounts for the improved outcome.[19] Systematic measuring of symptoms allows a sharpened and more refined evaluation of illness severity, treatment response, and timing of interventions. Several brief rating scales for depression have been published. The STAR*D trial utilized the QIDS-SR. Copies of the QIDS-SR and other scales employed in STAR*D are available online.[9] Several other published scales capable of quantifying and objectifying treatment outcomes in depression include, but are not limited to, the Patient Health Questionnaire[25] and the 7-item Hamilton Rating Scale for Depression.[26]

To recapitulate, the STAR*D trial provides real-world generalizable results regarding the treatment of depressed individuals in primary care services in both public and private sectors. The representativeness of patients as well as the clinical equipoise design provides meaningful and accessible data regarding next-step treatment. Unanswered questions from the STAR*D trial and vistas for future research remain: Should combination treatment be initiated as first-line therapy for depression? What is the role for atypical antipsychotics in the symptomatic treatment of depression? and What is the optimal duration of maintenance treatment for individuals achieving remission? The answers to these and several other clinically relevant questions will be informed by ongoing studies.

Drug names: aripiprazole (Abilify), buprenorphine (Buprenex, Subutex, and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), divalproex (Depakote), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), modafinil (Provigil), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), pindolol (Visken and others), pramipexole (Mirapex), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft and others), tranylcypromine (Parnate and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

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