The STAR*D Project Results: A Comprehensive Review of Findings

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The Sequenced Treatment Alternatives to Relieve Depression trial enrolled outpatients with nonpsychotic major depressive disorder treated prospectively in a series of randomized controlled trials. These were conducted in representative primary and psychiatric practices. Remission rates for treatment steps 1 to 4 based on the 16-item Quick Inventory of Depressive Symptomatology–Self-report were 37%, 31%, 14%, and 13%, respectively. There were no differences in remission rates or times to remission among medication switch or among medication augmentation strategies at any treatment level. Participants who required increasing numbers of treatment steps showed greater depressive illness burden and increasingly greater relapse rates in the naturalistic follow-up period (40%–71%). Prognosis was better at all levels for participants who entered follow-up in remission as opposed to those who entered with response without remission. These results highlight the prevalence of treatment-resistant depression and suggest potential benefit for using more vigorous treatments in the earlier steps.

Introduction

The World Health Organization has projected that major depressive disorder (MDD) will be the second-leading cause of disability worldwide by 2020 [1]. The lifetime risk of MDD is 7% to 12% for men and 20% to 25% for women [2], and its annual cost was estimated to be $83.1 billion in 2000 [3]. Most individuals with MDD have a chronic or recurrent course, often with considerable symptomatology and disability even between episodes [4–6].

Remission is the accepted goal of acute MDD treatment [7,8] because remitters function better [9] and have a better prognosis [10] than those who respond (have a symptom reduction) without remitting. Efficacy trials with symptomatic volunteers report remission rates of 22% to 40% [11]. However, these results may not generalize to participants typically seen in clinical practices because efficacy trials often exclude patients with chronic depression or multiple general medical or psychiatric comorbid conditions [12,13]. In effectiveness studies with more representative populations, remission rates are low (11%–30%) even after 8 to 12 months of treatment [14–17]. Furthermore, relapse rates of 10% to 45% are found within 1 year or less of remission during maintenance treatment for chronic or recurrent depressions [18]. In spite of extensive evidence supporting the efficacy of antidepressants in patients with MDD and the recognition of modest remission rates with first-step antidepressants, gaps in our knowledge remain about the choice of second- or third-step treatments if the first step does not work. Furthermore, previous research has focused on strict, protocol-driven, research setting–based studies, thus limiting the generalizability to "real world" patients in clinical practice with attendant medical and psychiatric comorbidities.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial [19,20,21••] is the largest prospective, randomized treatment study to date of outpatients with MDD recruited from real world psychiatric and primary care settings who did not receive adequate benefit with initial and, if needed, subsequent antidepressant treatments. To date, more than 60 manuscripts have been published from the STAR*D sample, with more in preparation or under review (see http://www.star-d.org for a list of current publications). This review summarizes STAR*D findings to date that address the following questions:

1. What are the remission and response rates and time to remission with an initial selective serotonin reuptake inhibitor (SSRI)?
2. What participant characteristics are related to remission with an initial SSRI?

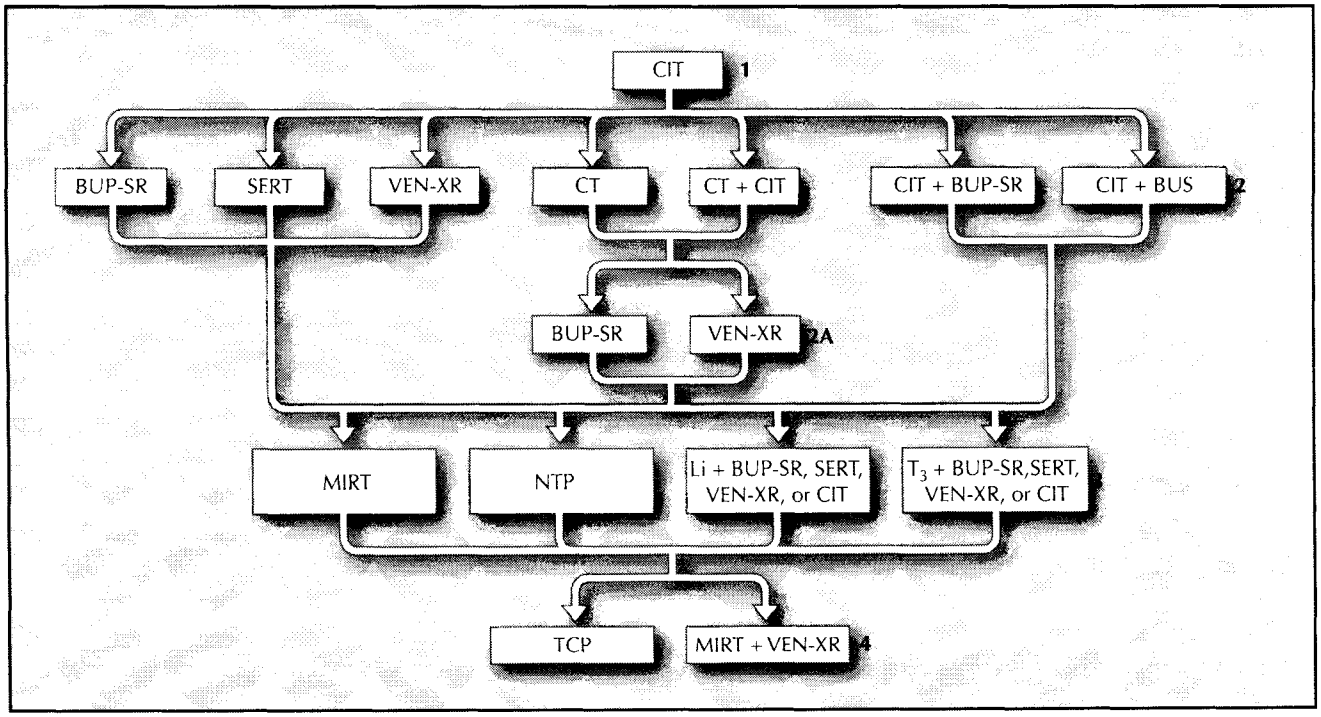

Figure 1. Treatment strategies and options in Levels 1 to 4. BUP-SR—bupropion sustained release; BUS—buspirone; CIT—citalopram; CT—cognitive therapy; Li—lithium; MIRT—mirtazapine; NTP—nortriptyline; SERT—sertraline; T_3—triiodothyronine; TCP—tranylcypromine; VEN-XR—venlafaxine extended release.

3. Do participants differ in their acceptance of different treatment strategies or options at subsequent treatment steps?
4. What are the remission and response rates and times to remission and response for subsequent treatment steps?
5. How does cognitive therapy compare with medication treatments at the second treatment step?
6. What participant characteristics are associated with the need for a greater number of treatment steps?
7. What are relapse rates in those who respond or remit after one to four treatment steps?
8. What characteristics distinguish participants who leave treatment prematurely?
9. What characteristics distinguish participants treated in primary versus psychiatric care?

STAR*D Study Overview

STAR*D was designed to determine which treatments are most effective following nonremission or intolerance to an initial SSRI or to any of a series of subsequent randomized treatments. Over a 37-month period, STAR*D enrolled 4041 outpatients aged 18 to 75 years with nonpsychotic MDD at 41 clinical sites across the United States (18 primary and 23 psychiatric care settings). The study enrolled only treatment-seeking patients (as opposed to symptomatic volunteers) with a clinical diagnosis of nonpsychotic MDD confirmed with a *DSM-IV* checklist and a score greater than or equal to 14 on the 17-item Hamilton Rating Scale of Depression ($HRSD_{17}$) [22]. To maximize generalizability of results, the study included patients with most concurrent psychiatric and general medical conditions, including those with active substance abuse or suicidality, as long as outpatient care was appropriate.

Figure 1 depicts the treatment options at each of the four steps in the series of trials. All participants began with citalopram treatment (Level 1). Those intolerant to or not remitting with citalopram could enter Level 2, which included switching to bupropion-sustained release (SR), cognitive therapy, sertraline, or venlafaxine-extended release (XR), or augmentation of citalopram with bupropion-SR, buspirone, or cognitive therapy. Those without adequate benefit from medication-only treatments in Level 2 could proceed to Level 3. For those with inadequate benefit from cognitive therapy as a switch or augmentation in Level 2, the next step (Level 2A) was a switch to a second medication (bupropion-SR or venlafaxine-XR) to ensure that all Level 3 enrollees had received and not obtained adequate benefit from at least two prior medication trials. Level 3 included switches to mirtazapine or nortriptyline and augmentation of the Level 2 or 2A medication with thyroid hormone (T_3) or lithium. Level 4 treatments were a switch to tranylcypromine or to venlafaxine-XR plus mirtazapine.

An innovative study design feature—an equipoise stratified randomized design [23]—permitted participants, as in clinical practice, to accept or decline switch or augment treatment strategies as long as sufficient options for

randomization remained. For example, participants could allow randomization to all available treatment options, exclude randomization to all switches or to all augments at Level 2 (or 3), exclude or include cognitive therapy as a switch and/or augment, or exclude all medication switches and augments at Level 2 to guarantee cognitive therapy.

The protocol recommended that treatment visits at each level occur at baseline and at weeks 2, 4, 6, 9, and 12, with an additional visit at week 14 if needed. Participants who remitted or received an adequate benefit could enter a 1-year naturalistic follow-up period, although all who did not remit were encouraged to move to the next level. Participants could move to the next level whenever intolerable side effects were encountered or dosing had been maximized, but substantial symptoms remained after several weeks.

In the naturalistic follow-up phase, visits were recommended every 2 months, and clinicians were urged to continue the acute treatment at the same dosage found to be effective previously. Outcomes in follow-up were gathered using an interactive voice response system [24].

The primary research outcome was remission defined by a score of 7 or less on the $HRSD_{17}$, obtained by blinded telephone-based assessors. The secondary outcome was remission defined by a score of 5 or less on the Quick Inventory of Depressive Symptomatology–Self-report ($QIDS\text{-}SR_{16}$) [25–27] obtained at each treatment visit. Response was defined as a 50% or greater reduction in the baseline $QIDS\text{-}SR_{16}$ score. $HRSD_{17}$ remission rates were generally lower than $QIDS\text{-}SR_{16}$ rates because participants without an exit $HRSD_{17}$ score were deemed nonremitters. Intolerance was defined *a priori* as discontinuation before week 4 for any reason or discontinuation thereafter for intolerable side effects.

To ensure adequate dosing for an appropriate period of time, treatment was delivered using measurement-based care (MBC) [28••,29]. Thus, nonremission could not be attributed to an inadequate medication trial. MBC included guided but flexible dosing recommendations at critical decision points based on symptom and side effect measurements at each treatment visit using the Quick Inventory of Depressive Symptomatology–Clinician-rated ($QIDS\text{-}C_{16}$) [25–27] and the Frequency, Intensity, and Burden of Side Effects Rating [30]. A web-based treatment monitoring system [29,31] was used to flag and follow up with the study clinicians when dosing deviations were found. Clinical research coordinators assisted clinicians and participants with study assessments and treatment delivery at each clinical site.

STAR*D Findings

Pretreatment characteristics of participants in Level 1

Of 4041 consenting participants, 607 had $HRSD_{17}$ scores less than 14 when rated by the telephone assessors, and 234 did not return after the baseline visit. The remaining evaluable sample of 2876 participants entered Level 1. Racial and ethnic distribution was consistent with the US Census. In this effectiveness sample, participants averaged 3.3 concurrent general medical conditions, and about two thirds had at least one concurrent Axis I psychiatric disorder. The sample averaged moderately severe depression ($HRSD_{17}$ = 21.8). More than one fourth had chronic depression (index episode > 2 years), and three fourths had recurrent depression. This is in stark contrast to the samples typically studied in efficacy trials, in which strict inclusion and exclusion criteria often exclude Axis I or III comorbidities, chronic depression, and substance abuse, thus limiting the generalizability of findings.

Treatment with citalopram: Level 1

Figure 2 shows outcomes for all medication treatments. Of 2876 participants, approximately 28% (n = 790) remitted based on the $HRSD_{17}$, and approximately 33% remitted based on the $QIDS\text{-}SR_{16}$ [28••]. The response rate, which included those who remitted, was 47%. Remission and response rates and times to remission or response were not different between those treated in primary and psychiatric care settings. These remission rates are comparable to the 22% to 40% remission rates found in 8-week randomized controlled efficacy trials [11] that typically recruit less complicated symptomatic volunteers.

Mean time to $QIDS\text{-}SR_{16}$ remission for those who remitted within the 14-week period was 6.7 weeks. About one half of the remissions occurred after week 6 (Fig. 3). Mean time to response among those who responded was 5.7 weeks. Of those who responded, one third did so after week 6. Mean dose of citalopram at exit was 41.8 mg/d, an adequate dose. Mean dose was similar in those who reached remission and those who did not.

Which participant characteristics are related to remission with an initial SSRI?

Participants who were white, female, married, more educated, had higher income, had private insurance, or were employed had significantly higher remission rates with citalopram. Those disadvantaged by increased numbers of concurrent general medical and psychiatric disorders, longer current episodes, and poorer function and quality of life had significantly lower remission rates [28••].

Level 2

Of the participants in Level 1, 1439 were intolerant to citalopram or received inadequate benefit and moved on to Level 2.

Acceptability of Level 2 treatments

The equipoise stratified randomization design resulted in somewhat unexpected findings for the 1439 participants who agreed to enter Level 2 [32]. Only 1% accepted randomization to all seven treatment options. Approximately 50% accepted medication augment, and 57% accepted medica-

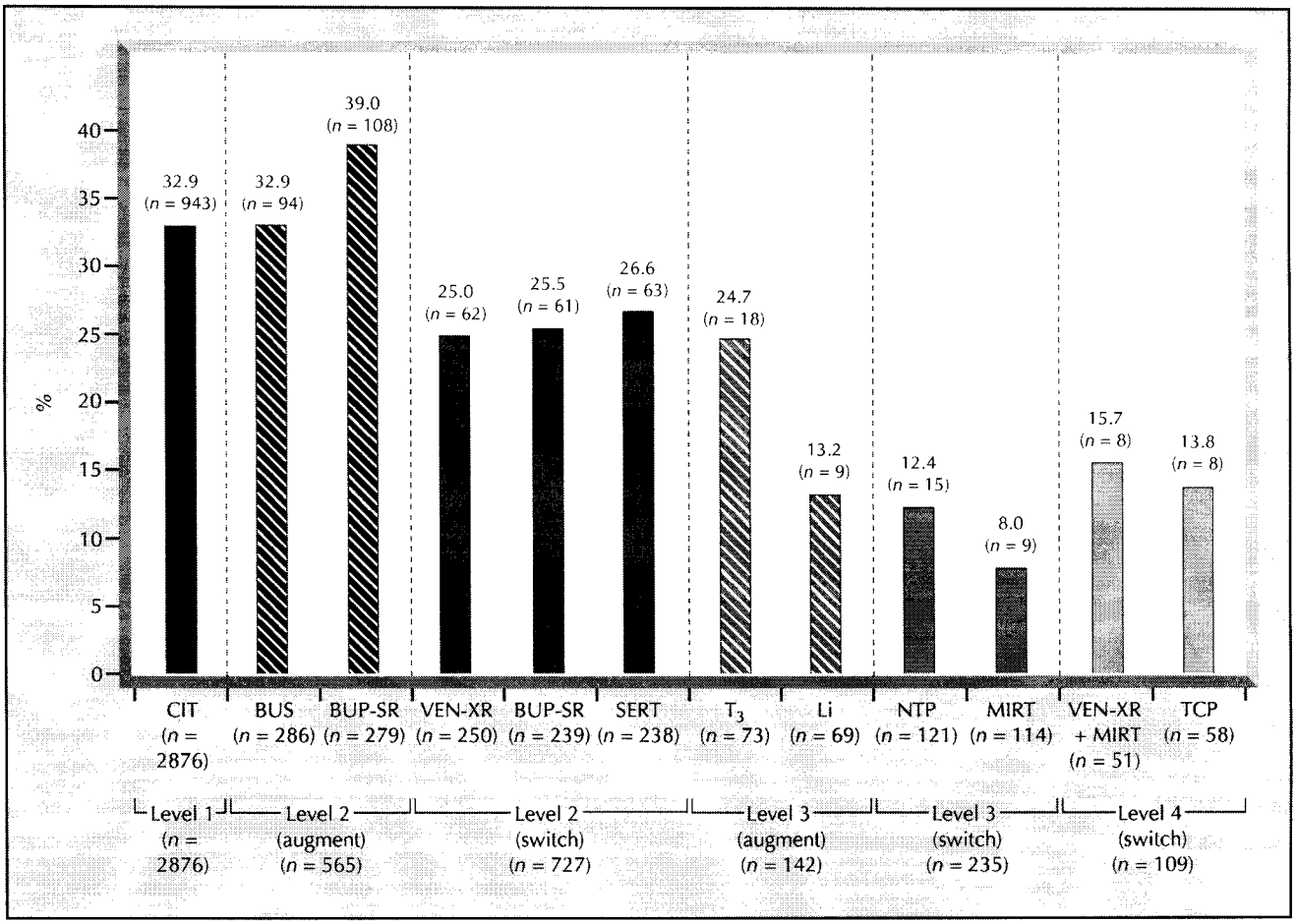

Figure 2. Diminishing remission rates with greater levels of treatment resistance. Remission rates at treatment exit were based on the 16-item Quick Inventory of Depressive Symptomatology—Self-report. BUP-SR—bupropion sustained release; BUS—buspirone; CIT—citalopram; Li—lithium; MIRT—mirtazapine; NTP—nortriptyline; SERT—sertraline; T_3—triiodothyronine; TCP—tranylcypromine; VEN-XR—venlafaxine extended release.

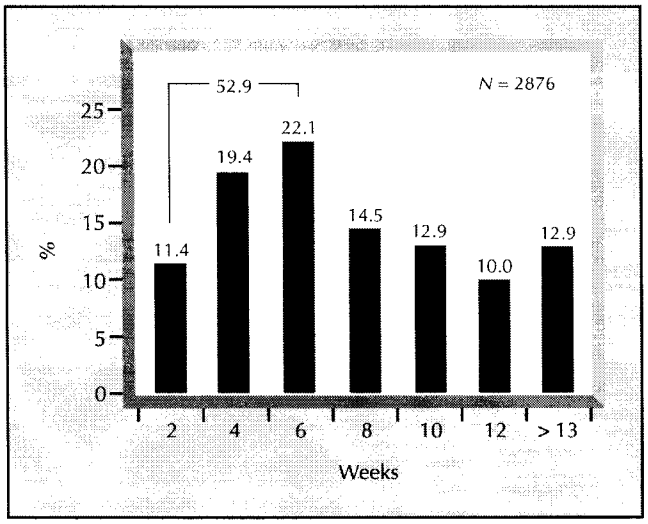

Figure 3. Time to remission with citalopram (Level 1) for remitters. Remission was defined as a score of 5 or less on the 16-item Quick Inventory of Depressive Symptomatology–Self-report.

tion switch. Only 7% accepted randomization to medication switch and augment. Not surprisingly, those who accepted switch treatments had experienced greater intolerance or less improvement with citalopram than those who accepted augment treatments. Those with recurrent MDD and concurrent drug abuse preferred augments. Approximately 26% were willing to accept randomization that included cognitive therapy, and 3% accepted only cognitive therapy (switch or augment). Those who accepted cognitive therapy had more years of education and more frequent family history of mood disorder than those who did not.

As most participants elected to allow randomization to switch or augment strategies (not both), the study was not adequately powered to compare outcomes for switch versus augment treatments. This finding suggests that patients have clear preferences about switch versus augment as a second step.

Level 2 medication switch

The medication switches at Level 2 were designed to compare medications with different pharmacologic effects (ie, sertraline, a second SSRI; bupropion-SR, a nonserotonin active agent; venlafaxine-XR, a reuptake blocker of both norepinephrine and serotonin) [19,20].

Participants entering a medication switch started with a mean $HRSD_{17}$ of 18.9, and about one fourth of these participants remitted ($QIDS\text{-}SR_{16}$) [33••]. Remission rates for bupropion-SR, sertraline, and venlafaxine-XR were not different; neither were time to remission or time to response. Mean time to remission for those who remitted ranged from 5.4 to 6.2 weeks.

These remission and response rates are lower than would be expected from open-label trials with medication switch [33••,34–36]. This is likely due to STAR*D's inclusion of participants with general medical or psychiatric comorbidities or chronic depression, as well as the study's longer first-step treatment. These low remission rates do not appear to result from inadequate treatment, as the doses and durations of treatment seemed robust, except for a somewhat lower mean dose of venlafaxine-XR (~ 194 mg/d) than the potential maximum dose.

Those intolerant to citalopram (Level 1) tolerated sertraline and bupropion-SR equally well, and a lack of citalopram efficacy did not portend a lack of efficacy with sertraline. The dual-action agent (venlafaxine-XR) did not produce significantly higher remission rates. Thus, it seems reasonable to switch within class, out of class, or to a dual-action medication as a second step.

Level 2 medication augment

No prior randomized controlled trials in real world settings have directly compared second-step augmentation with nontricyclic antidepressants [37]. Participants randomized to augmentation had gained some benefit with the previous citalopram monotherapy before entry into a medication augment (mean $HRSD_{17}$ = 15.8) [38••].

Both medication augmentations appear to be helpful, with some advantages for bupropion-SR. About one third of participants remitted with bupropion-SR or buspirone, with no differences between groups in remission, response, or times to remission or response. Participants treated with bupropion-SR showed greater baseline-to-exit symptom improvement, lower exit symptom severity, and fewer dropouts due to intolerance (12.5% vs 20.6%). Both medications were delivered at adequate doses for adequate time periods.

Level 2 cognitive therapy switch or augment

Overall, 147 participants received a cognitive therapy switch or augment. Sixty-five cognitive therapy augment participants were compared with 117 participants who received medication augmentation, and 36 cognitive therapy switch participants were compared with 86 participants who received medication switch [39•]. About one third of cognitive therapy augment and medication augment participants remitted. No significant differences were found in remission or response rates, tolerability, or numbers of weeks in treatment. There was a statistically significant difference in mean time to remission (55 days for cognitive therapy augment, 40 days for medication augment). If speed of remission is important, medication augment has an advantage.

A little more than one fourth of cognitive therapy switch and medication switch participants remitted. There were no differences in time in treatment, remission, response, or time to remission or response between those switching to cognitive therapy and those switching to medication. Of participants who switched to medication, 48% experienced at least moderate side effects, whereas none of those who switched to cognitive therapy reported side effects, although there were no significant differences in discontinuations due to intolerance.

Statistical power for cognitive therapy comparisons was low given the smaller participant samples. This low acceptability of cognitive therapy (26% accepted the possibility of randomization) is not consistent with prior findings [40–42]. Perhaps the use of cognitive therapy in this study as a second rather than first treatment dissuaded patients who preferred psychotherapy from enrolling in STAR*D. Alternatively, an increased co-pay burden (because of the increased number of visits) or the need to travel to another location to see a therapist may have played a role.

Level 3

Of the participants in Level 2 and 2A, 377 experienced intolerance or received inadequate benefit and moved on to Level 3.

Level 3 switch

This study [43•] is the first to compare two medication switch treatments as a third step following intolerance or lack of remission, prospectively determined, to an SSRI and a second antidepressant. The two switch treatments (mirtazapine [n = 114] and nortriptyline [n = 121]) have different pharmacologic mechanisms of action. Nortriptyline represented a third reuptake blocker, whereas mirtazapine does not directly block reuptake. The mean $HRSD_{17}$ score at entry was 19.2.

There were no significant differences in the modest remission rates between mirtazapine and nortriptyline by the $HRSD_{17}$ (12.3%, 19.8%) or the $QIDS\text{-}SR_{16}$ (8.0%, 12.4%), or in response rates or times to remission or response. Medication tolerability in the previous step was unrelated to outcome. Both medications were dosed adequately for adequate time periods.

Level 3 augment

This study [44•] is the first to compare medication augmentation treatments as a third step following two trials with newer antidepressants. Augmentation consisted of adding lithium (n = 69) or T_3 (n = 73) to one of the medication switch options in Level 2 or 2A or to citalopram (for those who had received a Level 2 augmentation treatment). Mean $HRSD_{17}$ score at entry was 18.1.

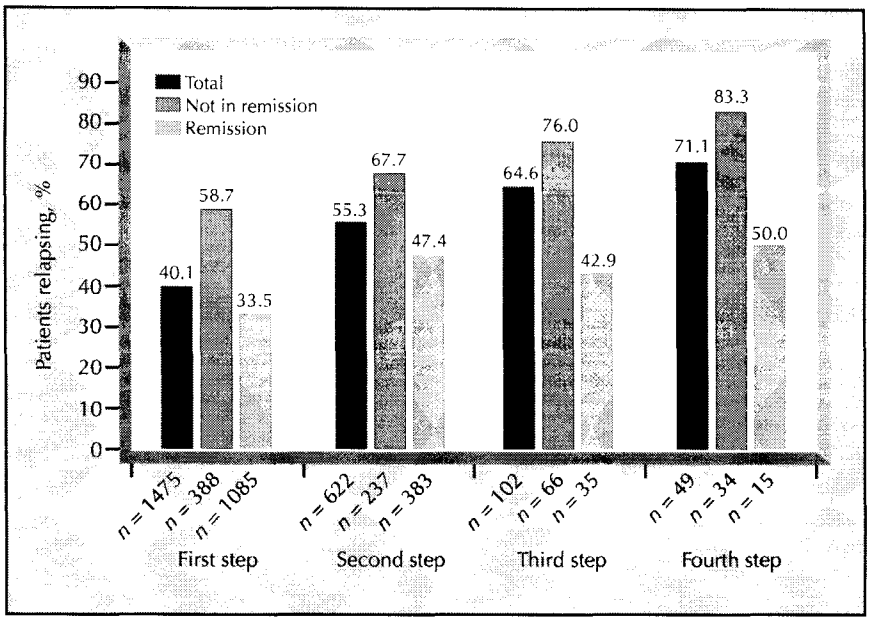

Figure 4. Relapse rate increases with each treatment step. Relapse rate was calculated from those patients who made at least one postbaseline call to the interactive voice response system. Treatment step pairwise comparisons showed only Step 1 to differ significantly from the rest ($P < 0.0001$).

Remission rates were very modest. There were no significant differences in remission rates for lithium or T_3 augment by the $HRSD_{17}$ (15.9%, 24.7%) or the $QIDS\text{-}SR_{16}$ (13.2%, 24.7%), or in response rates or time to remission or response. Remission rates were not significantly different for those using any of the medications in Level 2.

Those taking lithium had more frequent side effects and were more likely to leave the study due to intolerable side effects despite moderate dosing of lithium. T_3 may be the preferential treatment due to its lower intolerance rate and lack of a necessity to check blood levels, although long-term safety data are lacking.

Level 4

This is the first available report [45•] of a fourth randomized medication trial based on prospective observations. Participants with intolerance or lack of remission with three prior medication treatments were randomized to tranylcypromine, a monoamine oxidase inhibitor (n = 58), or venlafaxine-XR plus mirtazapine (n = 51). The mean $HRSD_{17}$ score at entry into Level 4 was 19.6.

Remission rates were remarkably low and similar between tranylcypromine and venlafaxine-XR plus mirtazapine on the $HRSD_{17}$ (6.9%, 13.7%) or the $QIDS\text{-}SR_{16}$ (13.8%, 15.7%). However, the tranylcypromine mean dose of approximately 37 mg/d did not approach the protocol-recommended maximum dosage of 60 mg/d. There were no differences between the medications in response, time to remission, or side effects, although participants taking tranylcypromine were more likely to leave the study prematurely and to leave due to side effects. The 2-week washout period requirement for tranylcypromine, during which five participants dropped out, also may have been a barrier. There were no differences in remission based on intolerance in Level 3. The combination of venlafaxine-XR and mirtazapine seems to be a better option than tranylcypromine, given better acceptance and tolerability and lack of dietary restrictions.

Overall outcomes and treatment resistance

To provide an overall evaluation of outcomes, enrollees were divided into groups based on the total number of acute treatment steps (Levels 1, 2, 2A, 3, 4) [46–48]. Of the 4041 participants, only the 370 without a postbaseline visit were excluded. Those with an $HRSD_{17}$ entry score less than 14 were included, which resulted in 3671 evaluable participants.

For the intent-to-treat group, $QIDS\text{-}SR_{16}$ remission rates were approximately 37% for step 1, 31% for step 2, 14% for step 3, and 13% for step 4. Treatment intolerance was 16% for step 1, 20% for step 2, 26% for step 3, and 34% for step 4.

At study entry, those who received more acute treatment steps had greater general medical illness burden, including longer illness duration (15–20 years), longer index episodes (25–42 months), a greater proportion with anxious features (45%–57%), and a higher mean $HRSD_{17}$ score at study entry (19.9–23.3). They also had a larger proportion of those with at least one Axis I comorbidity (61%–72%) and more concurrent general medical conditions (3.0–3.9).

Longer-term outcomes

Figure 4 shows relapse rates during the 1-year naturalistic follow-up by number of acute treatment steps received. Overall, when more acute treatment steps were used, higher relapse rates (40%–71%) were found. Participants in remission at follow-up entry were less likely to relapse (34%–50%) than those not in remission at entry into follow-up (59%–83%). Participants and clinicians may be increasingly willing to accept higher levels of symptoms as

the number of treatment attempts increases. Mean time to relapse at all steps was short for remitters and those not in remission, ranging from 2.5 to 4.5 months. Time to relapse was shorter for those requiring multiple treatment steps.

These long-term results highlight the need to achieve remission with acute treatment (as opposed to response) and indicate the need to aggressively achieve the desired outcome as early as possible.

Who drops out of treatment?

The large STAR*D sample provided a unique opportunity to describe which patients drop out of treatment and when they do so. Cost did not play a major role, as treatments and treatment visits were provided at no cost. Dropout is an important problem, but little research has been published regarding the phenomenon. Of the original sample of 4041 participants who entered citalopram treatment, 1034 (26%) left the study for nonmedical reasons [49] in Level 1. About one third of these dropped out after only a baseline visit. These immediate attriters were younger, less educated, and perceived their mental health functioning to be better than those remaining in treatment. Those who had at least one postbaseline visit but who dropped out before 12 weeks were more likely to be black, younger, and less educated. Hispanics were more likely to drop out after returning once. Having public insurance and having more psychiatric comorbid conditions were related to greater overall attrition. Of note, participants with recurrent depression were more likely to remain in treatment than those with a single episode. These data suggest that these individuals may benefit from focused retention efforts. Although certain characteristics are associated with higher dropout rates, the overall attrition from the study at all levels of treatment indicates a need to institute preventive procedures involving patient education and attrition-monitoring approaches for all patients.

Participants in primary versus psychiatric care

Primary care patients have been reported to have lower severity of depression [50] and a milder course of illness [51] than psychiatric care patients.

Based on a comparison of the first 1500 STAR*D participants, minimal differences were found in clinical presentation of depression between patients in these two settings [52], including depression severity. Not surprisingly, primary care participants did have more general medical comorbidities.

In primary care, onset of the first episode occurred more frequently after age 18 years, time since onset of the first major depressive episode (MDE) was longer, and the current episode was longer. In specialty care, participants were more likely to have previously attempted suicide and to have current suicidal ideation. Analyses of the subsequent 2541 participants confirmed these findings [53].

Our finding of minimal differences in clinical presentation between primary care and specialty care patients supports the use of the same methods for screening and measuring treatment outcomes in both settings.

STAR*D: Conclusions and Implications

STAR*D addresses questions of substantial public health significance related to treatment for increasingly treatment-resistant MDD. Results are generalizable to typical primary and psychiatric clinical practices.

Chronicity and comorbidity are common

For these participants, MDD was longstanding, with an average length of illness of 15 years. The course of illness was most frequently chronic and/or recurrent and typically associated with other psychiatric and medical comorbid conditions. Increasing chronicity and number of comorbid conditions are related to treatment resistance. These participants are not usually included in efficacy trials but may represent a substantial proportion of those seen in clinical practice. The results of efficacy trials are likely to be more generalizable when criteria for inclusion can be safely expanded.

MBC may help to improve outcomes

Clinicians in practice settings typically use patient and clinician subjective judgment regarding treatment efficacy and tolerability rather than a measurement-based approach. Use of this approach could be related to the high rates of treatment inadequacy found in clinical practice settings [2].

Using objective measurements of symptoms and side effects may be helpful when making adequate dosing and time frame determinations to maximize symptom reduction and minimize side effects. MBC may identify symptom severity changes that would be less apparent in discussion with a patient. In this study, MBC may have impacted the similarity in outcomes between participants in primary and psychiatric care.

MBC, including the use of participant self-report ratings of symptoms and side effects, was easy to use and acceptable in clinical practice settings. Self-ratings also may assist participants in learning to monitor and manage their own disease.

Remission can take time

A large percentage of participants at each treatment step did not reach remission by week 6 or 8. Some remitted in week 14 or later. In the context of acceptable side effects, clinicians may want to consider at least 8 weeks of treatment before making a treatment change due to lack of efficacy. Study periods of greater than 8 weeks also are needed for clinical trials that have remission as the endpoint.

Many steps may be needed to reach remission

Two thirds of participants did not remit with initial citalopram treatment based on the QIDS-SR_{16}. Additional treatments resulted in decreasing remission probabilities. The current study was the first to make this determination based on remission rates.

However, the cumulative remission rate after two steps was approximately 50%. With all steps included, almost 70% of participants who remained in the study experienced remission. Patients and clinicians are encouraged to not give up. Sharing specific expectations at the beginning of treatment regarding the probability of remission with each subsequent step may help retain patients in treatment without the discouragement that can come from unrealistic expectations.

Remission is less likely for participants with a longer time since first-episode onset, a longer length of current MDE, or more medical and psychiatric comorbidities. These participants require particular focus in treatment.

The modest remission rates that result from multiple treatments, especially the third or fourth medication trials, along with premature treatment discontinuation by a large percentage of participants, suggest the need for more effective treatments.

Treatment choices for increasingly treatment-resistant participants

Remarkably, there were no statistical or meaningful clinical differences in remission rates, response rates, or times to remission or response among any of the medications compared in this study. All medications were safe and well-tolerated. Bupropion-SR had some advantages over buspirone as a second-step medication augment agent, including greater improvement in symptoms and fewer dropouts due to intolerance. There were also advantages for T_3 over lithium as a third medication treatment due to fewer side effects, and advantages for venlafaxine-XR plus mirtazapine over tranylcypromine as a fourth medication treatment due to fewer side effects and lack of need for dietary restrictions.

These results did not support the following commonly held notions: 1) the advantage of a dual-action switch agent as a second-step treatment, 2) lack of efficacy when switching to a second SSRI after an initial trial with an SSRI resulting in intolerance or lack of efficacy, and 3) the greater efficacy of a second-step switch to an antidepressant with a different mechanism of action compared with a switch to an agent with the same mechanism. However, based on the very modest outcomes in Level 3 switch treatments, three consecutive monotherapies do not produce efficacious results.

Similarly, we found no differences in outcome when cognitive therapy as a second-step switch or augment was compared with medication switch or augment, respectively, although remission occurred more slowly with cognitive therapy augment to citalopram than with medication augment to citalopram. Surprisingly, medication augment was almost as well tolerated as cognitive therapy augment. When speed of remission is important, medication augment has an advantage.

When selecting medication options, clinicians must consider efficacy, side effect burden and tolerability, convenience of dosing, drug interactions, and participant fidelity. Clinicians must weigh the possibility of remission with continuation of a current treatment against the probable efficacy and side effect burden of the other options. Adequate dosing for an adequate duration of time is important for a well-tolerated treatment. However, dosages needed to reach remission may be higher than those often administered in clinical practice.

In clinical practices, patients and their physicians select acceptable treatment approaches. In this study, it was striking that only 1% of participants found it acceptable to be randomized to all seven treatment options at Level 2. However, it is not surprising that those with greater side effect burden or less symptomatic improvement with citalopram preferred a switch rather than an augmentation approach. The extent of patient preferences found in the study raises questions about the generalizability of findings from randomized clinical trials without an acceptability component.

Remission results in better long-term outcomes

Remission is not a safe haven given the high relapse rates for participants in remission who entered follow-up and the decreased time to relapse found in those who required more treatment steps. However, response without remission is even more precarious given the higher probability of a relapse, especially as additional steps are needed. This argues for all reasonable efforts to be made to assist participants in reaching remission and for the continuation of careful clinical monitoring beyond the time of remission or response.

Participant attrition is high

Participant attrition from antidepressant treatment is a substantial public health concern, although it has been addressed in only a limited fashion. In the current study, about one fourth of participants left initial treatment with citalopram. Participants with sociodemographic disadvantages and more psychiatric comorbidities and minorities were more likely to drop out, whereas those who had prior experience with depressive episodes were more likely to remain. In both clinical trials and practice, it may be advantageous to direct outreach efforts toward participants from populations at high risk for attrition and those with illness-related features associated with attrition. Eliciting and addressing individual barriers to remaining in treatment may be helpful, as may educational intervention regarding depression, its chronic or recurrent

course, expectations about improvement in treatment, the importance of objective assessment of improvement, and the consequences of dropping out of treatment.

Conclusions

STAR*D has begun to answer specific questions about depression and its treatment in representative practice settings, but many questions remain. Remission rates at the end of two treatment steps were approximately 50% and thus are encouraging when compared with other chronic medical illnesses. Also, the modest and decreasing remission rates found with the third and fourth steps lead to speculation that combination treatments may be valuable earlier in treatment. Concerns about cost, adverse effects, drug-drug interactions, and long-term effects of such combinations suggest the need to prospectively evaluate the usefulness of such a strategy.

Although pharmacologic differences did not translate into large clinical differences, the question remains how to match a treatment or treatment sequence to an individual patient using clinical characteristics (eg, anxious depression) or biomarkers. Upcoming STAR*D analyses are planned to address these issues.

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Dr. Warden currently owns stock in Pfizer, Inc. and previously owned stock in Bristol-Myers Squibb.

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Dr. Wisniewski has served as a consultant for Cyberonics, Inc., ImaRx Therapeutics, Inc., Bristol-Myers Squibb, Organon, Inc., and Case Western University.

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