Sequenced Treatment Alternatives to Relieve Depression (STAR*D): Lessons Learned

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Sequenced Treatment Alternatives to Relieve Depression (STAR*D), the largest prospective, randomized antidepressant treatment trial to date in outpatients with major depressive disorder (MDD) recruited from real-world clinical settings, enrolling 4011 outpatients aged 18 to 75 years with nonpsychotic MDD. Designed to determine which treatments are most effective after nonremission or intolerance to an initial selective serotonin reuptake inhibitor (SSRI), or to any of a series of subsequent randomized treatments, STAR*D was conducted in 18 primary and 23 psychiatric care settings across the United States. This review summarizes unique features of the study, initial remission rates and associated participant characteristics, remission rates for subsequent treatment steps, relapse rates during follow-up, and clinical implications.

Unique Features of the Design and Sample

STAR*D has several features that make it unique. (1) The study enrolled treatment-seeking patients (as opposed to symptomatic volunteers) with nonpsychotic MDD confirmed with a DSM-IV checklist and a score of ≥ 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D). (2) To maximize generalizability, few exclusions were utilized. Thus, 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. (3) As in clinical practice, patients could accept or decline certain strategies as long as sufficient options for randomization remained. (4) Patients, clinicians, and raters always knew the medication and dose administered.

Overall Design

All patients started with citalopram (level 1). Those whose depression did not remit or who were intolerant to citalopram could enter level 2 and elect to switch to bupropion sustained release (SR), sertraline, venlafaxine extended release (XR), or cognitive therapy (CT) or augment citalopram with CT, bupropion SR, or buspirone. For those with inadequate benefit from switching to or augmenting with CT, the next step (level 2A) was a switch to bupropion SR or venlafaxine XR. Those without adequate benefits from medications at level 2 or 2A could proceed to level 3, which included switches to either mirtazapine or nortriptyline or augmentation of the level 2 or 2A drug with lithium or triiodothyronine (T_3). Level 4 treatments were switches to tranylcypromine or to venlafaxine XR plus mirtazapine.

Patients who did not remit were encouraged to move to the next level. Patients who remitted or responded at any level could enter a 1-year naturalistic follow-up with medications provided.

Sample Characteristics

Medical conditions and psychiatric disorders (including anxiety disorders and substance abuse) were common. Patients in primary care and psychiatric settings did not differ clinically except for slightly higher rates of medical conditions in primary care settings and of prior suicide attempts in psychiatric settings.

Remission Rates With Citalopram and Related Participant Characteristics

For this report, remission is defined by a score of ≤ 5 on the 16-item Quick Inventory of Depressive Symptomatology—Self-Report, which is equivalent to a HAM-D score of ≤ 7. Of 3671 participants with at least 1 postbaseline visit, the remission rate with citalopram was 36.8% (Table 1).[1] Mean time to remission was 6.3 weeks, with over one third of patients remitting after 9 weeks. Sixteen percent of patients left the study due to "intolerance" of medications.[1]

Significantly higher remission rates were associated with being white, female, married, and more educated; having higher income; having private insurance; and being employed.[2] Those disadvantaged by more severe depressive episodes, increased numbers of concurrent general medical and psychiatric disorders (especially anxiety and drug abuse disorders), and poorer functioning and quality of life had significantly lower remission rates. Age, age at onset of first major depressive episode, current drinking, and whether care was delivered in a primary care or psychiatry specialty setting were not related to likelihood of remission.[2] Although a remission rate of 36.8% may seem modest, it is similar to remission rates reported in efficacy trials with "symptomatic volunteers" and compares favorably to rates found in effectiveness trials with "real-world" depressed patients.

Remission Rates for Subsequent Treatment Steps

Overall, second-step medication switches were equally effective, with remission rates of 25% to 27%.[3] Intolerance rates (21%–27%) were also not significantly different.[3] Few patients accepted randomization strategies involving psychotherapy, but there were no significant differences between switching to another medication or switching to CT.[4]

Second-step augmentation with medication or CT appeared beneficial and had similar remission rates.[4] Patients augmented with bupropion SR compared to buspirone showed greater symptom improvement, had lower exit symptom severity, and had fewer dropouts due to intolerance.[5]

Patients who had suboptimal outcomes to CT monotherapy or CT plus citalopram were encouraged to enroll in level 2A to be randomly assigned to bupropion SR or venlafaxine XR. The numbers were small (overall N = 31) and the results discouraging (remission rate of 7% and intolerance rate of 23%).[1]

After failure of 2 adequate trials, patients in level 3 experienced lower remission rates (overall, 14%) and higher intolerance rates (overall, 26%) than in prior levels.[1] Switching to an antidepressant with a novel mechanism of action, mirtazapine, or to nortriptyline resulted in similar, modest remission rates (8% and 13%, respectively) and high intolerance rates (32% and 33%, respectively).[6] Alternatively, augmenting with T_3 appeared more promising, with remission rates of 26% and intolerance rates of only 10%.[1] Although lithium remission rates were not statistically different than T_3 remission rates, patients taking lithium had more frequent side effects and were more likely to discontinue due to side effects, despite relatively low dosing of lithium.[7] Investigators noted that patients and many treating physicians were reluctant to consider randomization involving lithium, and physicians were reluctant to follow dosing guidelines.[7]

At level 4, overall remission rates were again low (13%) and not significantly different between tranylcypromine monotherapy and venlafaxine XR plus mirtazapine.[8] However, patients taking tranylcypromine were more likely to discontinue due to side effects: 40% vs. 20%.[8]

Overall, remission rates were highest for the initial treatment levels, and intolerance was highest in the later levels of treatment.[9] A cumulative remission rate of over 50% after 2 treatment steps and almost 70% after 4 steps argues for persistence in

Table 1. Results at Each Level of Treatment in STAR*D[a]

Level	Remission Rate (%)	Intolerance Rate (%)[b]	Relapse During 1-Year Follow-Up (%)
1			
Citalopram monotherapy	36.8	16	40
2			
Any level 2 treatment	30.6	19	55
Any switch	27	23	
Bupropion SR	26	27	
Sertraline	27	21	
Venlafaxine XR	25	21	
CT	31	17	
Any combination/augmentation	35	16	
Bupropion SR + citalopram	39	13	
Buspirone + citalopram	33	21	
CT + citalopram	31	9.2	
3			
Any level 3 treatment	13.7	26	65
Any switch	11	32	
Mirtazapine	8	32	
Nortriptyline	13	33	
Any combination/augmentation	21	15	
Lithium + prior ADT	15	21	
Triiodothyronine + prior ADT	26	10	
4			
Any level 4 treatment (switch)	13.0	34	71
Tranylcypromine	15	40	
Mirtazapine + venlafaxine XR	16	20	

[a]Data from Rush et al.[1]
[b]Patient left the relevant acute treatment step prior to 4 weeks of treatment for any reason, or left the step after 4 weeks and the treatment step exit form indicated intolerance.
Abbreviations: ADT = antidepressant treatment, CT = cognitive therapy, SR = sustained release, STAR*D = Sequenced Treatment Alternatives to Relieve Depression, XR = extended release.

the management of treatment-resistant depression.[9]

Relapse Rates for Patients Who Respond or Remit After 1 to 4 Treatment Steps

Relapse rates during the 1-year naturalistic follow-up period increased from 40% after level 1 to 71% after level 4, and with successive steps, time to relapse was shorter.[1] At each step, relapse rates were significantly higher for patients who did not reach full remission.[1]

Clinical Implications

Treatment-seeking patients with MDD often have chronic and/or recurring conditions with multiple medical and psychiatric comorbidities that interfere with remission. For patients who do not achieve full remission, relapse rates are particularly high.

It takes time to recover from MDD—50% of remitters did not remit until after week 6.[2] Clinicians may want to consider at least 8 weeks of treatment before making a treatment change due to lack of efficacy. For clinical trials that have remission as the endpoint, study periods of greater than 8 weeks are required.

Physicians can expect about 1 in 3 patients with MDD to remit with SSRI monotherapy and about that many to remit to second-step combination with bupropion SR. This raises the possibility that for MDD patients who are severely and recurrently ill and highly comorbid, it may be more effective to start with combination therapies at the initiation of treatment.

As more treatment steps are required, remission rates decline, intolerance rates climb, and relapse occurs sooner and more frequently. These results also fuel the argument for treating patients at risk for suboptimal outcome more vigorously than is presently the standard.

Patients have preferences. Only 21 of 1439 patients (1.5%) agreed to random assignment to all of the treatment choices at level 2.[3] We were surprised at how many participants refused to consider CT despite providing it at no cost, with well-trained therapists, and trying to make it convenient. The sample may have been biased by the requirement for an initial medication trial.

These results highlight the need for not only more effective acute treatments to achieve remission, but also more effective treatments to sustain remission over the long term.

Generally, pharmacologic differences did not translate into meaningful clinical differences. The question of how to match a treatment and an individual patient using clinical characteristics or biomarkers remains. These questions will be addressed in subsequent STAR*D analyses.

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