What to Expect When Switching to a Second Antidepressant Medication Following an Ineffective Initial SSRI:

A Report From the Randomized Clinical STAR*D Study

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ABSTRACT

Objective: An antidepressant medication switch often follows a failed initial trial with selective serotonin reuptake inhibitors (SSRIs). When, for whom, and how often second-step response and remission occur are unclear, as is preferred second-step trial duration. As more treatments are approved for use following 2 failed "adequate" trials, researchers and clinicians require an evidence-based definition of "adequate."

Methods: Following citalopram in the randomized Sequenced Treatment Alternatives to Relieve Depression (STAR*D) clinical trial (which ran July 2001–September 2006), participants with score ≥ 11 on the 16-item Quick Inventory of Depressive Symptomatology–Self-Rated (QIDS-SR_{16}) were randomized to bupropion sustained release, sertraline, or venlafaxine extended release (up to 14 weeks). The QIDS-SR_{16} defined response, remission, and no clinically meaningful benefit based on the modified intent-to-treat sample.

Results: About 80% of 438 participants completed ≥ 6 weeks of treatment with the switch medication. All treatments had comparable outcomes. Overall, 21% (91/438) remitted, 9% (40/438) responded without remission, and 58% (255/438) had no meaningful benefit. Half of the responses and two-thirds of remissions occurred after 6 weeks of treatment. Overall, 33% of responses (43/131) occurred after ≥ 9 weeks of treatment. No baseline features differentiated early from later responders or remitters. No early triage point was found, but those with at least 20% reduction from baseline in QIDS-SR_{16} score around week 2 were 6 times more likely to respond or remit than those without this reduction.

Conclusions: Following nonefficacy with an initial SSRI, only about 20% remit and more than half achieve no meaningful benefit with a second-step switch to another monoaminergic antidepressant. A 12-week trial duration seems necessary to capture as many second-step switch responders as possible.

Trial Registration: ClinicalTrials.gov identifier: NCT00021528

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Only about 50% of depressed patients respond to an initial selective serotonin reuptake inhibitor (SSRI), and only 35%–40% reach remission.[1–3] Patients with minimal symptomatic benefit or substantial side effects with their first treatment generally prefer switching to a different treatment rather than augmenting their initial treatment with a second agent.[4] The duration of a treatment trial needed before declaring treatment failure remains unclear.

Necessary decisions when switching treatments involve both strategic (which treatment is the next best) and tactical (how to best deliver the chosen treatment) issues. Tactical issues address questions such as "When does response/remission occur in those who will respond or remit?" or "Can we identify early the patients for whom a second-step switch treatment will fail?" The answers help inform clinical decision-making.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial provided a large group of representative depressed outpatients without adequate benefit and/or intolerant to the initial SSRI treatment (citalopram) such that they would accept a medication switch. Comparisons between second-step medication switch outcomes have been reported,[2,5] but several clinically important questions that affect care delivery have not been fully addressed using a large data set of representative depressed patients whose initial SSRI has failed.

This unplanned secondary data analysis was based on a sample of opportunity from the STAR*D trial[2,3,6] that included participants who accepted second-step randomization to bupropion sustained release (bupropion SR), sertraline, or venlafaxine extended release (venlafaxine XR). This report includes participants who demonstrated significant depressive symptom levels—defined as a 16-item Quick Inventory of Depressive Symptomatology–Self-Rated (QIDS-SR_{16}) score ≥ 11 when entering second-step treatment—to ensure that substantial depressive symptom severity most likely justified the medication switch.

This report addresses several questions for depressed outpatients with persistent and substantial

Clinical Points

- For depressed outpatients with an insufficient symptomatic response to an initial selective serotonin reuptake inhibitor (SSRI) who are switched to a second antidepressant medication, the probability and timing of both response and remission and the optimal duration of this second antidepressant medication treatment step are unknown.
- Of patients switched from an initial SSRI to another SSRI, a serotonin-norepinephrine reuptake inhibitor, or bupropion in the second treatment step, 20% achieved remission and another 10% achieved response without remission, whereas over half had no meaningful clinical benefit despite use of measurement-based care in this second step.
- In this second treatment step, a 12-week trial is recommended because one-third of those who ultimately responded did so after 9 weeks. Those with at least a 20% symptom reduction by week 2 were 6 times more likely to respond than those not achieving this threshold.

depressive symptoms following an initial well-delivered SSRI:

1. Were there meaningful differences in symptoms, function, or retention between the 3 medication switch strategies?
2. When do symptomatic response and remission with second-step treatment occur?
3. What baseline features (if any) distinguish those with early compared to later responses and distinguish those with early compared to later remissions?
4. What baseline features (if any) distinguish those who have no clinically meaningful benefit from those with at least some benefit?
5. What is the preferred duration for this second-step medication switch trial?
6. Does at least a 20% reduction in depressive symptom severity within the first 2–3 weeks of treatment distinguish responders from nonresponders and remitters from nonremitters?

METHODS

Overview of STAR*D Design

STAR*D used an equipoise stratified, randomized design[7] in which participants were strongly encouraged to accept all 7 potential second-step treatments: 4 switch options and 3 augmentation treatments (www.ClinicalTrials.gov identifier: NCT00021528). However, to mimic practice, participants could opt to exclude certain second-step treatment options (eg, exclude all switch options). Only treatments for which participants accepted randomization were compared.

The protocol was approved and monitored by the institutional review boards at the national coordinating center, data coordinating center, regional centers and relevant clinical sites, and the National Institute of Mental Health data safety and monitoring board. Participants provided written informed consent initially at STAR*D enrollment and again when they enrolled into all step 2 and subsequent step treatments.

Participants

Adult outpatients with a primary clinical diagnosis of nonpsychotic major depressive disorder, confirmed by a checklist completed by clinical research coordinators, were enrolled at primary and psychiatric public and private practice settings (July 2001–September 2006). Broad inclusion and minimal exclusion criteria were used to maximize the generalizability of the findings.[6,8,9] All participants received citalopram initially.[1] In STAR*D, all participants eligible for second-step treatments either had not remitted or could not tolerate citalopram. For this report, the analytic sample included all who received a medication switch, entered the second step with a QIDS-SR_{16} score of ≥11 regardless of side effects, and had at least one visit following the baseline step 2 visit.

Protocol Treatment

To mimic clinical practice, enhance safety, ensure a vigorous dosing regimen, and maximize generalizability, participants and treating clinicians were aware of treatment assignments and doses. A clinical treatment manual specified the measurement-based care procedures,[6,10] including starting doses and the critical decision points when dose changes should be made as informed by a measure of depressive symptom severity (QIDS-SR_{16}[11–13]; www.ids-qids.org) and of side effects (Frequency, Intensity, and Burden of Side Effects Rating or [FIBSER][14]) obtained at each treatment visit.

These measurement-based care procedures[1,15,16] were based on analogous efforts undertaken in the Texas Medication Algorithm Project[17] to ensure an optimal but tolerable and personally tailored medication dosing was implemented before declaring the treatment ineffective. These procedures enhance dosing and improve outcomes compared to treatment as usual.[18–20] To further ensure that medications were well delivered, the study used didactic instruction, support by the clinical research coordinators, and a centralized monitoring system with feedback.

At initiation of the switch medications, citalopram was discontinued without a tapering or washout period. The 3 second-step switch medications were randomized in a 1:1:1 ratio. The second step could last up to 14 weeks if needed to establish whether remission would occur. The recommended daily dose for bupropion SR was 150 mg/d from day 0–7, 200 mg/d from day 8–27, 300 mg/d from day 28–41, and 400 mg/d from day 42 onward; for sertraline, 50 mg/d from day 0–13, 100 mg/d from day 14–27, 150 mg/d from day 28–62, and 200 mg/d from day 63 onward; and for venlafaxine, 37.5 mg/d from day 0–7, 75 mg/d from day 8–14, 150 mg/d from day 15–27, 225 mg/d from day 28–41, 300 mg/d from day 42–62, and

375 mg/d from day 63 onward.[21] Dosing recommendations were flexible but informed by measurement-based care procedures with critical decision points at weeks 4, 6, 9, and 12 at which clinicians were recommended to optimize the dose based on improvement in symptoms and tolerability (see Supplementary Table 1 for details). The aim—symptom remission—was defined as a total QIDS-SR_{16} score of ≤ 5 at the last step 1 visit. (See Supplementary Appendix 1 for dosage and concomitant treatment details)

Clinical Measurements

The primary outcome for STAR*D was symptom remission, defined as a score ≤ 7 on the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$),[22] obtained by telephone-based, structured interviews (in English or Spanish) conducted by independent research-outcome assessors unaware of treatment-group assignment. Secondary outcomes in STAR*D included the QIDS-SR_{16} and the FIBSER.

For this report, the primary outcome was the QIDS-SR_{16} score obtained at every treatment visit. Remission was defined as a total score ≤ 5 at study exit. Response was defined as a ≥ 50% reduction (step 2 baseline to step 2 exit). No clinically meaningful benefit was defined as a < 35% reduction from step 2 baseline to step 2 exit, based on a recent report[23] that clinically meaningful improvement in quality of life occurred in patients with treatment-resistant depression when a 33% reduction in Montgomery-Asberg Depression Rating Scale score was achieved.

Information collected at STAR*D entry was used to describe comorbid psychiatric conditions for this report's analytic sample based on the Psychiatric Diagnostic Screening Questionnaire.[24,25] Function was defined using the 12-item Short Form Health Survey (SF-12),[26] from which 2 summary scores are reported: a mental component score (MCS-12) and a physical component score (PCS-12). We also administered the Work Productivity and Activity Impairment (WPAI) instrument[27] and the Work and Social Adjustment Scale (WSAS).[28] (See Supplementary Appendix 1 for details on SF-12 component scores and on the WPAI and WSAS.)

Statistical Analysis

All analyses were conducted using R statistical software.[29,30] Summary statistics are presented as mean (SD) for continuous variables and percentages for discrete variables. Parametric and nonparametric analysis-of-variance methods and χ^2 tests were used to compare the baseline clinical and demographic characteristics, treatment features, and rates of side effects and serious adverse events among treatment groups. To differentiate early from later responders or remitters, an a priori list of variables was identified and included in simple linear or general linear models to detect whether the means (proportions) differed among these variables. A linear contrast was used to test for a difference between the specific groups of interest. Reported *P* values were then adjusted to control the false discovery rate using the method proposed by Benjamini and Hochberg.[31] Specifically, raw *P* values were input to the *p.adjust* function in R, using the "fdr" adjustment method. Odds ratios were calculated to compare the remission and response rates of those achieving at least a 20% reduction in symptoms during the first 2 weeks of the study against those who did not, and the Fisher exact test was used to test for statistical significance. While the recommended visit weeks were 2, 4, 6, 9, 12, and 14, some participants had more than one visit during the visit window (eg, after their week 2 visit, they came a second time before the week 4 visit). In this scenario, the latest possible visit was used.

RESULTS

The analytic sample (n = 438) included participants randomized to second-step switch treatment with bupropion SR (n = 141), sertraline (n = 155), or venlafaxine XR (n = 142). Table 1 shows that without adjusting for multiple comparisons, no baseline clinical demographic variables differentiated the 3 treatment groups at the .05 significance level. Table 1 also shows the numbers of participants who exited the study at various time intervals from baseline in each treatment cell. The cells did not differ in attrition rates. About 80% of participants in each cell remained in treatment at week 6.

The measurement-based care process used in step 1 was designed to push the dose to tolerance. Of the patients with complete FIBSER data, 162 (45.4%) of 357 scored an average of at least 3 on the FIBSER, indicating at least a moderate degree of side effect burden with citalopram.

Measurement-based care was also used in the step 2 switch. Supplementary Table 2 shows the mean (SD) switch medication doses at various time points in step 2. At week 6, for example, the mean dose of bupropion SR was 287.6 (76.1) mg; for sertraline, it was 123.3 (43.6) mg, and for venlafaxine XR, it was 166.4 (72.3) mg. By and large, these doses are larger than what was typically achieved in clinical practice while the study was being conducted.

Were There Meaningful Differences in Symptoms, Function, or Retention Between the 3 Medication Switch Strategies?

There were no statistical differences in depression remission (20.6%, 19.7%, 22.0%; $\chi^2 = 0.22$, $P = .89$), response (27.1%, 33.8%, 29.1%; $\chi^2 = 1.66$, $P = .44$), or no benefit (60.0%, 52.1%, 62.4%; $\chi^2 = 3.40$, $P = .18$) rates between the sertraline, venlafaxine XR, and bupropion SR groups, respectively. The mean (SD) QIDS-SR_{16} scores at exit by treatment group were sertraline, 10.9 (5.8); venlafaxine XR, 11.2 (6.3); and bupropion SR, 11.3 (5.8) ($F = 0.16$, $P = .85$). There was no significant difference among groups in number of weeks in treatment, with means (SDs) of 9.3 (4.2), 10.0 (4.0), and 9.2 (4.3) weeks for sertraline, venlafaxine XR, and bupropion SR, respectively ($F = 1.47$, $P = .23$). There were no significant differences in side effect frequency, intensity, or duration based on FIBSER scores, nor in functional

Table 1. Participant Baseline Demographic and Clinical Information and Number of Participants Exiting Treatment at Each Time Point in Step 2 by Treatment Group[a]

Variable	Sertraline (n = 155)	Venlafaxine XR (n = 142)	Bupropion SR (n = 141)	Test Statistic	*P* Value
Baseline Information					
Female, %	58.7	61.3	51.8	$\chi^2 = 2.80$	.25
Black, %	16.8	21.1	24.8	$\chi^2 = 2.92$	.23
White, %	82.6	76.1	73.0	$\chi^2 = 4.05$	.13
Employed, %	51.9	49.6	52.9	$\chi^2 = 0.31$	.85
	Mean (SD)	Mean (SD)	Mean (SD)		
Age	44.1 (13.0)	40.7 (11.9)	42.6 (12.6)	F = 2.80	.06
Age at onset, y	24.9 (13.9)	23.4 (12.1)	25.7 (14.8)	*F* = 1.04	.36
Years of education	12.8 (2.9)	13.4 (2.7)	13.5 (2.8)	*F* = 2.34	.09
No. of MDEs[a]	3.0 (4.0)	3.0 (4.0)	3.0 (5.5)	$\chi^2 = 1.07$	.59
Duration of current episode, d[a]	303.0 (668.0)	279.5 (606.8)	257.0 (810.0)	$\chi^2 = 0.62$	.73
Level 1 baseline QIDS-SR_{16} score	16.8 (3.9)	16.7 (3.8)	17.2 (3.7)	*F* = 0.58	.56
Level 2 entry QIDS-SR_{16} score	15.2 (3.5)	15.6 (3.8)	15.7 (3.6)	*F* = 0.746	.48
Time Period of Treatment Exit, n					
0 to < 2 wk	2	0	0		
2 to < 4 wk	12	10	20		
4 to < 6 wk	14	14	9		
6 to < 9 wk	31	13	20		
9 to < 12 wk	21	29	24		
≥ 12 wk	75	76	68		

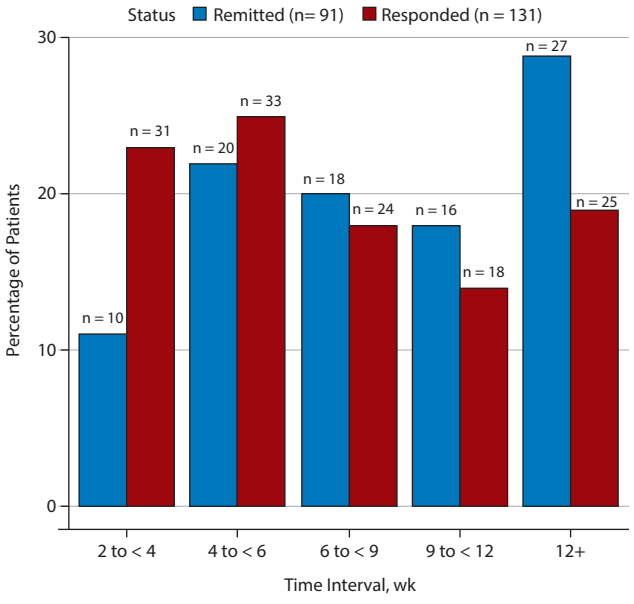
[a]Median and IQR reported due to skewed distributions.
Abbreviations: IQR = interquartile range, MDE = major depressive episode, QIDS-SR_{16} = 16-item Quick Inventory of Depressive Symptomatology–Self-Rated, SR = sustained release, XR = extended release.

outcomes based on the WSAS, MSC-12, PCS-12, and WPAI scores (data available upon request). Comparable outcomes across medications enabled us to combine the 3 groups for all subsequent analyses.

When Do Symptomatic Response and Remission Occur?

Figure 1 shows when the first remissions and responses occurred for those who ultimately did achieve either response or remission in second-step treatment. Overall, 20.8% (91/438) of participants remitted and 29.9% (131/438) achieved at least a response (which includes those who remitted). About half of those who eventually achieved a response (64/131) did so in the intervals from 2 to < 4 weeks (31/64) or 4 to < 6 weeks (33/64) following initiation of the medication switch. Notably, 33% of ultimate responders did so only at or after 9 weeks of treatment, despite the use of measurement-based care to drive medication doses. For those who ultimately achieved a remission, only about one-third (30/91) did so within the first 6 weeks (10 in the interval from 2 to < 4 weeks and 20 in the interval from 4 to < 6 weeks).

Figure 1. Time to First Response or First Remission for Those Patients Who Ultimately Responded or Remitted[a]



[a]The numbers above each bar indicate the number of participants achieving response or remission at that time point.

What Baseline Features (if any) Distinguish Those With Early Compared to Later Responses and Distinguish Those With Early Compared to Later Remissions?

We defined early remissions and responses as occurring no later than 4 weeks following initiation of the medication switch, with later remissions and responses being ascribed when either occurred for the first time after 4 weeks. This calculation does not require sustained remission or response at the end of step 2. Nearly 23% (27/118) of remitters did not sustain that remission through the end of step 2. For responders, the percentage was 25.6% (45/176).

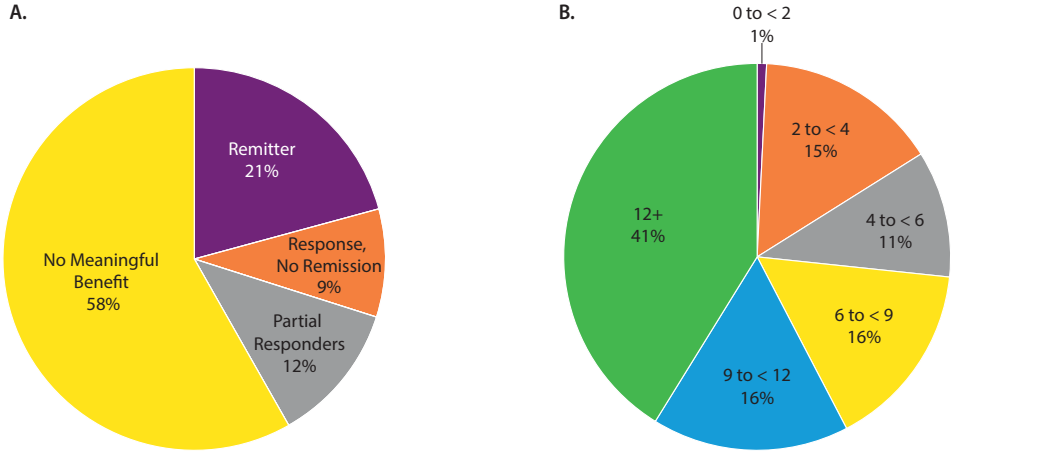
Early responders reported greater side effect burden at the start of step 2 and were more likely to report a positive family history of depression (62.6%) than later responders (50.2%). Early remitters were more likely to have a positive family history of depression than later remitters (66.7% vs

Table 2. Baseline Features That Differentiate Early From Later Responders and Early From Later Remitters[a]

	Response					Remission				
Variable	Early (n = 91)	Late (n = 85)	Never (n = 262)	Raw *P* Value	Adjusted *P* Value	Early (n = 48)	Late (n = 70)	Never (n = 320)	Raw *P* Value	Adjusted *P* Value
Positive family history of mood disorder[b]	62.60	50.20	50.00	.037743	.321	66.70	47.10	53.80	.037743	.592
Anxiety disorder (PDSQ)	19.10	18.80	29.00	.139237	.631	21.70	11.40	28.30	.536911	.83
White	81.30	85.90	73.30	.492382	.785	87.50	82.90	74.70	.492382	.83
Alcohol use disorder (PDSQ)	13.50	15.30	11.90	.500781	.785	17.40	12.90	12.20	.500781	.83
African American	15.40	12.90	25.20	.536911	.785	10.40	14.30	23.80	.139237	.592
Substance use disorder (PDSQ)	7.90	7.10	5.40	.680052	.889	10.90	8.60	5.00	.680052	.863
Hispanic	5.50	17.60	9.90%	.863116	.913	10.40	11.40	10.30	.863116	.863
	Mean (SD)	Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)	Mean (SD)		
Baseline side effect burden in step 2 (FIBSER score)	2.0 (2.2)	1.2 (1.8)	1.6 (2.1)	.030285	.321	1.6 (2.0)	1.7 (2.0)	1.6 (2.1)	.81029	.863
No. of MDEs	5.2 (9.2)	7.9 (16.1)	7.5 (11.8)	.174952	.631	3.6 (5.6)	7.9 (15.5)	7.4 (12.2)	.097593	.592
Length of current MDE, y	2.8 (5.6)	1.7 (2.9)	2.8 (6.0)	.18558	.631	3.1 (6.8)	1.8 (3.0)	2.7 (5.7)	.215642	.672
No. of psychiatric comorbidities (per the PDSQ)	1.2 (1.5)	1.6 (1.7)	2.0 (2.1)	.230294	.653	1.2 (1.5)	1.2 (1.5)	1.9 (2.1)	.834357	.863
Baseline SF-12 physical component score in step 2	48.1 (11.2)	46.0 (12.8)	43.2 (12.8)	.286744	.696	49.1 (10.5)	47.4 (12.5)	43.5 (12.7)	.457305	.83
SF-12 mental component score	27.7 (7.4)	26.8 (8.4)	26.3 (8.2)	.478314	.785	27.7 (7.1)	28.0 (7.9)	26.3 (8.2)	.816686	.863
Age at onset of first MDE, y	24.8 (13.9)	23.5 (12.6)	24.9 (13.9)	.554175	.785	26.6 (14.6)	23.5 (11.1)	24.2 (14.0)	.23729	.672
Baseline QIDS-SR_{16} score in step 2	15.1 (3.0)	14.9 (3.7)	15.8 (3.7)	.785791	.913	13.8 (2.5)	14.3 (3.2)	16.0 (3.7)	.49014	.83
Years of schooling	13.6 (2.7)	13.5 (3.8)	13.0 (2.5)	.812375	.913	13.4 (2.3)	14.2 (3.6)	13.0 (2.6)	.115388	.592
Age, y	41.6 (12.6)	41.8 (12.9)	43.1 (12.5)	.912744	.913	40.9 (12.5)	41.7 (12.3)	43.0 (12.7)	.747987	.863

[a]"Early" defined as ≤ 4 weeks in step 2, and "late" defined as > 4 weeks into step 2. Values are shown as percentages unless otherwise noted. Sample sizes varied depending on the measure.
[b]Family history was defined as positive if either bipolar disorder or major depressive disorder was noted in first-degree relatives by patient report.
Abbreviations: FIBSER = Frequency, Intensity, and Burden of Side Effects Rating; MDE = Major depressive episode; PDSQ = Psychiatric Diagnostic Screening Questionnaire; QIDS-SR_{16} = 16-item Quick Inventory of Depressive Symptomatology–Self-Rated; SF-12 = 12-item Short-Form Health Survey.

Figure 2. (A) Depressive Symptom Outcome Categories for the Analytic Sample (n = 438) at Exit From the Second Treatment Step and (B) Treatment Duration (in Weeks) for Those With No Clinically Meaningful Benefit (n = 254)



47.1%, respectively) (Table 2). However, after controlling for the false discovery rate (using the "fdr" adjustment method in the *p.adjust* function in R), these parameters did not differentiate early from late responders or remitters.

What Baseline Features (if any) Distinguish Those Who Have No Clinically Meaningful Benefit From Those With at Least Some Benefit?

Over half of the participants had no clinically meaningful benefit at exit from this second treatment step (Figure 2A). This finding is most likely not due to early attrition because for those with no clinically meaningful benefit at study exit (n = 254), the vast majority (about three-fourths) received at least 6 weeks of treatment (Figure 2B). Participants with more impaired physical function—very likely reflecting concurrent general medical conditions—and those with more concurrent psychiatric conditions were less likely to obtain a meaningful benefit from this medication switch (Table 3).

What Is the Preferred Duration for This Second-Step Medication Switch Trial?

Given the modest overall response rate (which includes both remitters and responder-nonremitters) of 29.9%

Table 3. Baseline Features That Differentiate Participants With No Clinically Meaningful Benefit From Those With at Least Some Benefit[a,b]

Variable	No Meaningful Benefit (n = 255)	At Least Some Benefit (n = 183)	Raw *P* Value	Adjusted *P* Value
Anxiety disorder (PDSQ)	27.90	20.90	.1	.22
African American	23.50	16.90	.09	.22
White	75.30	80.30	.21	.33
Substance use disorder (PDSQ)	5.20	7.70	.28	.40
Alcohol use disorder (PDSQ)	11.90	14.30	.46	.57
Positive family history of mood disorder[c]	54.50	53.60	.84	.95
Hispanic	10.60	10.40	.94	.95
	Mean (SD)	Mean (SD)		
Baseline SF-12 physical component score in step 2	43.0 (12.6)	47.1 (12.3)	.001	**.01**
No. of psychiatric comorbidities (per the PDSQ)	2.0 (2.2)	1.4 (1.6)	.003	**.027**
Age, y	43.7 (12.7)	41.0 (12.3)	.03	.15
Length of current MDE, y	2.9 (6.4)	2.1 (3.8)	.1	.22
Baseline QIDS-SR_{16} score in step 2	15.8 (3.7)	15.1 (3.5)	.06	.22
Years of schooling	13.0 (2.6)	13.5 (3.1)	.09	.22
SF-12 mental component score	26.2 (8.1)	27.4 (8.1)	.14	.27
Age at onset of first MDE, y	25.4 (14.3)	23.6 (12.6)	.16	.27
Baseline side effect burden in step 2 (FIBSER score)	1.7 (2.1)	1.5 (2.0)	.47	.57
No. of MDEs	7.1 (11.3)	7.2 (13.7)	.94	.95

[a]Those with no clinically meaningful benefit exited this treatment step with less than 35% reduction in baseline QIDS-SR_{16}.
[b]Values are shown as percentages unless otherwise noted. Boldface indicates statistical significance.
[c]Family history was defined as positive if either bipolar disorder or major depressive disorder was noted in first-degree relatives by patient report.
Abbreviations: FIBSER = Frequency, Intensity, and Burden of Side Effects Rating; MDE = major depressive episode; PDSQ = Psychiatric Diagnostic Screening Questionnaire; QIDS-SR_{16} = 16-item Quick Inventory of Depressive Symptomatology–Self-Rated; SF-12 = 12-item Short-Form Health Survey.

(131/438) in this trial averaging 8 weeks, and the finding that about one-third (43/131) of those who ultimately responded did so at or after 9 weeks, it would seem that the preferred duration of this treatment step should be 12 weeks to avoid missing very late responders.

Does at Least a 20% Reduction in Depressive Symptom Severity Within the First 2 to 3 Weeks of Treatment Distinguish Responders From Nonresponders and Remitters From Nonremitters?

STAR*D did not mandate that all patients have their first post-baseline visit at week 2. Overall, 346 (79.0%) of the 438 patients in the analytic sample completed their first post-baseline visit reasonably near week 2 (defined a priori as within 7 to 21 days, inclusive after their initial visit).

The remission rate was 37.5% (51/136) for those who met this threshold as compared to 8.6% (18/210) for those who did not. The odds of remitting for those in the 20% reduction group were estimated to be 6.4 times the odds of those not obtaining a 20% reduction within the first 2 weeks. This odds ratio was found to be significantly larger than 1 ($P < .0001$ from Fisher exact test; 1-sided 95% CI, 3.7 to ∞).

Analogously, 50% (68/136) of those who met the threshold responded (NB: responders include remitters) as compared to 14.3% (30/210) for those who did not. The odds of responding for those in the 20% reduction group were estimated to be 6 times the odds of those not obtaining a 20% reduction within the first 2 weeks. This odds ratio was found to be significantly larger than 1 ($P < .0001$ from Fisher exact test; 1-sided 95% CI, 3.8 to ∞).

DISCUSSION

As expected from prior reports,[2,5,32] we found no meaningful differences in symptoms, function, or side effects across the 3 switch treatments (each used for about 8 weeks on average) in this analytic sample that employed a modified intent-to-treat sample. Comparable but modest treatment outcomes on switching to an alternate SSRI (sertraline) as opposed to a mechanistically different antidepressant (bupropion SR or venlafaxine XR) reflect previous reports.[32,33]

The 29.9% response rate (which includes remission) and the 20.8% remission rate were modest. About 60% of participants had no clinically meaningful benefit. Of those who ultimately responded, half did so after 6 weeks of treatment, as did two-thirds of those who ultimately reached remission. No baseline features distinguished early from late remitters or responders. Those who received no meaningful benefit had more concurrent psychiatric comorbidities and poorer physical health function. No clear triage point was found by which to shorten the duration of this second treatment step, as one-third of participants who ultimately responded did so after 9 weeks.

Using the 20% reduction in baseline symptoms by about week 2, we did find that those who met this threshold were 6

and 6.4 times more likely to achieve response or remission, respectively, than those who did not meet the threshold. Nevertheless, the low response and remission rates would argue against triaging at week 2, as we would have stopped treatment for 18 of 69 ultimate remitters and for 30 of 98 ultimate responders.

Overall, our response and remission rates in the second-step medication switch were lower than those found in other reports.[34–44] These results could be explained by the longer trial duration (up to 14 weeks) with initial SSRI treatment and the enhanced dosing (measurement-based care).[10,19] In addition, participants in this second step had an efficacy failure with the initial citalopram trial, as we required a QIDS-SR_{16} score of ≥ 11, which approximates an $HDRS_{17}$ score of ≥ 14,[12,13] which was the required threshold to enter STAR*D initially. Basically, the enhanced delivery of the initial SSRI and the requirement of efficacy failure in step 1 enriched the sample of truly step 1–resistant patients who entered step 2 compared to other second-step switch studies. Other potential reasons for poor response rates may include undiagnosed comorbid psychiatric and medical illnesses such as eating disorders or obstructive sleep apnea.[45] As previously reported,[46,47] patients were enrolled in STAR*D from "real-world" primary care and psychiatric clinics, where the eligibility criteria were quite permissive in contrast to those used for typical phase 3 studies of depression.

We did not find a clinically useful triage point or a way to identify individuals at baseline who would not respond or would have no meaningful benefit. We found no meaningful distinctions between early versus late remitters or between early versus late responders in this second step, despite findings by some[48–51] that larger earlier changes are associated with better longer-term outcomes. In previous studies,[52,53] we found that with the initial antidepressant medication treatment, early change in symptom severity was associated with better acute-phase outcomes. In this report of patients with a prior failed first step due to non-efficacy, those with more impaired physical function or more concurrent psychiatric conditions were less likely to receive meaningful benefit. Perhaps this longer-than-typical second-step trial with measurement-based care, and the more aggressive first-treatment delivery, created a sample that requires longer treatment exposure on this second step medication switch. This phenomenon may be due to spontaneous remission (we cannot know without a control group), or it might speak to the biological heterogeneity within major depressive disorder such that those who take far longer to respond may be presenting with a different biological substrate than those who respond much earlier.

The present results have implications for clinicians and researchers. Regulatory authorities evaluate and approve new treatments for treatment-resistant depression (TRD),[54] which is typically ascribed when a patient has experienced at least 2 adequate but failed treatment trials. The clinical conundrum is the definition of an adequate trial. The tools available for gauging the dose and duration of a depression treatment trial typically define an adequate trial as 4 to 6 weeks while dose thresholds are within the middle of the "therapeutic ranges" as specified in the medication package insert. These dose and duration thresholds do not ensure that the dose is personalized sufficiently by pushing doses to tolerance with measurement-based care, yet there is evidence that higher doses produce better outcomes.[19] Trials that are too brief will not recognize and help the 50% of potential responders who will not respond until after 6 weeks. The risk is that TRD will be misdiagnosed, which may move some non-TRD patients on to more costly, risky, and/or inconvenient treatments that might have been unnecessary had the initial 2 treatments been delivered more assiduously. If the present data are valid, clinicians and patients should consider prolonged courses of treatment (9–12 weeks) before declaring failure with a second-step medication switch.

Another implication for clinicians and researchers is the clear need to identify clinical and biological markers (moderators and mediators) by which to identify subgroups of patients who are more likely to improve with switching to one as opposed to another type of antidepressant. To date, efforts to identify moderators and mediators of antidepressant response have focused predominantly on first-step treatment.[55–57]

Some might argue that augmentation would be the better course for these patients, but most of these STAR*D second-step medication switch participants declined a second-step augmentation. Most wanted to start a new agent rather than add to a largely ineffective first-step agent. Regulatory agencies like the European Medicines Agency[58] explicitly state that patients with TRD and nonresponse to antidepressant therapy should be switched to an alternative antidepressant.

The recently completed Canadian Biomarker Integration Network in Depression antidepressant medication study[59] found high rates of response with atypical antipsychotic augmentation in patients with inadequate improvement after an 8-week trial of escitalopram. Additionally, the recently completed Veterans Administration Augmentation and Switching Treatments for Improving Depression Outcomes study[60] demonstrated superiority of augmentation with aripiprazole over switch to bupropion. In an ongoing study,[61] augmentation with aripiprazole is being compared head-to-head with switch to venlafaxine and augmentation with repetitive transcranial magnetic stimulation. The findings of these studies will quite likely inform our strategy to identify second-step treatment options after failure to respond adequately to an initial adequate course of SSRI.

Limitations

Study limitations include the following: (1) it is unknown whether the results apply to other medications used in a second-step medication switch paradigm; (2) current results apply to persons with minimal symptom benefit from citalopram in the first treatment step, but it is unknown

whether these results would occur with different step 1 medications or in those with some greater step 1 symptom benefit; (3) it is unknown whether these same results would occur in routine practice when measurement-based care is not used; (4) it is unknown whether these results apply to those who switched in the second step due to intolerable side effects; and (5) without a no-treatment or placebo control, we do not know to what degree spontaneous improvement might account for our findings.

CONCLUSION

For depressed patients with little symptomatic benefit from a well-delivered first treatment step with an SSRI (citalopram), response and remission rates are modest in the second medication switch step. There is no obvious triage point in this second step. The duration of the second step should be 12 weeks to avoid missing those who respond and remit later.

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Supplementary Material

Article Title: What to Expect When Switching to a Second Antidepressant Medication Following an Ineffective Initial SSRI: A Report From the Randomized Clinical STAR*D Study

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List of Supplementary Material for the article

1. Appendix 1 Supplementary Methods
2. Table 1 Recommended algorithm for medication management in level 2 of STAR*D
3. Table 2 Mean medication doses (+SD) by weeks in Step 2 Medication Switch

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What to expect when switching to a second antidepressant medication following an ineffective initial SSRI: A report from the randomized clinical STAR*D study

A. John Rush, Charles South, Manish K. Jha, Shailesh Bobby Jain, Madhukar H. Trivedi

Appendix 1

Dosage Recommendations

The recommended daily dose of bupropion-SR was 150 mg for seven days, 200 mg from day 8 to 27, 300 mg from day 28 to 41, and 400 mg from day 42 onward. Sertraline was started at a daily dose of 50 mg and increased to 100 mg at day 14, to 150 mg at day 28, and to 200 mg at day 63. For venlafaxine-XR, the starting daily dose of 37.5 mg for 7 days was increased to 75 mg from day 8 to 14, to 150 mg from day 15 to 27, to 225 mg from day 28 to 41, to 300 mg from day 42 to 62, and to 375 mg from day 63 onward.

Concomitant Treatments

Stimulants, anticonvulsants, antipsychotic agents, mood stabilizers, non-protocol antidepressant medications, and potential antidepressant augmenting agents (e.g., buspirone) were proscribed. Otherwise, any concomitant medication was allowed as necessary to manage concurrent general medical conditions or the side effects of protocol antidepressants (e.g., sexual dysfunction), as were anxiolytic agents (with the exception of alprazolam) and sedative hypnotic agents (including trazodone, at a dose of 200 mg or less at bedtime, for sleep).

12-item Short Form Health Survey Physical Component Scores (PCS-12) and Mental Component Scores (MCS-12)

The scores may be reported as Z-scores (difference compared to the population average, measured in standard deviations). The United States population averages for PCS-12 and MCS-12 are both 50 points, with standard deviations of 10 points. So, each 10 points change above or below 50 corresponds to one standard deviation away from the average.

The Work Productivity and Activity Impairment (WPAI) Instrument

The WPAI consists of six questions: (1) currently employed?; (2) work hours missed due to health problems; (3) work hours missed due to other reasons; (4) hours actually worked; (5) degree health has affected productivity while working (using a 0 to 10 Visual Analogue Scale (VAS)); (6) degree health has affected productivity in regular unpaid activities (VAS). The recall period for questions 2 through 6 is seven days. Four main outcomes can be generated from the WPAI and expressed in percentages by multiplying the following scores by 100: (1) percent of work time missed due to health = Q2/(Q2 + Q4) for those who were currently employed; (2) percent of impairment while working due to health = Q5*10 for those who were currently employed and actually worked in the past seven days; (3) percent of overall work impairment due to health = Q2/(Q2 + Q4) + ((1 - Q2/(Q2 + Q4)) × (Q5/10)) for those who were currently employed; and (4) percent of activity impairment due to health = Q6*10 for all respondents. For those who missed work and did not actually work in the past seven days, the percent of overall work impairment due to health would be equal to the percent of work time missed due to health.

The Work and Social Adjustment Scale (WSAS)

The WSAS is a simple and reliable measure of impairment in functioning. The WSAS assesses the impact of a person's mental health difficulties on their ability to function in terms of work, home management, social leisure, private leisure, and personal or family relationships. This instrument has five questions and is a sensitive and useful outcome measure with correlations to severity of depression and some anxiety symptoms. Cronbach's alpha measure of internal

scale consistency ranged from 0.70 to 0.94. The scores were sensitive to patient differences in disorder severity and treatment-related change. The total WSAS score is calculated by adding up all of the items. A WSAS score above 20 appears to suggest moderately severe or worse functioning. Scores from 10 to 20 are associated with significant functional impairment but less severe clinical symptomatology. Scores below 10 appear to be associated with subclinical populations.

Supplementary Table 1: Recommended algorithm for medication management in level 2 of STAR*D[1]

Level 2 Medication Switch Sertraline

CDP, Week 0	STAR*D Level 2 Sertraline
	Start patient on sertraline 50 mg/day for 2 weeks, then 100 mg/day
Return to clinic:	Return in 2 weeks
CDP, Week 4	**STAR*D Level 2 Sertraline**
Symptom Improvement (SEs tolerable)	
QIDS-$C_{16} \geq 9$	Increase dose to 150 mg/day.
QIDS-C_{16} = 6-8	Continue current dose, *or* Increase dose to 150 mg/day
QIDS-$C_{16} \leq 5$	Continue current dose.
Improved, but SEs are intolerable	Continue current dose and address SEs, *or* Go to the next level.
Not improved and SEs are intolerable	Go to the next level.
Return to clinic:	Return in 2 weeks.
CDP, Week 6	**STAR*D Level 2 Sertraline**
Symptom Improvement (SEs tolerable)	
QIDS-$C_{16} \geq 9$	Increase dose to 150 mg/day.
QIDS-C_{16} = 6-8	Increase dose to 150 mg/day, if not done previously *or* continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose.
Improved, but SEs are intolerable	Continue current dose and address SEs, *or* Decrease dose and continue for 2 additional weeks, *or* Go to the next level
Not improved and SEs are intolerable	Go to the next level.
Return to clinic:	Return in 3 weeks.
CDP, Week 9	**STAR*D Level 2 Sertraline**
Symptom Improvement (SEs tolerable)	
QIDS-$C_{16} \geq 9$	Go to the next level.
QIDS-C_{16} = 6-8	Increase dose to 200 mg/day, *or* Go to next level.
QIDS-$C_{16} \leq 5$	Continue current dose.

SEs are intolerable	Go to the next level.
Return to clinic:	Return in 3 weeks.

CDP, Week 12	**STAR*D Level 2 Sertraline**
Symptom Improvement (SEs tolerable)	
QIDS-$C_{16} \geq 9$	Go to the next level.
QIDS-C_{16} = 6-8	Continue current dose and go to follow-up[2], *or* Go to the next level.
QIDS-$C_{16} \leq 5$	Continue current dose and go to follow-up.
SEs are intolerable	Go to the next level.
Return to clinic:	If remitted, • Return in 3 months or as needed. If starting new level, • Return in 2 weeks.

[1] Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med.* 2006;354(12):1231-1242. DOI: 10.1056/NEJMoa052963.

[2] Because of the severity of some patients, clinicians may choose to keep patient on current dose and move to follow-up if at week 12 the patient has maintained a score of 6-8 on the QIDS-C or if the patient does not want to change medications and/or the patient is satisfied with the level of improvement.

Level 2 Medication Switch Bupropion SR

CDP, Week 0	STAR*D Levels 2 Bupropion SR
	Start patient on BupropionSR 150 mg/day for 7 days, then 200 mg/day
Return to clinic:	Return in 2 weeks
CDP, Week 4	**STAR*D Levels 2 Bupropion SR**
Symptom Improvement *(SEs tolerable)*	
QIDS-$C_{16} \geq 9$	Increase dose to 300 mg/day.
QIDS-C_{16} = 6-8	Continue current dose, *or* Increase dose to 300 mg/day
QIDS-$C_{16} \leq 5$	Continue current dose.
Improved, but SEs are intolerable	Continue current dose and address SEs, *or* Go to the next level.
Not improved and SEs are intolerable	Go to the next level.
Return to clinic:	Return in 2 weeks.
CDP, Week 6	**STAR*D Levels 2 Bupropion SR**
Symptom Improvement *(SEs tolerable)*	
QIDS-$C_{16} \geq 9$	Increase dose to 400 mg/day.
QIDS-C_{16} = 6-8	Increase dose to 400 mg/day *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose.
Improved, but SEs are intolerable	Continue current dose and address SEs, *or* Decrease dose and continue for 2 additional weeks, *or* Go to the next level.
Not improved and SEs are intolerable	Go to the next level.
Return to clinic:	Return in 3 weeks or as needed.
CDP, Week 9	**STAR*D Levels 2 Bupropion SR**
Symptom Improvement *(SEs tolerable)*	
QIDS-$C_{16} \geq 9$	Go to the next level.
QIDS-C_{16} = 6-8	Increase dose to 400 mg/day, if not done previously, *or* Go to the next level.
QIDS-$C_{16} \leq 5$	Continue current dose.
SEs are intolerable	Go to the next level.
Return to clinic:	Return in 3 weeks or as needed.

CDP, Week 12	STAR*D Levels 2 Bupropion SR
Symptom Improvement *(SEs tolerable)*	
QIDS-$C_{16} \geq 9$	Go to the next level.
QIDS-C_{16} = 6-8	Continue current dose and go to follow-up[1], *or* Go to the next level.
QIDS-$C_{16} \leq 5$	Continue current dose and go to follow-up.
SEs are intolerable	Go to the next level.
Return to clinic:	If remitted, • Return in 3 months or as needed. If starting new level, • Return in 2 weeks.

[1] Because of the severity of some patients, clinicians may choose to keep patient on current dose and move to follow-up if at week 12 the patient has maintained a score of 6-8 on the QIDS-C or if the patient does not want to change medications and/or the patient is satisfied with the level of improvement.

Level 2 Medication Switch Venlafaxine

CDP, Week 0	STAR*D Levels 2 Venlafaxine XR
	Start patient on VenlafaxineXR 37.5 for 7 days, then 75 mg/day for 7 days, then 150 mg/day
Return to clinic:	Return in 2 weeks
CDP, Week 4	**STAR*D Levels 2 Venlafaxine XR**
Symptom Improvement *(SEs tolerable)*	
QIDS-$C_{16} \geq 9$	Increase dose to 225 mg/day.
QIDS-C_{16} = 6-8	Continue current dose, *or* Increase dose to 225 mg/day
QIDS-$C_{16} \leq 5$	Continue current dose.
Improved, but SEs are intolerable	Continue current dose and address SEs, *or* Go to the next level.
Not improved and SEs are intolerable	Go to the next level.
Return to clinic:	Return in 2 weeks.
CDP, Week 6	**STAR*D Levels 2 Venlafaxine XR**
Symptom Improvement *(SEs tolerable)*	
QIDS-$C_{16} \geq 9$	Increase dose to 300 mg/day.
QIDS-C_{16} = 6-8	Increase dose to 300 mg/day *or* Continue current dose.
QIDS-$C_{16} \leq 5$	Continue current dose.
Improved, but SEs are intolerable	Continue current dose and address SEs, *or* Decrease dose and continue for 2 additional weeks, *or* Go to the next level.
Not improved and SEs are intolerable	Go to the next level.
Return to clinic:	Return in 3 weeks.
CDP, Week 9	**STAR*D Levels 2 Venlafaxine XR**
Symptom Improvement *(SEs tolerable)*	
QIDS-$C_{16} \geq 9$	Go to the next level.
QIDS-C_{16} = 6-8	Increase dose to 375 mg/day, *or* Go to the next level.
QIDS-$C_{16} \leq 5$	Continue current dose.
SEs are intolerable	Go to the next level.
Return to clinic:	Return in 3 weeks.

CDP, Week 12	STAR*D Levels 2 Venlafaxine XR
Symptom Improvement *(SEs tolerable)*	
QIDS-$C_{16} \geq 9$	Go to the next level.
QIDS-C_{16} = 6-8	Continue current dose and go to follow-up[1], *or* Go to the next level.
QIDS-$C_{16} \leq 5$	Continue current dose and go to follow-up.
SEs are intolerable	Go to the next level.
Return to clinic:	If remitted, • Return in 3 months or as needed. If starting new level, • Return in 2 weeks.

[1] Because of the severity of some patients, clinicians may choose to keep patient on current dose and move to follow-up if at week 12 the patient has maintained a score of 6-8 on the QIDS-C or if the patient does not want to change medications and/or the patient is satisfied with the level of improvement.

Supplementary Table 2: Mean medication doses (+SD) by weeks in Step 2

Medication Switch

Week	BUP		SERT		VEN	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
2	118	197.7 (63.6)	137	70.1 (30.0)	116	91.8 (38.8)
4	105	234.5 (72.6)	119	99.2 (35.6)	103	125.5 (47.3)
6	107	287.6 (76.1)	116	123.3 (43.6)	104	166.4 (72.3)
9	87	331.9 (79.8)	86	148.0 (42.6)	98	210.8 (86.3)
12	53	349.5 (78.8)	54	164.4 (43.9)	64	241.4 (92.3)

BUP=bupropion; Sert=sertraline; VEN=venlafaxine-XR

[1] Trivedi MH, Rush AJ, Gaynes BN, Stewart JW, Wisniewski SR, Warden D, Ritz L, Luther JF, Stegman D, Deveaugh-Giess J, Howland R. (2007). Mazimizing the Adequacy of Medication Treatment in Controlled Practice: STAR*D Measurement-Based Care. *Neuropsychoharmacology* 32: 2479-2489.