

# A Comparison of Lithium and T<sub>3</sub> Augmentation Following Two Failed Medication Treatments for Depression: A STAR\*D Report

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**Objective:** More than 40% of patients with major depressive disorder do not achieve remission even after two optimally delivered trials of antidepressant medications. This study compared the effectiveness of lithium versus triiodothyronine (T<sub>3</sub>) augmentation as a third-step treatment for patients with major depressive disorder.

**Method:** A total of 142 adult outpatients with nonpsychotic major depressive disorder who had not achieved remission or who were intolerant to an initial prospective treatment with citalopram and a second switch or augmentation trial were randomly assigned to augmentation with lithium (up to 900 mg/day; N=69) or with T<sub>3</sub> (up to 50 µg/day; N=73) for up to 14

weeks. The primary outcome measure was whether participants achieved remission, which was defined as a score ≤7 on the 17-item Hamilton Depression Rating Scale.

**Results:** After a mean of 9.6 weeks (SD=5.2) of treatment, remission rates were 15.9% with lithium augmentation and 24.7% with T<sub>3</sub> augmentation, although the difference between treatments was not statistically significant. Lithium was more frequently associated with side effects (p=0.045), and more participants in the lithium group left treatment because of side effects (23.2% versus 9.6%; p=0.027).

**Conclusions:** Remission rates with lithium and T<sub>3</sub> augmentation for participants who experienced unsatisfactory results with two prior medication treatments were modest and did not differ significantly. The lower side effect burden and ease of use of T<sub>3</sub> augmentation suggest that it has slight advantages over lithium augmentation for depressed patients who have experienced several failed medication trials.

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While antidepressant medications are effective for major depressive disorder, only 25%–45% of patients experience remission after one acute trial of an antidepressant (1–3). For patients whose depression does not remit after an adequate trial, clinicians generally switch to a different antidepressant, add a second antidepressant to the initial one, or augment the antidepressant with another agent. The most widely studied medications used for augmentation of antidepressant treatment are lithium and triiodothyronine (T<sub>3</sub>), but most of the evidence supporting their use in augmentation was collected in studies with patients who did not respond initially to tricyclic antidepressants (4). We know of no studies that have compared the effectiveness of these two augmentation treatments as third-step options for depressed patients who did not receive sufficient benefit from treatment trials with selective serotonin reuptake inhibitors (SSRIs) or other second-generation antidepressants.

## Augmentation With Lithium or T<sub>3</sub>

The rationale for using lithium as an augmenting agent in antidepressant treatment for patients with major depression was based on preclinical data showing that lithium increases the presynaptic formation, storage, and release of serotonin (5). It was postulated that the increase in serotonergic function induced by lithium would have a synergistic effect on the mechanism of action of antidepressants. Most studies of lithium augmentation used small samples of patients who had not responded to tricyclic antidepressants, and most found that augmenting a tricyclic with lithium was effective. A meta-analysis of nine placebo-controlled studies (total N=234) supported the conclusion that lithium augmentation was effective, with a number needed to treat of 3.8 (6). Patients who responded and who continued taking lithium in addition to their antidepressant stayed well longer than those who

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were randomly switched to placebo augmentation (7). However, there is no good evidence that lithium is effective in augmentation of serotonin reuptake inhibitors (8).

The hypothalamic-pituitary-thyroid axis and its reciprocal relationship with depression have long been a subject of inquiry (9, 10). Although pretreatment thyroid function may or may not mediate response to antidepressants (11, 12), thyroid hormone augmentation is useful even in the absence of thyroid abnormalities (13). Putative mechanisms of action include desensitization of 5-HT<sup>1A</sup> inhibitory receptors, direct effects on nuclear receptors affecting gene expression (14), and increased brain metabolism (15). A meta-analysis of eight studies (total N=292) supported the efficacy of T<sub>3</sub> augmentation, with a number needed to treat of 4.3 (16). In contrast to lithium augmentation, to our knowledge no studies have examined the durability of response to T<sub>3</sub> augmentation with a placebo-substitution design. A meta-analysis (17) showed that T<sub>3</sub> augmentation may speed up response to antidepressants, especially in women, but neither an acceleration effect nor a gender effect was replicated in a small controlled study with paroxetine (18).

## Effectiveness and Comparison Studies

Few studies have assessed the effectiveness (that is, in representative patients treated in typical practice settings) of using other agents to augment antidepressants, particularly to augment the more modern antidepressants. Even fewer studies have prospectively generated a cohort of patients who obtained insufficient benefit from adequately delivered initial treatments and then underwent randomized assignment to receive augmentation with lithium or other agents (8, 19, 20). Similarly, few studies have examined the efficacy or effectiveness of T<sub>3</sub> augmentation for patients with major depression who did not have an adequate response to one of the second-generation antidepressants (15). Joffe et al. (21), in the only study we know of that directly compared lithium and T<sub>3</sub> augmentation of tricyclic antidepressants as a second-step treatment, found the two agents to be equally effective and more effective than placebo.

In this study, we compared the effectiveness, tolerability, and safety of lithium and T<sub>3</sub> augmentation in a representative group of primary and specialty care clinic outpatients who had nonpsychotic major depressive disorder. The study participants had not obtained adequate benefit from prospective treatment with two or more trials of antidepressant monotherapy or an initial trial of monotherapy with citalopram followed by a second trial in which citalopram was augmented with buspirone or sustained-release bupropion. In addition, a small number of patients who entered this trial (N=9) initially received citalopram, then received cognitive therapy either alone or combined with citalopram, and then underwent randomized assignment to either sustained-release bupropion or extended-

release venlafaxine alone before moving on to the augmentation treatment we report here.

## Method

This trial was conducted as part of the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study, which was designed to assess the effectiveness of medications or cognitive therapy for outpatients who had not had a satisfactory response to an initial treatment or to one or more subsequent prospective treatments (3, 22–24). The rationale, design, and methods of STAR\*D have been detailed elsewhere (25, 26).

### Participants

The institutional review boards at the STAR\*D National Coordinating Center, the Data Coordinating Center, each regional center and relevant clinical site, and the Data Safety and Monitoring Board of the National Institute of Mental Health (Bethesda, Md.) approved and monitored the protocol. All participants received a complete description of the study and provided written informed consent at the time of enrollment into the initial treatment step and into each subsequent treatment step, including the augmentation treatment described here.

Between July 2001 and April 2004, a total of 4,041 outpatients 18 to 75 years of age were enrolled in STAR\*D from primary care (N=18) and psychiatric practice settings (N=23) that serve patients with public as well as private insurance. To be eligible for enrollment, patients had to have a primary clinical diagnosis of nonpsychotic major depressive disorder according to DSM-IV criteria, confirmed by a checklist completed by clinical research coordinators at each site. Advertising for participants was proscribed. The study used minimal exclusion criteria, aiming for broad inclusion in order to maximize the generalizability of findings (25, 26). Of the 4,041 participants enrolled in STAR\*D, 142 enrolled in the augmentation treatment step, which was the third treatment level in the study.

### Progression to STAR\*D Level 3

STAR\*D consisted of four levels of medication treatment, and for some participants it included an additional treatment trial with cognitive therapy either alone or combined with citalopram (Level 2A). At each level, participants who achieved remission (defined as a score  $\leq 5$  on the 16-item Quick Inventory of Depressive Symptomatology—Clinician Rating [QIDS-C] [27–29]) and had no trouble tolerating the medication could proceed to the 12-month naturalistic follow-up stage of the project. Those who had a partial response to the medication (defined as a reduction  $\geq 50\%$  from the baseline QIDS-C score) but did not remit at any treatment level could enter the follow-up stage but were encouraged to enroll in the next treatment level; the same protocol applied to those who neither achieved remission nor had a response to treatment and those who were intolerant of the treatment.

All STAR\*D participants entered treatment Level 1 and underwent a trial of citalopram. Participants who entered Level 2 were randomly assigned either to switch to one of four alternative treatments (sustained-release bupropion, sertraline, extended-release venlafaxine, or cognitive therapy) or to receive augmentation of the citalopram with one of three treatments (sustained-release bupropion, buspirone, or cognitive therapy) (30). Those who had an unsatisfactory response (intolerance or lack of remission) could enter treatment Level 3. Participants who had an unsatisfactory response to cognitive therapy during Level 2, whether they were enrolled in cognitive therapy as a medication switch or as augmentation, could enter Level 2A, which compared the effectiveness of two of the switch options (sustained-release bupropion and extended-release venlafaxine). The inclusion of treat-

ment Level 2A in the study ensured that all participants entering Level 3 had not had a satisfactory response to two different medication treatments.

On entry to treatment Level 3, participants were asked whether they were willing to accept random assignment to a medication switch to either nortriptyline or mirtazapine and whether they were willing to accept random assignment to augmentation of their current antidepressant with lithium or T<sub>3</sub>. Those who would accept only a medication switch strategy were randomly assigned to switch to nortriptyline or mirtazapine; those who would accept only an augmentation strategy were randomly assigned to augmentation with either lithium or T<sub>3</sub>; and those who would accept either a switch or an augmentation strategy were randomly assigned to one of the four treatment options.

In this report we compare the main outcomes for Level 3 participants who agreed to random assignment to treatment strategies that included any of the augmentation treatments. Participants were randomly assigned to these treatments in a 1:1 ratio stratified for treatment acceptability and regional center. Of the 18 patients who exited Level 2A, nine were willing to accept a medication switch only, and nine were willing to accept augmentation only. Of the nine who accepted augmentation only, six received lithium and three received T<sub>3</sub>.

### Protocol Treatment

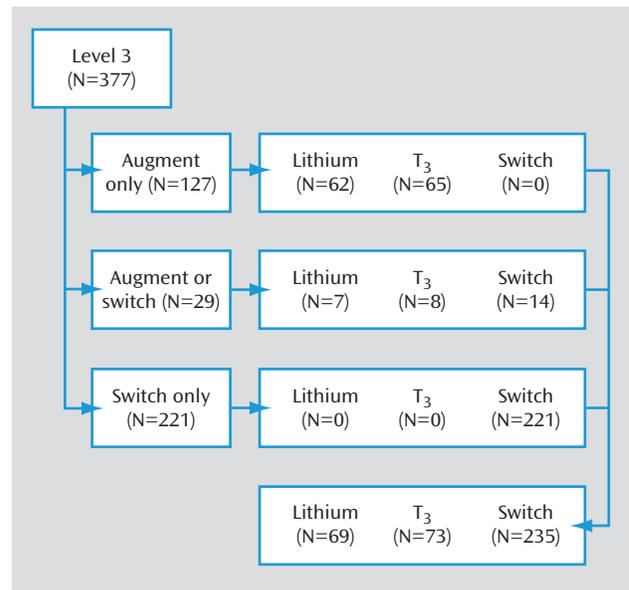
To mimic clinical practice, enhance safety, and ensure vigorous dosing, treatment assignment and dose were not masked to participants or treating clinicians. A clinical procedures manual (31) recommended starting doses and dose changes for each medication treatment in order to deliver measurement-based care (22, 32). The dosing protocol was flexible, however, and could be adjusted according to the clinician's assessment of symptoms and side effects as measured at each visit with the QIDS-C and with ratings of the frequency, intensity, and burden of side effects (26, 33, 34). In addition, didactic instruction, clinical research coordinator support, and a centralized monitoring system (35) with feedback were used to ensure that timely dose increases were made as long as symptom reduction was inadequate and side effects remained acceptable. Clinical management aimed to achieve symptom remission (a QIDS-C score  $\leq 5$  at treatment exit). The protocol recommended treatment clinic visits at weeks 0, 2, 4, 6, 9, and 12 but allowed for flexibility (e.g., the week 2 visit could take place within 6 days before or after that date), and extra visits could be made if needed. For participants who achieved remission, treatment was maintained for an additional 2 weeks to determine whether the remission would be sustained. For participants who had a response but had not remitted by week 12, treatment could be extended for an additional 2 weeks.

The two augmentation options used at treatment Level 2, bupirone and sustained-release bupropion, were discontinued without tapering at the initial Level 3 treatment visit. Lithium or T<sub>3</sub> was added to ongoing treatment with citalopram, sertraline, sustained-release bupropion, or extended-release venlafaxine. Lithium was started at 450 mg/day, and at week 2 it was increased to the recommended dose of 900 mg/day. If participants could not tolerate the initial dose, it could be reduced to 225 mg/day for 1 week then increased to 450 mg/day. T<sub>3</sub> was started at 25  $\mu$ g/day for 1 week and then increased to the recommended dose of 50  $\mu$ g/day. As noted, this protocol was flexible, allowing a role for clinical judgment and ratings of symptoms and side effects.

### Concomitant Treatments

Stimulants, anticonvulsants, antipsychotics, mood stabilizers, antidepressants that were not included in the study's protocol, and potential antidepressant augmenting agents (e.g., bupirone) were proscribed. Otherwise, any concomitant medication was allowed for management of concurrent general medical conditions

**FIGURE 1. Participant Flow (CONSORT Chart) for Treatment Level 3 of the STAR\*D Study**



as well as side effects of antidepressants used in the study (e.g., sexual dysfunction). Anxiolytics (except alprazolam) and sedative-hypnotics were permitted (including up to 200 mg of trazodone at bedtime for sleep).

### Measures

Clinical and demographic characteristics were recorded at baseline for treatment Level 1 (22). The Cumulative Illness Rating Scale (36, 37) was used to assess for general medical conditions and the Psychiatric Diagnostic Screening Questionnaire (38–40) to assess for comorbid psychiatric disorders. At entry and exit from treatment Level 3, overall functioning and satisfaction were assessed with the 12-item Short-Form Health Survey (41), the Work Productivity and Activity Impairment Questionnaire (42), the Work and Social Adjustment Scale (43), and the Quality of Life Enjoyment and Satisfaction Questionnaire (44), all administered through an automated interactive voice response telephone system (45, 46).

The primary outcome measure was whether participants achieved symptom remission, defined as a score  $\leq 7$  on the 17-item Hamilton Depression Rating Scale (HAM-D) (47). The HAM-D was administered via telephone in the course of structured interviews (conducted in English or Spanish) within 5 days of entry and exit from treatment Level 3 by independent research outcomes assessors who were blind to participants' treatments. The assessors also administered the 30-item Inventory of Depressive Symptomatology—Clinician-Rated (27, 29, 48) to assess depressive symptom severity and associated symptom features. The secondary outcome measures were whether participants experienced remission and response as assessed by the Quick Inventory of Depressive Symptomatology—Self-Report (QIDS-SR) (27–29, 33), with remission defined as a total QIDS-SR score  $\leq 5$  at exit from treatment Level 3 and response defined as a reduction of  $\geq 50\%$  from the Level 3 baseline QIDS-SR score. The QIDS-SR was administered at each treatment visit, along with ratings of the frequency, intensity, and burden of side effects.

### Statistical Methods

For summary statistics, means and standard deviations were computed for continuous variables, and counts and percentages

TABLE 1. Baseline Demographic and Clinical Characteristics, at Entry to STAR\*D Study, of Outpatients With Major Depressive Disorder Receiving Lithium or T<sub>3</sub> Augmentation Treatment in STAR\*D Level 3, by Augmentation Agent<sup>a</sup>

Characteristic	Augmentation Agent						Analyses <sup>b</sup>		
	Total (N=142)		Lithium (N=69)		T <sub>3</sub> (N=73)		Test Statistic	df	p
	Mean	SD	Mean	SD	Mean	SD			
Age (years)	42.0	12.0	40.6	12.2	43.2	11.8	t=-1.3177 <sup>c</sup>	140	0.1897
Education (years)	13.2	2.9	13.1	3.0	13.3	2.9	$\chi^2=0.5566$	1	0.4556
Monthly household income (\$)	1,977	1,703	2,074	1,827	1,881	1,579	$\chi^2=0.0926$	1	0.7609
Female sex	N	%	N	%	N	%	$\chi^2=0.3234$	1	0.5696
Race	83	58.5	42	60.9	41	56.2	$\chi^2=0.6378$	2	0.7269
White	118	83.1	59	85.5	59	80.8			
Black	16	11.3	7	10.1	9	12.3			
Other	8	5.6	3	4.3	5	6.8			
Hispanic	17	12.0	8	11.6	9	12.3	$\chi^2=0.0182$	1	0.8928
Employment status							$\chi^2=0.1940$	2	0.9076
Employed	80	56.3	40	58.0	40	54.8			
Unemployed	55	38.7	26	37.7	29	39.7			
Retired	7	4.9	3	4.3	4	5.5			
Medical insurance							$\chi^2=1.8339$	2	0.3997
Private	74	54.4	32	48.5	42	60.0			
Public	15	11.0	8	12.1	7	10.0			
None	47	34.6	26	39.4	21	30.0			
Marital status							$\chi^2=3.2034$	3	0.3613
Single	40	28.2	22	31.9	18	24.7			
Married or cohabiting	58	40.8	23	33.3	35	47.9			
Divorced or separated	39	27.5	21	30.4	18	24.7			
Widowed	5	3.5	3	4.3	2	2.7			
Number of psychiatric disorders, per Psychiatric Diagnostic Screening Questionnaire							$\chi^2=0.9842$	4	0.9122
None	45	31.9	22	31.9	23	31.9			
1	35	24.8	15	21.7	20	27.8			
2	32	22.7	16	23.2	16	22.2			
3	9	6.4	5	7.2	4	5.6			
4 or more	20	14.2	11	15.9	9	12.5			
Family history of depression	83	58.5	40	58.0	43	58.9	$\chi^2=0.0127$	1	0.9102
Prior suicide attempt	28	19.7	14	20.3	14	19.2	$\chi^2=0.0277$	1	0.8678
Psychiatric care setting	96	67.6	45	65.2	51	69.9	$\chi^2=0.3496$	1	0.5544
Recurrent depression	106	81.5	54	88.5	52	75.4	$\chi^2=3.7262$	1	0.0536
Duration of index episode $\geq 2$ years	35	25.4	16	23.9	19	26.8	$\chi^2=0.1510$	1	0.6975
Age <18 years at onset of first episode	63	44.7	37	53.6	26	36.1	$\chi^2=4.3716$	1	0.0365
	Mean	SD	Mean	SD	Mean	SD			
Age at onset of first episode (years)	23.5	13.7	21.2	12.9	25.8	14.1	$\chi^2=4.8774$	1	0.0272
Duration of index episode (months) <sup>d</sup>	29.5	74.2	29.1	80.9	29.9	67.8	$\chi^2=0.0336$	1	0.8547
Duration of illness (years)	18.3	13.4	19.4	13.6	17.3	13.2	$\chi^2=0.9284$	1	0.3353
Number of episodes	7.4	14.6	8.4	15.3	6.5	13.9	$\chi^2=3.3347$	1	0.0678
Cumulative Illness Rating Scale, number of categories	3.5	2.5	3.3	2.7	3.7	2.3	$\chi^2=1.8157$	1	0.1778
Cumulative Illness Rating Scale, total score	5.0	4.2	4.5	4.2	5.4	4.1	$\chi^2=2.7193$	1	0.0991
Cumulative Illness Rating Scale, severity index	1.2	0.6	1.1	0.6	1.3	0.6	$\chi^2=3.2044$	1	0.0734

<sup>a</sup> Sums do not always equal N because of missing data; percentages are based on number of subjects for whom data were available.

<sup>b</sup> Kruskal-Wallis chi-square is used for continuous variables.

<sup>c</sup> Student's t.

<sup>d</sup> Median=8.1 overall, median=7.6 for lithium group, and median=8.4 for T<sub>3</sub> group.

**TABLE 2. Baseline Clinical Measures and Characteristics, at Entry to STAR\*D Level 3, of Outpatients With Major Depressive Disorder Receiving Lithium or T<sub>3</sub> Augmentation Treatment<sup>a</sup>**

Characteristic	Total (N=142)		Augmentation Agent				Analyses		
	Mean	SD	Lithium (N=69)		T <sub>3</sub> (N=73)		Test Statistic <sup>b</sup>	df	p
Quality of Life and Enjoyment Satisfaction Questionnaire	41.2	13.5	39.6	14.0	42.8	12.9	t=-1.2652	107	0.2086
Short Form Health Survey, mental subscale	30.0	10.0	28.9	10.9	31.2	9.1	t=-1.2082	107	0.2296
Short Form Health Survey, physical subscale	45.5	12.8	45.2	12.7	45.7	12.9	t=-0.1844	107	0.8540
Work and Social Adjustment Scale	23.5	8.8	24.1	7.7	22.9	9.8	t=0.7073	107	0.4809
Hamilton Depression Rating Scale	18.1	6.5	19.0	6.6	17.2	6.2	t=1.5990	124	0.1124
Inventory of Depressive Symptomatology—Clinician-Rated	32.3	11.8	34.4	12.4	30.4	11.0	t=1.9036	122	0.0593
Quick Inventory of Depressive Symptomatology—Clinician-Rated	12.7	3.9	13.1	3.7	12.4	4.1	t=1.1396	140	0.2564
Quick Inventory of Depressive Symptomatology—Self-Report	12.4	4.0	13.0	3.9	11.8	4.1	t=1.8795	140	0.0623
	N	%	N	%	N	%			
Anxious features	52	40.6	25	41.0	27	40.3	$\chi^2=0.0062$	1	0.9372
Atypical features	23	18.1	14	23.3	9	13.4	$\chi^2=2.0921$	1	0.1481
Melancholic features	16	12.5	10	16.4	6	9.0	$\chi^2=2.0921$	1	0.1481

<sup>a</sup> Sums do not always equal N because of missing data; percentages are based on number of subjects for whom data were available.

<sup>b</sup> Student's t and chi-square.

for discrete variables. Student's t tests and Kruskal-Wallis tests were used to compare continuous baseline clinical and demographic characteristics, treatment features, and ratings of side effects and serious adverse events across treatments. Chi-square tests were used to compare discrete characteristics across treatments.

Logistic regression models were used to compare remission and response rates after adjusting for treatment acceptability category ("augmentation only" or "switch or augmentation"), baseline severity of depression as assessed by the QIDS-SR, and age at onset of first major depressive episode. The time to first remission was defined as the first clinic visit with a QIDS-SR score  $\leq 5$ , and time to first response was defined as the first clinic visit with a reduction  $\geq 50\%$  from the baseline QIDS-SR score. Log-rank tests were used to compare the cumulative proportion of participants who experienced remission or response across the two treatment groups.

Participants whose exit HAM-D scores were missing were assumed not to have achieved remission. Sensitivity analyses were conducted to determine whether this method of addressing the missing data had an impact on the results of the study. An additional method of addressing these missing data used an imputed value generated from an item response theory analysis of the relationship between the HAM-D and the QIDS-SR.

## Results

### Patient Disposition

Figure 1 summarizes the Level 3 treatment groups by treatment acceptability category. The 127 Level 3 participants who agreed only to augmentation strategies were randomly assigned to receive either lithium or T<sub>3</sub>. Of the 29 participants who agreed to either an augmentation or a switch strategy, 15 were randomly assigned to receive lith-

ium or T<sub>3</sub>. Thus, a total of 142 participants began Level 3 augmentation treatment.

### Overall and Group Baseline Characteristics

Table 1 summarizes demographic characteristics and relevant elements of participants' pretreatment clinical history, along with results of the statistical tests used to compare the two augmentation treatment groups. No statistically significant differences were observed between the two groups except that a greater proportion of participants in the lithium group had their first major depressive episode before the age of 18 years, and the mean age at onset of the first episode was lower in the lithium group.

### Baseline Symptom Severity, Functioning, and Depressive Features

Table 2 summarizes the participants' clinical characteristics and baseline scores on various assessment instruments at the time of randomization for STAR\*D treatment Level 3. Assessment scores indicate a moderate degree of symptom severity overall. Baseline scores on the Quality of Life Enjoyment and Satisfaction Questionnaire, the physical and mental subscales of the 12-item Short-Form Health Survey, and the Work and Social Adjustment Scale revealed very poor life satisfaction and function. There were no statistically significant differences between groups on measures for depressive symptoms, functioning, or depressive features.

**TABLE 3. Treatment, Side Effect Ratings, and Change in Symptom Severity During Prior STAR\*D Treatment Level (2 or 2A) Among Outpatients With Major Depressive Disorder Receiving Lithium or T<sub>3</sub> Augmentation Treatment in STAR\*D Level 3, by Augmentation Agent<sup>a</sup>**

Treatment, Side Effects, and Change in Symptom Severity	Augmentation Agent						Analyses		
	Total (N=142)		Lithium (N=69)		T <sub>3</sub> (N=73)		Test Statistic <sup>b</sup>	df	p
	N	%	N	%	N	%			
Treatment in prior level							$\chi^2=8.1484$	4	0.0863
Bupropion (sustained-release)	30	21.1	21	30.4	9	12.3			
Citalopram and bupropion (sustained-release)	34	23.9	14	20.3	20	27.4			
Citalopram and buspirone	27	19.0	10	14.5	17	23.3			
Sertraline	21	14.8	11	15.9	10	13.7			
Venlafaxine (extended-release)	30	21.1	13	18.8	17	23.3			
Maximum side effect frequency in prior level <sup>c</sup>							$\chi^2=7.7247$	3	0.0521
No side effects	27	20.3	13	20.6	14	20.0			
10%–25% of the time	37	27.8	22	34.9	15	21.4			
50%–75% of the time	40	30.1	12	19.0	28	40.0			
90%–100% of the time	29	21.8	16	25.4	13	18.6			
Maximum side effect intensity in prior level <sup>c</sup>							$\chi^2=2.1913$	3	0.5337
No side effects	27	20.3	13	20.6	14	20.0			
Minimal to mild	29	21.8	17	27.0	12	17.1			
Moderate to marked	55	41.4	23	36.5	32	45.7			
Severe to intolerable	22	16.5	10	15.9	12	17.1			
Maximum side effect burden in prior level <sup>c</sup>							$\chi^2=3.1096$	3	0.3750
No side effects	35	26.3	18	28.6	17	24.3			
Minimal to mild	41	30.8	22	34.9	19	27.1			
Moderate to marked	46	34.6	17	27.0	29	41.4			
Severe to intolerable	11	8.3	6	9.5	5	7.1			
Exited prior level due to intolerance	25	17.6	9	13.0	16	21.9	$\chi^2=1.9258$	1	0.1652
	Mean	SD	Mean	SD	Mean	SD			
Percentage change during prior level in score on Quick Inventory of Depressive Symptomatology—Clinician Rating	0.6	84.4	6.7	113.4	-5.3	41.7	$\chi^2=0.2091$	1	0.6474

<sup>a</sup> Sums do not always equal N because of missing data; percentages are based on number of subjects for whom data were available.

<sup>b</sup> Chi-square and Kruskal-Wallis.

<sup>c</sup> The maximum side effect intensity, frequency, and burden in previous level refer to the highest ratings participants gave these measures over the course of all clinic visits during STAR\*D Level 2 or 2A.

### Prior Treatment

As shown in Table 3, in the prior treatment step (Level 2 or 2A), participants had been undergoing treatment with sustained-release bupropion, sertraline, extended-release venlafaxine, citalopram plus sustained-release bupropion, or citalopram plus buspirone, in proportions ranging from about 15% to 24%. Some 43% had been receiving citalopram and thus continued to receive citalopram in Level 3, augmented with either lithium or T<sub>3</sub>. Overall mean daily doses at exit from treatment Levels 2 or 2A were as follows: sustained-release bupropion, 395.0 mg (SD=48.0); sertraline, 183.3 mg (SD=24.2); extended-release venlafaxine, 316.3 mg (SD=73.5); sustained-release bupropion (combined with citalopram), 326.5 mg (SD=87.2); and buspirone (combined with citalopram), 46.7 mg (SD=15.2). The mean durations of Level 2 treatments were as follows: sustained-release bupropion, 12.7 weeks (SD=

2.4); sertraline, 12.1 weeks (SD=3.0); extended-release venlafaxine, 12.9 weeks (SD=2.4); sustained-release bupropion combined with citalopram, 11.3 weeks (SD=3.8); and buspirone combined with citalopram, 10.4 weeks (SD=4.1). Because participants who were taking citalopram in Level 2 had already been taking it as monotherapy in Level 1, the mean time on citalopram was 22.0 weeks (SD=4.5), almost twice as long as for the other antidepressants administered in Level 2. No statistically significant differences in the durations of these treatments were observed between the lithium and T<sub>3</sub> groups.

The median change in QIDS-C scores for these participants during Level 2 or 2A treatment was 10.8% (range, 70%–900%); one patient entered Level 2 with a QIDS-C score of 1 and left with a score of 10). During these treatment levels, 51.9% of participants had side effects more than half of the time, 57.9% had at least moderate side ef-

**TABLE 4. Treatment, Outcome, and Side Effect Measures Among Outpatients With Major Depressive Disorder Receiving Lithium or T<sub>3</sub> Augmentation Treatment in STAR\*D Level 3, by Augmentation Agent<sup>a</sup>**

Treatment, Outcome, and Side Effect Measures	Total (N=142)		Augmentation Agent				Analyses			
			Lithium (N=69)		T <sub>3</sub> (N=73)		Test Statistic <sup>b</sup>	df	p	
	N	%	N	%	N	%				
<b>Treatment</b>										
Treatment duration										
<4 weeks	25	17.6	13	18.8	12	16.4	$\chi^2=0.1411$	1	0.7072	
<8 weeks	49	34.5	26	37.7	23	31.5	$\chi^2=0.5984$	1	0.4392	
<12 weeks	70	49.3	36	52.2	34	46.6	$\chi^2=0.4448$	1	0.5048	
	<b>Mean</b>	<b>SD</b>	<b>Mean</b>	<b>SD</b>	<b>Mean</b>	<b>SD</b>				
Total treatment duration (weeks)	9.6	5.2	9.3	5.4	9.9	5.0	$\chi^2=0.3807$	1	0.5372	
Number of postbaseline visits	3.8	1.5	3.8	1.5	3.7	1.5	$\chi^2=0.0853$	1	0.7703	
Time to first postbaseline visit (weeks)	2.6	1.3	2.5	1.1	2.7	1.5	$\chi^2=0.2830$	1	0.5948	
Exit dose (mg/day)			859.8	373.1	45.2	11.4				
Exit dose duration (weeks)	3.1	2.1	3.0	1.7	3.2	2.4	$\chi^2=0.0155$	1	0.9010	
<b>Outcome measures<sup>c</sup></b>										
Score at exit on Quick Inventory of Depressive Symptomatology—Self-Report	10.4	5.2	11.4	5.2	9.5	5.0	t=1.54	1	0.1271	
Percentage change from Level 3 baseline in score on Quick Inventory of Depressive Symptomatology—Self-Report	-14.7	33.8	-13.6	27.2	-15.7	39.1	t=0.79	1	0.4330	
	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>				
Remission, defined as score $\leq 7$ on Hamilton Depression Rating Scale	29	20.4	11	15.9	18	24.7	$\chi^2=0.63$	1	0.4258	
Remission, defined as score $\leq 5$ at exit on Quick Inventory of Depressive Symptomatology—Self-Report	27	19.1	9	13.2	18	24.7	$\chi^2=1.50$	1	0.2205	
Response, defined as $\geq 50\%$ reduction of baseline score on Quick Inventory of Depressive Symptomatology—Self-Report	28	19.9	11	16.2	17	23.3	$\chi^2=1.70$	1	0.1918	
<b>Side effects and adverse events</b>										
Maximum side effect frequency <sup>d</sup>							$\chi^2=8.0370$	3	0.0453	
No side effects	24	18.0	12	18.8	12	17.4				
10%–25% of the time	33	24.8	12	18.8	21	30.4				
50%–75% of the time	42	31.6	17	26.6	25	36.2				
90%–100% of the time	34	25.6	23	35.9	11	15.9				
Maximum side effect intensity <sup>d</sup>							$\chi^2=1.1182$	3	0.7727	
No side effects	24	18.0	12	18.8	12	17.4				
Minimal to mild	28	21.1	11	17.2	17	24.6				
Moderate to marked	53	39.8	27	42.2	26	37.7				
Severe to intolerable	28	21.1	14	21.9	14	20.3				
Maximum side effect burden <sup>d</sup>							$\chi^2=0.8059$	3	0.8481	
No side effects	29	21.8	13	20.3	16	23.2				
Minimal to mild	42	31.6	22	34.4	20	29.0				
Moderate to marked	49	36.8	22	34.4	27	39.1				
Severe to intolerable	13	9.8	7	10.9	6	8.7				
At least one serious adverse event	8	5.6	5	7.2	3	4.1	$\chi^2=0.6565$	1	0.4178	
Exited because of intolerance	23	16.2	16	23.2	7	9.6	$\chi^2=4.8331$	1	0.0279	

<sup>a</sup> Sums do not always equal N because of missing data; percentages are based on number of subjects for whom data were available.

<sup>b</sup> Student's t and chi-square; Kruskal-Wallis chi-square is used for continuous variables and Wald chi-square where analyses are adjusted.

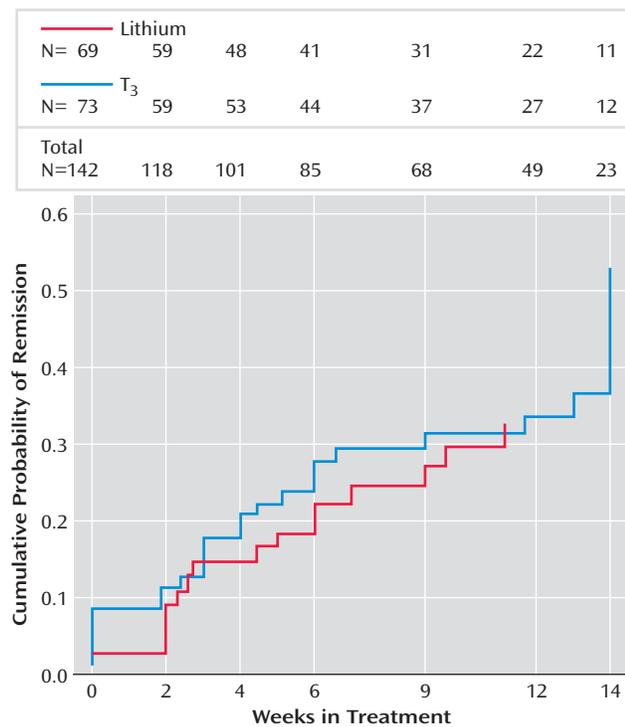
<sup>c</sup> Analyses were adjusted for treatment acceptability category, age at onset of first depressive episode, and score at entry to STAR\*D treatment Level 3 on the Quick Inventory of Depressive Symptomatology—Self-Report.

<sup>d</sup> The maximum side effect intensity, frequency, and burden refer to the highest ratings participants gave these measures over the course of all clinic visits they made while receiving Level 3 augmentation treatment.

fect intensity, and 42.9% had at least a moderate side effect burden. No statistically significant differences were observed between the lithium and T<sub>3</sub> groups in any of these variables. Although the mean baseline QIDS-SR score at

entry into Level 3 was higher in the lithium group, the difference was clinically, although not statistically, significant, so baseline QIDS-SR score was used as an adjustment factor for the analyses of outcomes.

FIGURE 2. Cumulative Probability of Remission<sup>a</sup> for Outpatients With Major Depressive Disorder Receiving Lithium or T<sub>3</sub> Augmentation Treatment in STAR\*D Level 3, by Time in Treatment



<sup>a</sup> Remission was defined as the first score score  $\leq 5$  on the Quick Inventory of Depressive Symptomatology—Self-Report.

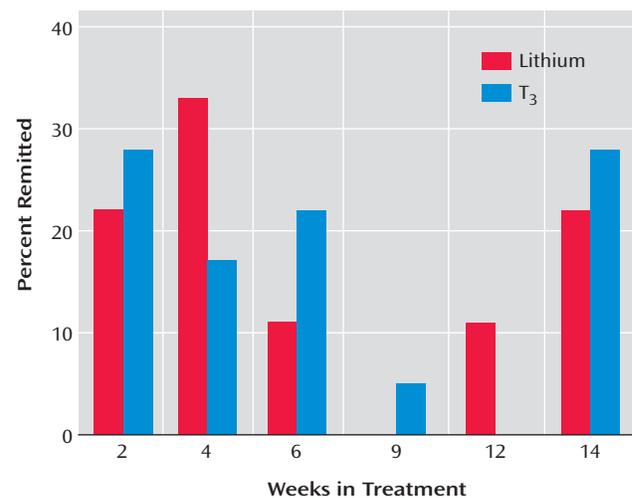
**Duration and Dose of Lithium and T<sub>3</sub> Augmentation**

The overall mean duration of augmentation treatment during Level 3 was 9.6 weeks (SD=5.2); 17.6% of the participants received augmentation treatment for less than 4 weeks and 34.5% for less than 8 weeks (Table 4). The mean time on the exit dose was 3.1 weeks (SD=2.1). The duration of treatment was not significantly different between the two groups. Mean daily doses at exit were 859.8 mg (SD=373.1) for lithium and 45.2  $\mu$ g (SD=11.4) for T<sub>3</sub>. The median lithium blood level, which was assessed in 39 (56.5%) of the 69 participants who received lithium augmentation, was 0.6 meq/liter.

**Outcomes for Lithium and T<sub>3</sub> Augmentation**

On the primary outcome measure, 15.9% of participants in the lithium group and 24.7% of those in the T<sub>3</sub> group achieved remission; the difference between groups was not significant after adjustment for treatment acceptability category, age at onset of first major depressive episode, and QIDS-SR score at entry into Level 3. There were no statistically significant differences in mean QIDS-SR scores at exit or in overall remission rates as assessed by the QIDS-SR (score  $\leq 5$  at exit from Level 3), the percentage reduction from the baseline QIDS-SR score, or the proportion of par-

FIGURE 3. For Outpatients With Major Depressive Disorder Receiving Lithium or T<sub>3</sub> Augmentation Treatment in STAR\*D Level 3 Who Achieved Remission<sup>a</sup> (N=29), Percentage of Those Who Remitted at Weeks 2, 4, 6, 9, 12, and 14



<sup>a</sup> Remission was defined as the first score score  $\leq 5$  on the Quick Inventory of Depressive Symptomatology—Self-Report.

ticipants who responded to augmentation treatment (reduction of  $\geq 50\%$  from baseline QIDS-SR). No significant differences were observed in the proportion of participants who reached remission with lithium or T<sub>3</sub> augmentation for those who were taking citalopram, sertraline, sustained-release bupropion, or extended-release venlafaxine (data not shown).

Among participants who responded, the mean time to response was 5.7 weeks (SD=5.1) for participants receiving lithium augmentation and 6.0 weeks (SD=5.1) for those receiving T<sub>3</sub> augmentation. Among those who remitted, the mean time to remission was 7.4 weeks (SD=4.4) for those receiving lithium and 6.6 weeks (SD=4.8) for those receiving T<sub>3</sub>. Kaplan-Meier survival estimates showed that time to response (log rank=0.065, p=0.80) and time to remission (log rank=1.0205, p=0.3124) were not significantly different between the two groups (Figure 2).

Figure 3 shows the proportions of participants, among all those who eventually achieved remission, who remitted after 2, 4, 6, 9, 12, and 14 weeks of treatment. At week 2, about one-quarter of those who eventually remitted from each treatment group reached remission, and at week 4, another 33% from the lithium group and another 17% from the T<sub>3</sub> group reached remission. The cumulative proportions of participants, among all those who eventually remitted, who had remitted by weeks 4 and 6 were 55% and 66% for the lithium group and 45% and 67% for the T<sub>3</sub> group; 22% in the lithium group and 28% in the T<sub>3</sub> group did not reach remission until week 14. None of the baseline variables listed in Table 2 differentiated those who remitted in the two groups.

## Side Effects and Tolerability

Few participants experienced serious adverse events, and no serious psychiatric adverse events occurred. More of those in the lithium group reported the maximum frequency, intensity, and burden of side effects, although the difference between groups was significant only for frequency. Significantly more of those taking lithium exited treatment because of side effects. In general, the odds of experiencing side effects were higher in the lithium group relative to the T<sub>3</sub> group, independent of the effect of treatment acceptability category, age at onset of first major depressive episode, severity of depressive symptoms at baseline for Level 3, and side effect measures (frequency, intensity, and burden) in the prior level. However, these results were significant only with respect to frequency of side effects (odds ratio=2.0,  $p=0.0465$ ), and not the intensity (odds ratio=1.4,  $p=0.3512$ ) and burden (odds ratio=1.3,  $p=0.4531$ ) of side effects.

## Discussion

### Effectiveness and Tolerability

This is the first randomized, controlled effectiveness study to compare lithium and T<sub>3</sub> augmentation for outpatients with nonpsychotic major depressive disorder who had not obtained adequate benefit from two prior medication treatment attempts. Only a modest proportion of participants achieved remission. The two treatment groups did not differ significantly in the proportion who responded or remitted, in time to response or remission, or in exit measures of depressive symptom severity. While no significant differences were observed in the symptom-based outcome measures between the two groups, the group receiving T<sub>3</sub> augmentation consistently had greater proportions of responders and remitters, greater decreases in HAM-D and QIDS-SR scores, and greater toleration of treatment.

The modest remission rates observed with lithium augmentation may have been due to the low doses used as a result of limited toleration of side effects. Nevertheless, these results probably reflect what clinicians can expect with lithium augmentation in actual practice. The doses of T<sub>3</sub> used in this study approximate those used in placebo-controlled trials, and given the drug's tolerability, they were easily reached. For both lithium and T<sub>3</sub> augmentation, the duration of treatment was not only sufficient, but it was substantially greater than those of previously reported augmentation trials of these agents, none of which exceeded 6 weeks (6, 20, 21). In this study, the mean duration of augmentation treatment was more than 9 weeks, and hence participants very likely had an adequate exposure to the augmentation agents. The modest remission rates may reflect problems with tolerability of lithium augmentation and the difficult-to-treat nature of many cases of major depression in real-world settings.

## Patient Perspective

“Ms. B,” a 44-year-old divorced white woman, became depressed after losing her job as a secretary in a law firm. She initially sought treatment from her primary care physician and then entered the STAR\*D study. Ms. B met criteria for major depressive disorder and generalized anxiety disorder. Her baseline QIDS-SR score was 16. After 12 weeks on citalopram, her QIDS-SR score was 10. She was then randomly assigned to augmentation with buspirone; she soon experienced gastrointestinal distress, and she stopped taking buspirone after 6 weeks. She elected to try one more augmentation agent and was randomly assigned to T<sub>3</sub> augmentation. When she started T<sub>3</sub> augmentation, her QIDS-SR score was 12. After 4 weeks, she felt that her mood and energy had lifted substantially. She felt better able to make decisions, organize, and prioritize and felt that she was able and ready to look for another job. “I felt as if my brain suddenly had oxygen,” she said, “and everything became clearer.” After 12 weeks, Ms. B felt back to normal, and her QIDS-SR score was 0.

The remission rates observed in this study are consistent with those reported in other recent augmentation trials, including lithium augmentation of nortriptyline (21) and fluoxetine (8) and T<sub>3</sub> augmentation of fluoxetine (12). Compared with results reported by Joffe et al. (21) in the only prior study comparing augmentation with lithium and T<sub>3</sub> after unsatisfactory antidepressant monotherapy, our results show a substantially lower proportion of participants who experienced a response to treatment. Yet in the Joffe et al. study, both the duration of treatment with antidepressants before augmentation and the duration of augmentation treatment were substantially shorter than in our study. Joffe et al. studied 50 participants who received 2 weeks of augmentation with lithium (N=17), T<sub>3</sub> (N=17), or placebo (N=16) after 5 weeks of prospective treatment with either imipramine or desipramine. Although remission rates were not reported, response rates were around 60% for both active augmentation agents and 19% for placebo. One possible explanation for the greater percentage of responders in the Joffe et al. study is that the augmentation may have sped up response to a brief course of antidepressant therapy. It may be, too, that augmentation strategies are more efficacious in treatment with tricyclic antidepressants (8). A third possibility is that participants in our study, who had already undergone two prior medication trials without achieving remission, had more difficult-to-treat forms of depression. Joffe et al. examined the effects of augmentation after a single, relatively brief trial of antidepressant monotherapy. In an earlier STAR\*D report (3), for participants who had gone through one medication trial (treatment Level 1) without achieving remission and then underwent augmentation

with bupropion or buspirone (Level 2), remission rates and response rates were both around 30% (3).

The T<sub>3</sub> group appeared to tolerate the augmentation better than the lithium group. Almost twice as many participants in the lithium group exited augmentation treatment because of side effects. Few in either group had serious adverse events. Given the greater volume of evidence for lithium augmentation and the paucity of randomized trials of T<sub>3</sub> augmentation with the newer generation of antidepressants, the results we observed with T<sub>3</sub> augmentation were better than expected. Overall, if a clinician has a choice between lithium and T<sub>3</sub> augmentation, these results suggest slight advantages with T<sub>3</sub>, especially for patients who have already had two unsuccessful treatments.

### Strengths and Limitations

Among the strengths of this study are that it was conducted in representative real-world practices with patients who presented for care—they were not recruited through advertising. Participants had undergone two prospectively administered medication trials that had failed to bring them to remission. This effectiveness design enhances the ecological validity and the generalizability of the study's results. Medication treatment was open-label, and clinicians used evidence-based guidelines to optimize dose and duration of treatment. The primary outcome measures were collected by assessors who were blind to participants' treatments.

This study also had several limitations. First, it did not have the statistical power to reliably detect small differences in remission rates between the augmentation therapies. Second, we did not systematically assess laboratory indices, including pretreatment assessment of thyroid function and serial monitoring of lithium levels. Third, we used open-label administration of the augmentation therapies. Fourth, the study design did not include a placebo control group—a particularly noteworthy limitation, given the low remission rates: it is not possible to confirm that either augmentation therapy was more effective than supportive clinical management along with ongoing antidepressant therapy. Finally, participants in the lithium augmentation group took relatively low doses because of intolerable side effects, and as a result they had minimal blood lithium levels. This limitation leaves open the question of whether keeping the doses of lithium small limits its effectiveness for augmentation (6, 7). Yet, as noted earlier, patients in this study took the highest tolerable doses, reflecting the reality of prescribing lithium to patients with major depressive disorder who present for care in everyday practice.

### Conclusion

Difficult-to-treat depression presents a serious challenge for clinicians and patients. This study highlights the need for strategies beyond following a simple sequence of treatments. In a sample of outpatients with major depressive dis-

order who had not reached remission despite two prior prospective treatments, we observed modest remission rates with lithium and T<sub>3</sub> augmentation. Our results suggest that in cases where an augmentation trial is deemed appropriate for the patient, T<sub>3</sub> has slight advantages over lithium in effectiveness and tolerability. T<sub>3</sub> also offers the advantages of ease of use and lack of a need for blood level monitoring.

The focus of this study was on the acute outcome of augmentation treatment. Future analyses of STAR\*D data will describe longer-term outcomes for patients who entered the 12-month naturalistic follow-up stage of the project while continuing lithium or T<sub>3</sub> augmentation.

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### CME Disclosure

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APA policy requires disclosure by CME authors of unapproved or investigational use of products discussed in CME programs. Off-label use of medications by individual physicians is permitted and common. Decisions about off-label use can be guided by scientific literature and clinical experience.

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