T3 Augmentation in Major Depressive Disorder

Cristina Ivan, PGY3
Background

- MDD: common and disabling illness that leads to significant reductions in quality of life and considerable cost to society

- Delayed response (2-6 weeks)

- Full remission < 50%

- Remission even after two optimally delivered trials < 50%
Pharmacological Mechanisms of T3 Augmentation of Antidepressant Action

- Via nuclear receptors on gene expression
- Effects on membrane-bound receptors
- Actions at the second-messenger level
- Interactions of T3 with mechanisms involved in noradrenergic and serotonergic neurotransmission
- Subclinical thyroid abnormalities: prevalent in patients with MDD
Evidence

- Efficacy of T3 augmentation found mainly in combination with TCAs, and the trials were done in less treatment-resistant patients than those who typically receive TCAs today.

- Women seem to respond better than men.

- Most studies showed equivocal evidence.
PICO

- In outpatients with MDD
- Does triiodothyronine augmentation
- Compared to placebo/ lithium augmentation
- Improve remission rates
Search

- PubMed
- Search terms: different combination of depression, triiodothyronine, major depressive disorder, treatment resistant depression
- Two large, randomized, double-blind, placebo-controlled studies
- One large, randomized, open label, controlled study
Combined Treatment With Sertraline and Liothyronine in Major Depression

A Randomized, Double-blind, Placebo-Controlled Trial

Rena Cooper-Kazaz, MD; Jeffrey T. Apter, MD; Revital Cohen, MA; Leonid Karagichev, MD; Said Muhammed-Moussa, MD; Daniel Grupper, MD; Taly Drori, MD; Michael E. Newman, PhD; Harold A. Sackeim, PhD; Benjamin Glaser, MD; Bernard Lerer, MD

ARCH GEN PSYCHIATRY/VOL 64, JUNE 2007
Objective

Determine the antidepressant efficacy and safety of liothyronine sodium (triiodothyronine) when administered concurrently with sertraline hydrochloride to patients with major depressive disorder.
Study Design

Double-blind, randomized, 8-week, placebo controlled trial.
Setting/ Patients

- Outpatient referral centers: Hadassah-Hebrew University Medical Center (the central site), the Be’er Ya’akov Mental Health Center, and Global Medical Institutes.

- 124 adult outpatients meeting unmodified *DSM-IV* criteria for major depressive disorder without psychotic features.
Interventions

- sertraline hydrochloride (50 mg/d for 1 week; 100 mg/d thereafter) plus liothyronine sodium (20-25 μg/d for 1 week; 40-50 μg/d thereafter) or
- sertraline plus placebo for 8 weeks.

- Benzodiazepines, zolpidem, or zopiclone were permitted for sedation when needed.
Outcome Measures

- **Primary outcome measure**: categorical response to treatment (50% decrease in scores on the 21-item Hamilton Rating Scale for Depression from baseline to study endpoint).

- **Secondary outcome measure**: Remission rate (final Hamilton Rating Scale for Depression score < 6)
Methods: Patients

Inclusion criteria

- Male or female outpatients
- 18 to 70 years
- *DSM-IV* diagnosis of MDD without psychotic features
- a total 21-item Hamilton Rating Scale for Depression (HRSD) score of at least 16 with item 1 (depressed mood) scored 2 or greater.
Methods: Patients

Exclusion criteria

- significant suicidal risk
- any past or current thyroid disease (including subclinical hypothyroidism)
- a medical condition that could limit prescription of the study medication or make liothyronine treatment unsafe
- lifetime history of alcohol or other drug dependence or abuse in the preceding 12 months
- previous treatment with sertraline.
- pregnant, lactating women
Study Design

- 60% response rate to sertraline and a 25% better response in nonresistant patients receiving both drugs was anticipated.

- Power analysis indicated that a sample size of 100 would be needed to have 80% power to detect a difference in response rate between sertraline-liothyronine and sertraline-placebo that would be significant at p< 0.05, in the context of an intent-to-treat analysis including all patients who completed at least 1 clinic visit after randomization.
197 Patients Assessed for Eligibility

- 73 Excluded
  - 36 Did Not Meet Inclusion Criteria
  - 21 Met Any Exclusion Criterion
  - 16 Refused to Participate

124 Randomized to Treatment

64 Sertraline + Liothyronine (SERT-T₃)

- 11 Patients Discontinued
  - 6 Withdraw Consent
  - 1 Adverse Effects
  - 4 Other

53 SERT-T₃
Completed at Least 1 wk of Treatment Included in Final Analysis

13 Patients Discontinued
- 4 Withdraw Consent
- 6 Adverse Effects
- 2 Lost to Follow-up
- 1 Protocol Violation

60 Sertraline + Placebo (SERT-PLB)

- 10 Patients Discontinued
  - 4 Withdraw Consent
  - 6 Adverse Effects

50 SERT-PLB
Completed at Least 1 wk of Treatment Included in Final Analysis

13 Patients Discontinued
- 5 Withdraw Consent
- 4 Adverse Effects
- 2 Lack of Efficacy
- 1 Lost to Follow-up
- 1 Suicidality

77 Patients Completed 8 wk
37 SERT-PLB
40 SERT-T₃
Study Design
Baseline assessments

- Comprehensive medical evaluation and determination of TSH, total T3, and FT4’

- Psychiatric evaluation at baseline included the Hebrew version of the semistructured Mini–International Neuropsychiatric Interview, the HRSD, and a 100-mm visual analog scale (VAS) for self-rating of mood.
Study Design

- Antidepressant trials during the current episode were regarded as adequate if the dose of antidepressant was optimum and the length of treatment was 8 weeks.

- Treatment resistance was defined as failure to respond to at least 2 adequate antidepressant trials.
Study Design

- At follow-up visits, baseline evaluations other than the Mini–International Neuropsychiatric Interview were repeated.

- Adverse effects inventory consisting of 14 items and an unstructured inquiry.

- Thyroid measures were reevaluated at the last visit.
STATISTICAL ANALYSES

- *t* tests for continuous variables
- *Chi-square* tests for categorical variables
- Nominal logistic regression analysis
- Longitudinal random regression analysis
- Repeated measures analysis of covariance
- 2-way analysis of variance
Results

- No significant difference in demographic or clinical features.
- No patients with resistant depression.
- 4 (8%) of the 53 patients in the sertraline-liothyronine group and 7 (13%) of the 50 patients in the sertraline-placebo group had received an adequate antidepressant trial during the current episode.
Table 1. Demographic and Background Features of the Patient Groups

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SERT-T₃ (n = 53)</td>
</tr>
<tr>
<td>Age, y</td>
<td>45.15 ± 58.00</td>
</tr>
<tr>
<td>Sex, No. (%) F</td>
<td>29 (55)</td>
</tr>
<tr>
<td>Education, y</td>
<td>14.45 ± 2.77</td>
</tr>
<tr>
<td>Age at first depressive episode, y</td>
<td>33.89 ± 13.84</td>
</tr>
<tr>
<td>Duration of current episode, wk</td>
<td>47.29 ± 69.27</td>
</tr>
<tr>
<td>No. of depressive episodes</td>
<td>3.00 ± 2.20</td>
</tr>
<tr>
<td>No. of depressive episodes per year at risk</td>
<td>0.36 ± 0.31</td>
</tr>
<tr>
<td>Antidepressant trial during current episode, No. (%)</td>
<td>13 (25)</td>
</tr>
<tr>
<td>Adequate antidepressant trial during current episode, No. (%)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Baseline HRSD score</td>
<td>20.69 ± 4.91</td>
</tr>
</tbody>
</table>
Results

The sertraline-liothyronine group showed significant advantage over the sertraline-placebo group in both response and remission rate, as defined by the HRSD, and in remission rate based on VAS scores.
<table>
<thead>
<tr>
<th></th>
<th>HRSD</th>
<th>VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Response</td>
<td>Remission</td>
</tr>
<tr>
<td>SERT-T₃, No. (%) (n = 53)</td>
<td>37 (70)</td>
<td>31 (58)</td>
</tr>
<tr>
<td>SERT- PLB, No. (%) (n = 50)</td>
<td>25 (50)</td>
<td>19 (38)</td>
</tr>
<tr>
<td>χ²</td>
<td>5.64</td>
<td>5.14</td>
</tr>
<tr>
<td>P value</td>
<td>.02</td>
<td>.02</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>2.93 (1.23-7.35)</td>
<td>2.69 (1.16-6.49)</td>
</tr>
</tbody>
</table>
Results

- Baseline T3 values in the sertraline-liothyronine group were lower in patients who would later be classified as remitters than in those classified as nonremitters.

- Among patients treated with sertraline-liothyronine, greater reductions in thyrotropin values over the treatment course were associated with superior clinical outcome.

- Duration of current depressive episode was the only clinical characteristic significantly associated with the antidepressant effect of liothyronine.
Adverse Effects

- There were no significant differences in the frequency of adverse effects.
- 2 serious events led to withdrawal from the trial: a patient receiving sertraline-placebo developed severe suicidal ideation and a patient receiving sertraline-liothyronine required emergency thoracic surgery for a reason unrelated to the study.
## Adverse Effects

### Table 5. Adverse Effects by Treatment Group

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>SERT-T$_3$ (n = 53)</th>
<th>SERT-PLB (n = 50)</th>
<th>$\chi^2$</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite problems</td>
<td>34 (64)</td>
<td>34 (68)</td>
<td>0.17</td>
<td>.68</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>36 (68)</td>
<td>34 (68)</td>
<td>0.00</td>
<td>.99</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>31 (58)</td>
<td>34 (68)</td>
<td>1.00</td>
<td>.32</td>
</tr>
<tr>
<td>Nervousness</td>
<td>35 (66)</td>
<td>32 (64)</td>
<td>0.05</td>
<td>.83</td>
</tr>
<tr>
<td>Sleep difficulty</td>
<td>36 (68)</td>
<td>31 (62)</td>
<td>0.40</td>
<td>.53</td>
</tr>
<tr>
<td>Sweating</td>
<td>24 (45)</td>
<td>31 (62)</td>
<td>2.89</td>
<td>.09</td>
</tr>
<tr>
<td>Headache</td>
<td>32 (60)</td>
<td>28 (56)</td>
<td>0.20</td>
<td>.65</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (45)</td>
<td>27 (54)</td>
<td>0.78</td>
<td>.38</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26 (49)</td>
<td>25 (50)</td>
<td>0.01</td>
<td>.92</td>
</tr>
<tr>
<td>Dizziness</td>
<td>30 (57)</td>
<td>25 (50)</td>
<td>0.45</td>
<td>.50</td>
</tr>
<tr>
<td>Weight problems</td>
<td>20 (38)</td>
<td>22 (44)</td>
<td>0.42</td>
<td>.52</td>
</tr>
<tr>
<td>Palpitations</td>
<td>25 (47)</td>
<td>20 (40)</td>
<td>0.54</td>
<td>.46</td>
</tr>
<tr>
<td>Sexual arousal problems</td>
<td>14 (26)</td>
<td>20 (40)</td>
<td>2.15</td>
<td>.14</td>
</tr>
<tr>
<td>Orgasm problems</td>
<td>15 (28)</td>
<td>18 (36)</td>
<td>0.70</td>
<td>.40</td>
</tr>
<tr>
<td>Constipation</td>
<td>19 (36)</td>
<td>17 (34)</td>
<td>0.04</td>
<td>.84</td>
</tr>
<tr>
<td>Sexual desire problems</td>
<td>7 (13)</td>
<td>8 (16)</td>
<td>0.16</td>
<td>.69</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td>0.15</td>
<td>.70</td>
</tr>
<tr>
<td>Flashes</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td>1.17</td>
<td>.28</td>
</tr>
<tr>
<td>Chest constriction</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>0.41</td>
<td>.52</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>0.41</td>
<td>.52</td>
</tr>
</tbody>
</table>
Conclusion

- The results of this study provide statistically significant support for enhancement of the antidepressant effect of the SSRI sertraline by concurrent treatment with liothyronine.
- The enhancement manifested as an approximately 20% greater rate of response and remission.
- Patients receiving sertraline-liothyronine were 2.9 times more likely to respond and 2.7 times more likely to achieve remission than were patients treated with sertraline alone.
- The antidepressant effect of liothyronine could be directly linked to thyroid function.
Strengths

- Large sample size
- Double-blind, randomized, placebo controlled trial
- Controlled for a number of potential confounders
Limitations

- No washout period for previous antidepressant treatment before starting the study medication.

- The maximum dosage of sertraline hydrochloride was 100 mg/d.

- The hormone assays were performed in different laboratories.
Limitations

- Outpatient study

- Patients with a lifetime history of alcohol or other drug dependence or of abuse in the preceding 12 months were excluded, as were patients with a greater than minimal level of suicidal ideation.

- Are the findings are applicable to SSRIs other than sertraline?
Triiodothyronine Addition to Paroxetine in the Treatment of Major Depressive Disorder

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The Journal of Clinical Endocrinology & Metabolism 89(12):6271–6276, 2004
Objective

Investigate the efficacy of T3 addition to paroxetine in major depression
Study Design

- Double-blind, randomized, 8-week, placebo controlled trial
Setting/ Patients

- Outpatient
- October 1999 and June 2002; at two academic outpatient clinics (Departments of Psychiatry, Academic Medical Center, University of Amsterdam, and Vrije Universiteit Medical Center, Amsterdam).
- 113 patients with MDD
Patients: Inclusion Criteria

- 18-65 yr of age
- MDD per DSM-IV
- A score of 16 or more on the 17-item Hamilton Rating Scale for Depression (HRSD) at baseline
Patients: Exclusion Criteria

- bipolar disorder
- a history of psychotic symptoms
- severe cognitive disturbances
- severe antisocial or borderline personality disorder
- current suicidal risk
- substance abuse
- overt thyroid or adrenocortical disease (physical examination)
- angina pectoris; any serious unstable medical condition
- pregnancy or lactation
- corticosteroids, thyroid hormone, or antithyroid or psychotropic drugs during the last 3 months before inclusion, with the exception of a low dose of benzodiazepines (equivalent to 30 mg oxazepam or 10 mg temazepam daily).
Interventions

8 wk of double-blind outpatient treatment with low-dose T3 (25 g), high-dose T3 (25 g twice daily), or placebo in addition to paroxetine 30 mg daily.
Figure 1. Flowchart of participation in the study.
**Outcome Measures**

- **Primary Outcome**: the score on the 17-item HRSD at 8 wk.
  
  *Response* was defined as a 50% or greater reduction in the HRSD score from baseline to wk 8; *Remission* was defined as an end point HRSD score of 8 or less.

- **Secondary outcomes**: response in terms of the MADRS, HARS and BDI scales (50% reduction), response on the CGI (end point score 1 or 2), and remission as measured by the MADRS (end point score < 2).
Study Design

- Efficacy assessments were performed at 1, 2, 4, 6, and 8 wk after initiation of treatment.

- Efficacy assessments were made with the 17-item HRSD, the Montgomery Åsberg Depression Rating Scale (MADRS), the Hamilton Anxiety Rating Scale (HARS), the Beck Depression Inventory (BDI), and the Clinical Global Impression Scale (CGI).
Study Design

- Blood pressure and heart rate were measured at every visit.
- Spontaneous mentioned adverse events were documented at every visit.
- At 1, 4, and 8 wk, patients were asked whether they had experienced any of 11 common adverse events of T3 and/or paroxetine, whether or not thought to be related to treatment.
- In case of severe complaints a board-certified psychiatrist was consulted to discuss whether participation should be discontinued.
- Thyroid function tests were measured at baseline and end point.
Interim Analysis

- The study was to enroll 150 patients with MDD.

- With 75 index patients and 75 controls, the study had sufficient power (90%) to detect an increase in response rates from 60 to 85%.

- After the first 100 participants had completed the trial, an interim analysis was to occur.

- In May 2002 the data-monitoring committee advised to terminate trial enrollment because interim analysis revealed no effect whatsoever of T3 addition, compared with placebo addition.
Statistical Analysis

- *Paired t tests* were performed for comparison of baseline vs. end point outcome measurements within treatment groups.
- Differences between groups were compared by means of *chi-square* and *ANOVA*.
- More patients were randomized to placebo to allow for two contrasts in the analyses after overall *ANOVA*: 1) T3 addition vs. placebo addition, and 2) a dose-dependent effect of T3 addition.
Results

- Analyses revealed a significant improvement in the HRSD scores from baseline to wk 8 (or the last follow-up visit) within all three groups.
- Similar significant improvement was seen in the baseline vs. end point scores of all other psychiatric outcome measures.
- None of the primary or secondary outcome measures revealed any significant difference in treatment efficacy between the treatment groups.
### Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 53)</th>
<th>25 µg T₃ (n = 30)</th>
<th>50 µg T₃ (n = 30)</th>
<th>Total (n = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex (%)</td>
<td>34 (64%)</td>
<td>18 (60%)</td>
<td>18 (60%)</td>
<td>70 (62%)</td>
</tr>
<tr>
<td>Age (yr, mean ± SD)</td>
<td>46.2 ± 11.2</td>
<td>46.6 ± 10.9</td>
<td>47.0 ± 11.1</td>
<td>46.5 ± 11.0</td>
</tr>
<tr>
<td>White (%)</td>
<td>53 (100%)</td>
<td>30 (100%)</td>
<td>29 (97%)</td>
<td>112 (99%)</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (%)</td>
<td>7 (13%)</td>
<td>6 (20%)</td>
<td>4 (13%)</td>
<td>17 (15%)</td>
</tr>
<tr>
<td>Moderate (%)</td>
<td>35 (66%)</td>
<td>19 (63%)</td>
<td>22 (73%)</td>
<td>76 (67%)</td>
</tr>
<tr>
<td>Severe (%)</td>
<td>11 (21%)</td>
<td>5 (17%)</td>
<td>4 (13%)</td>
<td>20 (18%)</td>
</tr>
<tr>
<td>Course</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent (%)</td>
<td>29 (55%)</td>
<td>17 (57%)</td>
<td>13 (43%)</td>
<td>59 (52%)</td>
</tr>
<tr>
<td>Chronic major depression (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19 (36%)</td>
<td>19 (63%)</td>
<td>12 (40%)</td>
<td>50 (44%)</td>
</tr>
<tr>
<td>Thase &amp; Rush ≥ stage I (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20 (38%)</td>
<td>14 (47%)</td>
<td>9 (30%)</td>
<td>43 (38%)</td>
</tr>
<tr>
<td>Endocrine measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH basal (µU/ml, median, range)</td>
<td>1.90 (0.46–7.00)</td>
<td>1.80 (0.83–5.60)</td>
<td>2.20 (0.70–9.50)</td>
<td>1.90 (0.46–9.50)</td>
</tr>
<tr>
<td>fT4 basal (ng/dl, mean ± SD)</td>
<td>1.1 ± 0.15</td>
<td>1.1 ± 0.15</td>
<td>1.0 ± 0.18</td>
<td>1.06 ± 0.16</td>
</tr>
<tr>
<td>T₃ basal (ng/dl, mean ± SD)</td>
<td>143 ± 36</td>
<td>152 ± 34</td>
<td>136 ± 25</td>
<td>144 ± 34</td>
</tr>
</tbody>
</table>
Scores On Psychiatric Outcome Measures at Baseline and End-point

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Placebo (n = 50)</th>
<th>25 µg T₃ (n = 28)</th>
<th>50 µg T₃ (n = 28)</th>
<th>Test statistic (df); P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HRSD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean ± SD)</td>
<td>20.8 ± 3.1</td>
<td>21.0 ± 3.4</td>
<td>21.0 ± 3.8</td>
<td></td>
</tr>
<tr>
<td>End of treatment (mean ± SD)</td>
<td>11.5 ± 6.6</td>
<td>11.2 ± 5.7</td>
<td>13.0 ± 6.0</td>
<td></td>
</tr>
<tr>
<td>Difference (mean ± SD)</td>
<td>−9.4 ± 6.6</td>
<td>−9.8 ± 6.7</td>
<td>−8.3 ± 6.6</td>
<td>F = 0.420 (2, 103); P = 0.66</td>
</tr>
<tr>
<td>Responders (50% decrease; number, %)</td>
<td>23 46%</td>
<td>13 46%</td>
<td>13 46%</td>
<td>χ² = 0.002 (2); P = 0.99</td>
</tr>
<tr>
<td>Remission (HRSD ≤ 8; number, %)</td>
<td>18 36%</td>
<td>9 32%</td>
<td>9 32%</td>
<td>χ² = 0.175 (2); P = 0.92</td>
</tr>
<tr>
<td><strong>MADRS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean ± SD)</td>
<td>25.5 ± 6.9</td>
<td>26.2 ± 5.8</td>
<td>26.1 ± 6.5</td>
<td></td>
</tr>
<tr>
<td>End of treatment (mean ± SD)</td>
<td>12.3 ± 9.1</td>
<td>11.8 ± 8.6</td>
<td>14.4 ± 8.4</td>
<td></td>
</tr>
<tr>
<td>Difference (mean ± SD)</td>
<td>−13.1 ± 10.4</td>
<td>−14.4 ± 8.3</td>
<td>−11.7 ± 10.6</td>
<td>F = 0.524 (2, 103); P = 0.59</td>
</tr>
<tr>
<td><strong>BDI²</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean ± SD)</td>
<td>28.5 ± 7.4</td>
<td>27.9 ± 8.4</td>
<td>30.2 ± 8.1</td>
<td></td>
</tr>
<tr>
<td>End of treatment (mean ± SD)</td>
<td>16.9 ± 10.6</td>
<td>15.6 ± 8.6</td>
<td>19.4 ± 8.8</td>
<td></td>
</tr>
<tr>
<td>Difference (mean ± SD)</td>
<td>−11.6 ± 10.0</td>
<td>−12.2 ± 8.3</td>
<td>−10.9 ± 8.3</td>
<td>F = 0.154 (2, 102); P = 0.86</td>
</tr>
</tbody>
</table>
Results

- For treatment responders, the time interval to response did not significantly differ among the three groups.
- The course of the HRSD scores during the 8 wk of the trial was similar for all treatment groups.
- No different times to response were found if women were analyzed separately.
Conclusion

- Addition of T3 to paroxetine had no advantage over addition of placebo in the treatment of nonrefractory major depressive disorder.
- Treatment with T3: did not accelerate the response, did not influence response or remission rates.
- T3-addition groups: more adverse effects, compared with those on paroxetine alone, especially those who received 50 mcg T3 daily.
### Adverse effects at 8 wk

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n = 45)</th>
<th>25 μg T₃ (n = 26)</th>
<th>50 μg T₃ (n = 26)</th>
<th>Total (n = 97)</th>
<th>χ² (df; P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpitations</td>
<td>11 (24)</td>
<td>3 (11)</td>
<td>14 (54)</td>
<td>69 (29)</td>
<td>12.1 (2); 0.002</td>
</tr>
<tr>
<td>Sweating</td>
<td>24 (53)</td>
<td>21 (81)</td>
<td>20 (77)</td>
<td>65 (67)</td>
<td>7.2 (2); 0.027</td>
</tr>
<tr>
<td>Nervousness</td>
<td>6 (13)</td>
<td>8 (31)</td>
<td>10 (38)</td>
<td>24 (25)</td>
<td>6.3 (2); 0.043</td>
</tr>
<tr>
<td>Tremor</td>
<td>9 (20)</td>
<td>5 (19)</td>
<td>10 (38)</td>
<td>24 (25)</td>
<td>3.6 (2); 0.166</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (7)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>5 (5)</td>
<td>0.39 (2); 0.822</td>
</tr>
<tr>
<td>Headache</td>
<td>20 (44)</td>
<td>10 (38)</td>
<td>9 (35)</td>
<td>39 (40)</td>
<td>0.71 (2); 0.702</td>
</tr>
<tr>
<td>Somnolence</td>
<td>21 (47)</td>
<td>9 (35)</td>
<td>14 (54)</td>
<td>44 (45)</td>
<td>1.99 (2); 0.368</td>
</tr>
<tr>
<td>Insomnia</td>
<td>19 (42)</td>
<td>11 (42)</td>
<td>13 (50)</td>
<td>43 (44)</td>
<td>0.46 (2); 0.793</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>24 (53)</td>
<td>17 (65)</td>
<td>14 (54)</td>
<td>55 (57)</td>
<td>1.10 (2); 0.579</td>
</tr>
<tr>
<td>Decrease of libido</td>
<td>29 (64)</td>
<td>15 (58)</td>
<td>18 (69)</td>
<td>62 (64)</td>
<td>0.76 (2); 0.684</td>
</tr>
<tr>
<td>Erection/ejaculation problems</td>
<td>12 (27)</td>
<td>7 (27)</td>
<td>10 (38)</td>
<td>29 (30)</td>
<td>0.24 (2); 0.537</td>
</tr>
</tbody>
</table>
Strengths

- Double-blind, randomized, placebo controlled trial
- Large size
Limitations

- Mean HRSD score of 21
- Outpatients only
A Comparison of Lithium and T3 Augmentation Following Two Failed Medication Treatments for Depression: A STAR*D Report

Andrew A. Nierenberg, M.D., Maurizio Fava, M.D., Madhukar H. Trivedi, M.D., Stephen R. Wisniewski, Ph.D., Michael E. Thase, M.D., Patrick J. McGrath, M.D., Jonathan E. Alpert, M.D., Ph.D., Diane Warden, Ph.D., M.B.A., James F. Luther, M.A., George Niederehe, Ph.D., Barry Lebowitz, Ph.D., Kathy Shores-Wilson, Ph.D., A. John Rush, M.D., STAR*D Study Team

Am J Psychiatry 2006; 163:1519–1530
Objective

Compare the effectiveness of lithium versus triiodothyronine (T3) augmentation as a third-step treatment for patients with major depressive disorder.
Study Design

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.
Study Design

- Randomized
- Safety/Efficacy Study
- Model: Single Group Assignment
- Open Label
- Primary Purpose: Treatment
Setting/ Patients

- 07/ 2001- 04/ 2004

- 4,041 outpatients age 18 to 75 years

- 41 settings: primary care (N=18) and psychiatric practice (N=23)

- Nonpsychotic major depressive disorder (HAMD score 14 or greater)
Exclusion criteria

- pregnant, intending to become pregnant, or breastfeeding
- primary psychotic disorder
- substance abuse or dependence that required inpatient detoxification
- using medications excluded by the study
- seizure disorder or other general medical condition that contraindicated medications used in the first two protocol treatment steps
Intervention

- **Level 1**: citalopram

- **Level 2**: random assignment to 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).

- **Level 2A**: compared the effectiveness of two of the switch options (sustained-release bupropion and extended-release venlafaxine).

- **Level 3**: patients with an unsatisfactory response to two different medication treatments.
Level 3 Intervention

- Voluntary agreement to random assignment to a medication switch to either nortriptyline or mirtazapine versus random assignment to augmentation of their current antidepressant with lithium or T3.

- 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 T3.

- Those who would accept either a switch or an augmentation strategy were randomly assigned to one of the four treatment options.
Participant Flow Chart for Treatment Level 3

Level 3 (N=377)

- Augment only (N=127)
  - Lithium (N=62)  \(T_3\) (N=65)  Switch (N=0)

- Augment or switch (N=29)
  - Lithium (N=7)  \(T_3\) (N=8)  Switch (N=14)

- Switch only (N=221)
  - Lithium (N=0)  \(T_3\) (N=0)  Switch (N=221)

- Lithium (N=69)  \(T_3\) (N=73)  Switch (N=235)
Protocol Treatment

- Clinic visits at weeks 0, 2, 4, 6, 9, and 12.

- Lithium: 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.

- T3 was started at 25 μg/day for 1 week and then increased to the recommended dose of 50 μg/day.
Concomitant Treatments

- No stimulants, anticonvulsants, antipsychotics, mood stabilizers, antidepressants, alprazolam.

- Anxiolytics (except alprazolam) and sedative-hypnotics were permitted (including up to 200 mg of trazodone at bedtime for sleep).
Primary Outcome Measures

- **Symptom remission:** ≤ 7 on HAM-D.

- **Depressive symptoms severity and associated symptom features:** 30-item Quick-Inventory of Depressive Symptomatology—Clinician-Rated
The Secondary Outcome Measures

- **Remission** and **response** as assessed by the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR)

Remission: a total QIDS-SR score ≤5 at exit from treatment Level 3

Response: a reduction of ≥50% from the Level 3 baseline QIDS-SR score.
Statistical Methods

- **Student’s t tests and Kruskal-Wallis tests**: continuous baseline clinical and demographic characteristics, treatment features, and ratings of side effects and serious adverse events across treatments.

- **Chi-square tests**: discrete characteristics across treatments.

- **Logistic regression models**: 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.

- **Log-rank tests**: to compare the cumulative proportion of participants who experienced remission or response across the two treatment groups.
Results

- No statistically significant differences at baseline between the two groups with two exceptions:
  - a greater proportion of participants in the lithium group had their first major depressive episode before the age of 18
  - the mean age at onset of the first episode was lower in the lithium group.
Results

- No statistically significant differences at baseline between groups on measures for depressive symptoms, functioning, or depressive features.

- 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.

- The duration of treatment was not significantly different between the two groups.
Results

- Only a modest proportion of participants achieved remission: 15.9% of participants in the lithium group and 24.7% of those in the T3 group.

- 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, the percentage reduction from the baseline QIDS-SR score, or the proportion of participants who responded to augmentation treatment.
Results

- No significant differences in the proportion of participants who reached remission with lithium or T3 augmentation for those who were taking citalopram, sertraline, sustained-release bupropion, or extended-release venlafaxine.

- The odds of experiencing side effects were higher in the lithium group relative to the T3 group, however, these results were significant only with respect to frequency of side effects and not the intensity and burden of side effects.
<table>
<thead>
<tr>
<th>Treatment, Outcome, and Side Effect Measures</th>
<th>Total (N=142)</th>
<th>Lithium (N=69)</th>
<th>T₃ (N=73)</th>
<th>Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment duration &lt;4 weeks</td>
<td>25</td>
<td>17.6</td>
<td>13</td>
<td>18.8</td>
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<tr>
<td>&lt;8 weeks</td>
<td>49</td>
<td>34.5</td>
<td>26</td>
<td>37.7</td>
</tr>
<tr>
<td>&lt;12 weeks</td>
<td>70</td>
<td>49.3</td>
<td>36</td>
<td>52.2</td>
</tr>
<tr>
<td>Total treatment duration (weeks)</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>9.6</td>
<td>5.2</td>
<td>9.3</td>
<td>5.4</td>
</tr>
<tr>
<td>Number of postbaseline visits</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>859.8</td>
<td>57.1</td>
<td>873.1</td>
<td>54.2</td>
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<tr>
<td>Time to first postbaseline visit (weeks)</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>2.6</td>
<td>1.3</td>
<td>2.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Exit dose (mg/day)</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>3.1</td>
<td>2.1</td>
<td>3.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Outcome measures</td>
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<tr>
<td>Score at end on Quick Inventory of</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Depressive Symptomatology—Self-Report</td>
<td>10.4</td>
<td>5.2</td>
<td>11.4</td>
<td>5.2</td>
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<tr>
<td>Percentage change from Level 3 baseline on</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Depressive Symptomatology—Self-Report</td>
<td>-14.7</td>
<td>33.8</td>
<td>-13.6</td>
<td>27.2</td>
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<tr>
<td>Remission, defined as score ≤7 on Hamilton</td>
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<td></td>
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<tr>
<td>Depression Rating Scale</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Remission, defined as score ≤5 at end on</td>
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<tr>
<td>Quick Inventory of Depressive Symptomology</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response, defined as ≥50% reduction of</td>
<td></td>
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<tr>
<td>baseline score on Quick Inventory of</td>
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<tr>
<td>Depressive Symptomatology—Self-Report</td>
<td>28</td>
<td>19.9</td>
<td>11</td>
<td>16.2</td>
</tr>
<tr>
<td>Maximum side effect frequency^2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No side effects</td>
<td>24</td>
<td>18.0</td>
<td>12</td>
<td>18.8</td>
</tr>
<tr>
<td>10%-25% of the time</td>
<td>33</td>
<td>24.8</td>
<td>12</td>
<td>18.8</td>
</tr>
<tr>
<td>50%-75% of the time</td>
<td>42</td>
<td>31.6</td>
<td>17</td>
<td>26.6</td>
</tr>
<tr>
<td>90%-100% of the time</td>
<td>34</td>
<td>25.6</td>
<td>23</td>
<td>35.9</td>
</tr>
</tbody>
</table>
Strengths

- Representative for real-world practices
- Primary outcome measures collected by assessors who were blind to participants’ treatments.
- For both lithium and T3 augmentation, the duration of treatment was greater than in previously reported augmentation trials of these agents.
Limitations

- Lack of statistical power to reliably detect small differences in remission rates between the augmentation therapies.
- Did not systematically assess laboratory indices, including pretreatment assessment of thyroid function and serial monitoring of lithium levels.
- Open-label administration of the augmentation therapies.
- Absence of placebo control group.
- Participants in the lithium augmentation group took relatively low doses because of intolerable side effects.
Conclusion

- Modest role (if any) of T3 in augmentation therapy of MDD.

- Chronicity of depression may limit the degree to which T3 can increase response rate.

- T3 better tolerated than Lithium.

- Long-term outcome studies needed.