Article

Does Thyroid Supplementation Accelerate Tricyclic Antidepressant Response? A Review and Meta-Analysis of the Literature

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Objective: The delayed onset of therapeutic response to antidepressants remains a major problem in the treatment of depression. Among the strategies to accelerate response to treatment, the early addition of thyroid hormone to antidepressants has been suggested as a viable method. The authors performed a meta-analysis of the literature on the use of thyroid hormone supplementation to accelerate the treatment of depression to determine whether there is sufficient evidence to support the clinical efficacy of this strategy.

Method: Both a computer-aided search of the National Library of Medicine MEDLINE and an intensive search by hand were conducted to identify all double-blind, placebo-controlled studies assessing the concomitant administration of thyroid hormone and antidepressant to accelerate clinical response in patients with nonrefractory depression.

Results: Six studies were identified. All were conducted with triiodothyronine (T_3) and a tricyclic antidepressant. Five of the six studies found T_3 to be significantly more effective than placebo in accelerating clinical response. The pooled, weighted effect size index was 0.58, and the average effect was highly significant. Further, the effects of T_3 acceleration were greater as the percentage of women participating in the study increased.

Conclusions: This meta-analysis supports the efficacy of T_3 in accelerating clinical response to tricyclic antidepressants in patients with nonrefractory depression. Furthermore, women may be more likely than men to benefit from this intervention.

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Despite advances in the pharmacological treatment of depression, the delayed onset of therapeutic response to antidepressants remains a major clinical dilemma. Substantial mood benefits typically do not become evident until 2–3 weeks after the initiation of treatment with any of the currently available antidepressants (1). Findings in animal models from microdialysis and electrophysiological studies have led to a better understanding of the neurochemical basis for the delayed onset of action of antidepressant medications (1). Almost all currently used treatments for depression, including the tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors, and lithium, directly or indirectly enhance serotonin (5-HT) neurotransmission in a time course consistent with their delayed therapeutic effect (2). Such enhancement may be mediated by a range of mechanisms, including postsynaptic sensitization to 5-HT or desensitization of the presynaptic 5-HT_{1A} autoreceptors in the raphe area (1).

It has been hypothesized that strategies directly affecting serotonin receptor mechanisms could subsequently lead to an acceleration of the antidepressant response. One such strategy, the concurrent administration of the β-adrenergic/5-HT_{1A} receptor antagonist pindolol with an SSRI, appears promising (3), although not all placebo-controlled studies have yielded positive results (4–6). Another strategy reported to accelerate the antidepressant response of medications, which might be mediated by an increase in cortical 5-HT neurotransmission (7, 8), is the combination of thyroid hormones with antidepressants. The immediate addition of thyroid hormone to speed antidepressant treatment response was first reported in a controlled design in the classic study by Prange and associates in the late 1960s (9). Since then, two types of studies have been reported in the literature: 1) studies of acceleration strategies, which assess whether thyroid hormones prescribed initially with antidepressants speed the time for response to antidepressants in depressed subjects, and 2) studies of augmentation strategies, which assess whether thyroid supplementation added to treatment after a partial or minimal antidepressant response can potentiate the therapeutic response. The usefulness of thyroid augmentation for the treatment of a partial response or nonresponse to antidepressants has been assessed repeatedly over the past two decades (10–15), culminating in the positive meta-analysis by Aronson et al. (16). In contrast, the potential usefulness of thyroid hormones as a primary treatment to accelerate antidepressant response seems to have been lost in the literature.

TABLE 1. Characteristics and Results of Six Double-Blind, Placebo-Controlled Studies of the Coadministration of Triiodothyronine (T_3) and Tricyclic Antidepressants to Accelerate Response to Antidepressants in Relatively Untreated Patients

Study	N	Subjects Receiving Antidepressant Plus Placebo (N)	Subjects Receiving Antidepressant Plus T_3 (N)	T_3 Dose (μg/day)	Day T_3 Added	Antidepressant	Antidepressant Dose (mg/day)	Number of Days of Assessment[a]	Global Acceleration Outcome[b]
Prange et al. (9)	20	10	10	25	5	Imipramine	150	28	+
Wilson et al., 1970 (33)	20	10	10	25	5	Imipramine	150	28	+
Coppen et al. (34)	15	8	7	25	1	Imipramine	150	28	+
Feighner et al. (35)	21	9	12	25	1	Imipramine	200	22	–
Wheatley (31)	30	17	13	20	1	Amitriptyline	100	21	+
Wilson et al., 1974 (36)	19	9	10	25 or up to 62.5 by day 7	3	Imipramine	150	28	+

[a] Hamilton Depression Rating Scale (38) used as rating measurement for clinical change.
[b] Report of an overall positive (+) or no (–) effect of T_3 (a statistically significant difference in the time to a change in mean Hamilton depression scale scores or presentation of data that supports a statistical difference).

Despite several controlled studies with positive outcomes in the early 1970s, after the initial report by Prange et al. (9), the thyroid hormone acceleration paradigm has received little recent attention. To our knowledge, a meta-analysis to investigate the efficacy of adjunctive thyroid treatment in acceleration of antidepressant response has not been reported in the literature. The goal of this review and meta-analysis was to determine whether evidence exists to support the clinical efficacy of thyroid hormone for accelerating clinical response in nonrefractory depression.

Method

Data Sources

An attempt was made to identify all reports of studies of the use of thyroid hormones in treatment of depression. A computer-aided search of the National Library of Medicine MEDLINE database for 1966 to March 2000, with the subject headings "thyroid," "augmentation," "acceleration," and "depression," was performed, supplemented by an intensive search by hand of the bibliographies of reports identified from the MEDLINE database and from review articles on the use of thyroid hormones in affective illness (17–30). No language constraints were applied.

Study Selection

All identified articles were reviewed, and studies with a double-blind, placebo-controlled design in which subjects with nonrefractory depression were treated with antidepressant and thyroid hormone were selected for more in-depth review and meta-analysis. Further inclusion criteria were 1) the concomitant use of thyroid hormone at initiation of antidepressant treatment in studies assessing the effect of thyroid hormone on the rate of recovery in relatively untreated patients and 2) the use of a standardized rating scale for the measurement of depression as an outcome variable. Exclusion criteria were 1) a sample size of less than five subjects per cell, 2) addition of thyroid hormone later than 5 days after initiation of treatment with an antidepressant, and 3) assessment of the effect of adding thyroid hormone to the medication regimen of patients who had failed to respond to a standard treatment for depression. In trials that used multiple treatment arms, the data from only the thyroid hormone and placebo arms were included in the meta-analysis. In the one study that contained more than one treatment group and varying thyroid hormone doses (31), data from only the group that received the dose used in the majority of the other studies was included in the meta-analysis (31). If preliminary results of a study were published earlier, only the final version of the study was included in this meta-analysis.

Statistical Analysis

Statistical methods for the meta-analysis followed the procedures outlined by Hedges and Olkin (32). The first step was calculating or estimating a standard effect size for each study. Calculations were based on effect sizes expressed in terms of the standardized mean difference (d). In two studies (9, 33), the original authors reported only a significance level (e.g., $p<0.05$). For the current meta-analysis, a "lower-bound" estimate of d was calculated by determining the least possible mean difference that could have resulted in the stated significance level given the degrees of freedom. For one study, in which the original authors reported only that the finding was nonsignificant (34), an estimated d of zero was used in the current analysis. Although these estimated d values are probably conservative and thus somewhat underestimate the true pooled effect size, use of these conventions reduces the interstudy variability slightly. The net effect on the test of pooled significance is probably small.

With estimates of standard effect sizes tabulated, the next step was a formal test of the heterogeneity of the effect sizes across studies. The Q statistic described by Hedges and Olkin (32, p. 122) was used for this test. Because the Q test for homogeneity was not significant ($p=0.15$, see Results), the estimate and significance test of the pooled, weighted effect size was calculated. The linear association between effect size and the proportion of female subjects in the study was tested as described by Hedges and Olkin (32, p. 173). Those authors present simulation results that suggest these procedures are statistically reasonable with as few as six studies and with sample sizes as low as 10 subjects.

Results

Review of Placebo-Controlled Trials

Seven placebo-controlled, double-blind studies were identified: five by the use of MEDLINE (9, 31, 33–35) and two by a manual search (36, 37). The study by Steiner et al. (37) was excluded from the meta-analysis because only four subjects were included in each treatment group and all of the subjects were women with an unsuccessful outpatient treatment trial before hospital admission.

Thus, six studies comprising a total of 125 subjects met the inclusion criteria for the meta-analysis. Table 1 reports

details of these studies, including study group sizes, dose and day of addition of thyroid hormone, concomitant antidepressant medication, and global acceleration outcome (e.g., statistical data support an effect, or the authors report a significant positive impact of T_3 on antidepressant response). The review revealed homogeneity in the type and dose of the thyroid hormone and antidepressant used: all studies were conducted with the same thyroid hormone, triiodothyronine (T_3) (dose=20–25 μg/day in five studies and 25–62.5 μg/day in one study) and with a tricyclic antidepressant (imipramine in five studies and amitriptyline in one study; dose of tricyclic antidepressant=100–200 mg/day). All studies used the Hamilton Depression Rating Scale (38) as the primary instrument to measure the outcome of treatment. The time when T_3 was added to the antidepressant ranged from the first day of treatment (31, 34, 35) to the fifth day in the studies of Prange et al. (9) and Wilson et al. (33).

Review of Studies

Five of the six double-blind studies included in this analysis found T_3 to be significantly more effective than placebo in accelerating treatment response (Table 1 and Table 2).

Prange et al. (9) reported that among 20 patients with retarded depression, the group who received the combination of imipramine/T_3 was significantly improved compared to the imipramine/placebo group at day 10 of tricyclic antidepressant treatment (5 days after T_3 addition). The T_3 group had a 50% reduction in mean Hamilton depression scale score, compared to the baseline mean score at an average of 11 days after T_3 initiation. The placebo group required an average of 22 days of treatment to achieve the same improvement. The T_3 group attained a Hamilton depression scale score of eight or less in an average of 17.4 days (SD=9.7), whereas the placebo group took an average of 24.8 days (SD=6.2).

In a study by Wilson et al. (33) involving 20 subjects with nonretarded depression, the T_3 group was significantly improved compared to the placebo group, as measured by a mean group change of 50% on the Hamilton depression scale, as early as 2 days after initiation of the combined treatment. Significant differences in mood ratings between the two groups continued from day 7 to day 16. Statistically significant differences between groups were lost from day 17 to the end of the study (day 28). Six subjects (four in the T_3 group, two in the placebo group) discontinued the study treatment before the protocol concluded because they were clinically well enough to leave the hospital.

Coppen et al. (34) reported in their study of euthyroid depressed patients that the mean Hamilton depression scale score for the female T_3 group (N=3) dropped from a mean of 22.3 (SD=2.3) on day 0 of the trial to 0.0 (SD=0.0) on day 28. For the male T_3 group (N=4), the mean score changed from 18.5 (SD=1.0) on day 0 to 4.5 (SD=0.6) on day 28. The mean score for the female placebo group (N=5) went from 21.0 (SD=0.8) on day 0 to 12.6 (SD=3.7) on day 28. The male placebo group (N=3) showed a change from 22.0 (SD=1.5) on day 0 to 2.7 (SD=1.5) on day 28. Although men showed a better response to imipramine alone than women, women in the imipramine/T_3 group had significantly lower Hamilton depression scale scores and appeared to respond in fewer days than did men in the combined group. Overall, the imipramine/T_3 group improved significantly more than the imipramine/placebo group.

TABLE 2. Effect Size and Percentage of Female Subjects in Six Double-Blind, Placebo-Controlled Studies of the Coadministration of Triiodothyronine and Tricyclic Antidepressants to Accelerate Response to Antidepressants in Relatively Untreated Patients

Study	Effect Size (d)	Percentage of Female Subjects
Coppen et al. (34)	–0.14	53
Wheatley (31)	0.38	69
Feighner et al. (35)	0.00	71
Prange et al. (9)	1.24	80
Wilson et al. 1970 (33)	1.24	80
Wilson et al. 1974 (36)	0.93	100
All studies	0.58[a]	

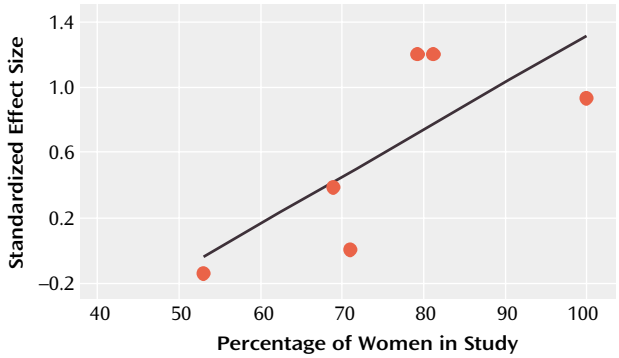
[a] 95% CI=0.21–0.94 (z=3.10, p<0.002).

In a double-blind study of euthyroid depressed patients, Feighner et al. (35) administered imipramine and either placebo or T_3 for 22 days. Hamilton depression scale scores showed no significant differences in rates of symptom remission between the T_3- and the placebo-treated patients until day 22 of assessment (assessments started on day 1 and were completed every 3 days).

Wheatley (31) compared amitriptyline plus placebo with amitriptyline plus T_3 at two dose levels (20 and 40 μg/day) in euthyroid depressed patients. Table 1 summarizes data for only the 20-μg T_3 group and the placebo group. The initial mean 24-item Hamilton depression scale scores were as follows (standard deviations were not provided): 26.0 for the 40-μg T_3 group (N=22), 23.3 for the 20-μg T_3 group (N=13), and 27.1 for the placebo group (N=17). By day 14, the mean Hamilton depression scale score was 6.8 for the 40-μg T_3 group and 10.1 for the 20-μg T_3 group; both T_3 groups were significantly improved, compared with the placebo group, which had a 14-day mean Hamilton depression scale score of 14.6. Women responded more favorably than men in the T_3 groups, a difference that was evident by day 3 of treatment.

Finally, Wilson et al. (36) studied the effect of increasing dosages of T_3, both with and without imipramine, in relatively untreated unipolar depressed euthyroid women. The active T_3 doses were increased to 50 μg on day 5 and to 62.5 μg on day 7 and were discontinued on day 12. Hamilton depression scale scores on days 7 and 9 showed that the imipramine/T_3 group had improved significantly more than the imipramine/placebo group. Both T_3 groups (with or without imipramine) worsened on days 9 and 12, after the T_3 dose was raised. The authors postulated thy-

FIGURE 1. Effect Size in Six Double-Blind, Placebo-Controlled Studies of the Coadministration of Triiodothyronine and Tricyclic Antidepressants to Accelerate Response to Antidepressants in Relatively Untreated Patients, by Percentage of Female Subjects in the Study[a]



[a] r=0.76, pooled N=125. Weighted linear regression analysis of the association between effect size and percentage of women was statistically significant (χ^2=4.17, df=1, p=0.04).

roid hormone toxicity at the higher thyroid dose. The imipramine/T_3 group had a significant improvement by day 9, and the imipramine/placebo group by day 20.

Meta-Analysis

Table 2 presents the estimated effect sizes and the proportion of female subjects for each of the six studies included in the meta-analysis. The Q test for homogeneity was not significant (χ2=8.14, df=5, p=0.15), indicating that estimation of a pooled effect size was appropriate. The pooled, weighted effect size index (d) was 0.58 (estimated standard error=0.19). The 95% confidence intervals for this value were 0.21 ("small") to 0.94 ("large"), using conventional terms to characterize these values according procedures outlined by Cohen (39). The average effect was highly significant (z=3.10, p=0.002). As shown in Figure 1, the effect size indices appeared to increase fairly linearly, as the percentage of female subjects in the study increased from lowest (53%) to highest (100%). A weighted linear regression analysis of the association was statistically significant (χ^2=4.17, df=1, p=0.04), confirming the visual impression that the effects of T_3 acceleration were greater as the percentage of women participating in the study increased.

Discussion

The results of this meta-analysis support an acceleration of antidepressant response when adjunctive T_3 is included early in antidepressant treatment. Five of six double-blind, placebo-controlled studies, conducted between 1969 and 1974, found that the addition of T_3 had a statistically significant effect on the time to treatment response, compared with the effects of placebo. Treatment with a dose of 20–25 μg/day of T_3 was well tolerated by patients, thus suggesting that the addition of T_3 is a viable treatment option to accelerate antidepressant response.

This meta-analysis also revealed that women may be more likely than men to benefit from the addition of T_3. Women have a greater prevalence of both clinical and subclinical thyroid dysfunction than men (40). Treatment response to antidepressants may be impaired among patients with overt and subclinical hypothyroidism (41). This might explain why women responded more favorably than men to the addition of T_3, particularly because thyroid status was not thoroughly examined in some of the studies included in this meta-analysis. However, a more recent study involving ECT suggested that T_3 has beneficial effects on rates of improvement in men as well (42). In that study, male patients with major depression undergoing ECT were randomly assigned under double-blind conditions to receive either T_3 (50 μg/day) or placebo the night before each ECT treatment. The patients who received T_3 and ECT required only eight treatments for improvement, while those who received placebo and ECT required 12 (p<0.001).

How can the acceleration effects of thyroid hormones be explained? Studies examining the relationship between thyroid hormones and neurotransmitter systems have focused on the noradrenergic and serotonin systems. In studies assessing the thyroid-serotonin systems, the effects of thyroid hormone application to experimentally induced hypothyroid or euthyroid animals include an increase in cortical 5-HT concentrations and a desensitization of autoinhibitory 5-HT_{1A} receptors in the raphe area, resulting in disinhibition of cortical and hippocampal 5-HT release (43, 44). A recent in vivo microdialysis study by Gur et al. (45) indicated a loss of autoinhibitory 5-HT_{1A} receptor sensitivity mediated by T_3. In the latter study, the decrease in hippocampal and cortical serotonin release, which should follow the application of a 5-HT_{1A} agonist, was significantly reduced in euthyroid rats by administration of T_3 or combined T_3 and clomipramine (45). These results indicate that thyroid hormone application may reduce autoinhibitory 5-HT_{1A} receptor activity and thus increase cortical serotonin release. In this way, it may have actions similar to those of pindolol, a 5-HT_{1A} receptor antagonist that when added to SSRI treatment facilitates serotonin release (3). Further evidence for an interaction between thyroid status and the serotonin system derives from studies that have demonstrated a significantly blunted cortisol and prolactin response to the 5-HT agonist *d*-fenfluramine in hypothyroid patients (46, 47). This blunted response to *d*-fenfluramine stimulation normalized with thyroid hormone replacement therapy, suggesting reduced central 5-HT functioning in hypothyroidism (47). Thyroid hormones also appear to play an important role in regulating central noradrenergic function, and its impact on this system may also contribute to the acceleration effect. Recent findings indicate that T_3 may function as a cotransmitter with norepinephrine in the adrenergic nervous system (48).

Due to its faster onset of action, T_3 is probably the prime thyroid candidate for accelerating antidepressant response. The efficacy of thyroxine (T_4) in patients with acute depression has been studied only as an augmentation strategy. The pharmacokinetic properties of T_4, e.g., long half-life and action as a prohormone, suggest that it is not a very promising agent for the acceleration paradigm. In one study, the onset of remission in depressed patients receiving T_4 as an augmentation strategy did not occur until between week 5 and 8 (15).

There are no published studies on the optimal length of time to continue T_3 in persons who have had a successful T_3 acceleration. In three of the studies described here, T_3 was discontinued after 12 (36) or 14 (34) days of treatment or between 19 and 28 days of treatment (9). In all three studies, the majority of the patients who had an initial positive response remained well after T_3 was discontinued. The investigators concluded that T_3 may exert its greatest therapeutic effect within the first week of use (36). It seems wise to continue T_3 at least until stable remission is achieved.

T_3 is generally well tolerated (19). A possible connection between the use of thyroid hormones and the risk of developing osteoporosis has been a concern. To our knowledge, no data address whether long-term use of T_3 affects bone mineral density in patients with mood disorders. However, treatment with supraphysiological doses of thyroxine (T_4) for 1 year or longer does not appear to significantly influence bone mineral density in pre- and postmenopausal women with mood disorders (49, 50).

The studies included in this meta-analysis were all performed more than 25 years ago and thus have some methodological limitations that could confound interpretation of the data. First, the studies included relatively small numbers of patients, evidently without matching groups by gender, age, and other clinical variables (e.g., duration or severity of the depressed episode). Second, the studies did not consistently screen for thyroid dysfunction before treatment, and ultrasensitive assays for determining the level of thyroid stimulating hormone, presumably the most accurate marker for thyroid dysfunction, were not available when the studies were conducted. Third, these trials included different types of depressed patients, and modern operationalized diagnostic criteria for depression were also not available; thus the samples may have been nonhomogeneous. On the other hand, it should be emphasized that these studies were homogeneous with respect to the type of antidepressant (all studies used tricyclic antidepressants, five of the six studies used imipramine), the dose of T_3, and the rating scale used to measure clinical outcome (Hamilton depression scale). Fourth, the overall dose of antidepressants was low (100–200 mg/day), perhaps lower than what would currently be used as monotherapy for a tricyclic antidepressant.

Given the limitations of the quality of the studies included in this meta-analysis, definite conclusions about the efficacy of T_3 as an accelerator of antidepressant response cannot be drawn. However, the results of this meta-analysis are strikingly positive and point to a need for further studies assessing the efficacy of T_3 acceleration with the newer, more selective antidepressant agents. The studies conducted on T_3 acceleration used tricyclic antidepressants. To our knowledge, no double-blind study has assessed the role of thyroid hormone in accelerating treatment response to SSRIs or other newer selective antidepressants. Thus, the generalizability of these findings to the ability of T_3 to accelerate SSRI or other nontricyclic antidepressant response remains to be tested.

Studies to specifically assess the role of T_3 in accelerating SSRI response are needed. Further studies may also shed light on whether there are gender-specific effects of T_3 on accelerating antidepressant response. Any agent that has a low side effect profile and reduces the delay in onset of antidepressant response (thus reducing the duration of patients' functional impairment) would be a welcome addition to the pharmacotherapeutic armamentarium.

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