Does thyroid supplementation accelerate tricyclic antidepressant response: a review and meta-analysis of the literature


Authors' objectives
To determine whether adding thyroid hormone to antidepressants increases the speed of response in patients with nonrefractory depression.

Searching
MEDLINE was searched from 1966 to March 2000; the key terms were stated. In addition, the reference lists of identified studies and reviews were checked. Studies published in any language were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Double-blind placebo-controlled trials (RCTs) were eligible for inclusion. Studies with less than five patients per treatment arm were excluded. The duration of follow-up ranged from 21 to 28 days.

Specific interventions included in the review
Studies that compared antidepressants plus placebo with antidepressants plus thyroid hormone were eligible for inclusion. Treatment with thyroid hormone had to start less than 6 days after the initiation of antidepressant treatment. All of the included studies used triiodothyronine (T3) as the thyroid hormone; the doses ranged from 20 to 62.5 microg/day (most studies used 20 to 25 microg). The included studies used either imipramine (dose of 150 to 200 mg/day in all but one study) or amitriptyline (100 mg) as the antidepressant. Thyroid hormone was added to the antidepressant treatment from day 1 to day 5 of treatment.

Participants included in the review
Studies of relatively untreated patients were eligible for inclusion. Studies of patients who failed to respond to standard antidepressant treatment were excluded. The proportion of females ranged from 53 to 100% across the studies. The studies included euthyroid patients, but not all studies assessed the thyroid status of the participants.

Outcomes assessed in the review
Studies that assessed the rate of recovery using a standardised rating scale for depression were eligible for inclusion. The 'acceleration' outcome was measured as a statistically-significant difference between thyroid hormone and placebo in the time to a change in depression. The included studies all assessed depression using the Hamilton Depression Rating Scale.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The tabulated information included: the sample size and number of patients per treatment arm; the dose of thyroid hormone and type and dose of tricyclic antidepressant; the duration of follow-up; and the percentage of female patients in the study. For studies that used more than one dose of thyroid hormone, only data for the dose used in the majority of the other studies were extracted. Only data for the final follow-up were used. An effect size was estimated.
for each study based on the standardised mean difference. Where such data were not reported, conservative values for
effect size were used (by using the lowest possible effect size that could give the P-value reported, and a value of zero
for a non significant result).

Methods of synthesis
How were the studies combined?
A pooled effect size and 95% confidence interval (CI) were estimated.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic. A weighted linear regression was used to assess the influence
of the proportion of females on the effect size.

Results of the review
Six RCTs (n=125) were included.

Five of the six RCTs found that T3 significantly increased the speed of response in comparison with placebo. The other
RCT found no significant difference between the treatments.

Overall, T3 increased the speed of response in comparison with placebo; the pooled effect size was 0.58 (95% CI: 0.21,
0.94). No significant heterogeneity was detected (P=0.15).

The speed of response increased linearly with the proportion of female patients (N=125, r=0.76, linear regression
P=0.04).

The included primary studies had several methodological limitations: all of the studies were conducted more than 25
years ago when modern diagnostic criteria had not been developed; the studies had small sample sizes; not all of the
studies screened the participants' thyroid status; different types of depressed patients were included; and the
antidepressant dose was lower than that used today.

Authors' conclusions
The authors reported that, in view of the limitations of the quality of the included studies, definite conclusions could not
be drawn. However, the results appeared to indicate that T3 speeds up the response to tricyclic antidepressant treatment
and that this effect appears to be greatest in women.

CRD commentary
The review question was clear in terms of the study design, intervention, participants and outcomes. The search terms
were stated and no language restrictions were applied. Only one database was searched and this may have resulted in the
omission of other relevant studies. No attempt was made to locate unpublished studies, thus raising the possibility of
publication bias. The methods used to select the studies, assess validity and extract the data were not described, hence
the adequacy of these methods cannot be judged. Only double-blind RCTs were included, but no formal validity
assessment was undertaken. Some relevant data were extracted and tabulated. The data were combined in a meta-
analysis and statistical heterogeneity was assessed. The authors discussed some of the limitations of the included studies
in the text. The evidence appears to support the authors' conclusions, with the proviso that the conclusions are not
definitive.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further studies are required to assess the role of thyroid hormone plus selective
serotonin re-uptake inhibitors in speeding up the patients' response to treatment with antidepressants. They also stated
that research is required to assess whether the gender of the patient influences the effect of thyroid hormone.
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