Triiodothyronine augmentation in the treatment of refractory depression: a meta-analysis
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Authors’ objectives
To assess the effectiveness of comparative clinical trials of adjunctive liothyronine sodium (triiodothyronine, T3) in euthyroid nonpsychotic depressed patients refractory to tricyclic antidepressant therapy.

Searching
MEDLINE was searched from 1966 to May 1995; the search terms are provided. Additional material was located by manual searches of reference lists of retrieved papers, and through personal correspondence with researchers in the field.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), ‘mirror-design’ (before-and-after) placebo-controlled study, and historically-controlled studies were included.

Specific interventions included in the review
Tricyclic antidepressant therapy (imipramine hydrochloride, desipramine hydrochloride, amitriptyline hydrochloride) augmented by T3 or placebo.

Participants included in the review
Male and female depressed adult patients (both unipolar and bipolar) treated in in- and out-patient settings, for whom there was biochemical evidence of euthyroidism.

Outcomes assessed in the review
Rates of response as defined by each investigator; change in mean scores on depression inventories (Hamilton Rating Scales for Depression (HRS-D), the Bunney Hamburg Scale and the Clinical Global Impression Scale).

How were decisions on the relevance of primary studies made?
The inclusion and exclusion criteria used are given. The trials identified for inclusion were reviewed to assess the clinical comparability of study populations, treatment protocols and outcome measures.

Assessment of study quality
A streamlined version of the Chalmers’ quality assessment scale (see Other Publications of Related Interest no.1) was used. The study methods were evaluated independently by two appraisers. The results were subsequently compared and any differences were settled by consensus.

Data extraction
The data abstraction was performed using standardised forms to record outcomes, withdrawals and cointerventions.

Methods of synthesis
How were the studies combined?
A quantitative meta-analysis was undertaken. For studies presenting categorical data, relative risks were pooled using generalised linear mixed modelling methods. Absolute differences in proportions of patients responding in treatment versus control groups were assessed using the approach of DerSimonian and Laird (see Other Publications of Related Interest no.2). For studies presenting continuous outcome measures (e.g. depression inventory scores), standardised effect sizes were calculated and standard size-weighting methods were used to generate pooled effect sizes.
How were differences between studies investigated?
Sensitivity analyses were performed to sequentially remove groups of studies that shared methodological deficiencies.

**Results of the review**
Four RCTs (95 participants), one before-and-after study (12 participants) and 3 historically-controlled studies (185 participants) were included.

When the 4 RCTs were pooled, the relative response rate of augmentation therapy with T3 was 1.53 (95% confidence interval, CI: 0.70, 3.35, p=0.29), compared with control. The mean decrease in HRS-D score was 0.60 (p= 0.001). Inter-trial heterogeneity was significant.

When the trials were combined regardless of methodology, the relative response rate of augmentation therapy with T3 was 2.09 (95% CI: 1.31, 3.32, p=0.002), compared with control. The mean decrease in HRS-D score was 0.62 (p<0.001). Inter-trial heterogeneity was significant.

The 5 studies that included assessment of side-effects reported no significant differences between T3 groups and controls.

**Authors' conclusions**
T3 augmentation in tricyclic antidepressant non-responders appears to be an effective, inexpensive and safe empirical method of producing a response and decreasing depression severity scores in a subgroup of patients with refractory depression. However, only 292 patients in controlled studies were available for meta-analysis and fewer still in trials with a randomised placebo-controlled design. A definitive verdict demands additional data from placebo-controlled trials.

**CRD commentary**
This was a well-documented systematic review detailing a quantitative meta-analysis. The results were presented from pooling the more reliable trials (the 4 RCTs), and from pooling all trials regardless of methodological quality. However, there was a tendency for the latter, less reliable analysis to be given precedence; this provided a statistically-significant result unlike the more conservative pooling. The authors acknowledged the need for more good quality research.

**Implications of the review for practice and research**
More good quality RCTs are needed to establish that augmentation with T3 is beneficial in tricyclic antidepressant non-responders.

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