Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin reuptake inhibitors

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CRD summary

The authors said that although there was support for a conclusion that triiodothyronine enhanced and augmented serotonin reuptake inhibitors in major depressive disorder, there was no conclusive evidence. Evidence was limited and the restricted search, lack of reporting of review methods and lack of validity assessment mean that the conclusions may not be reliable.

Authors' objectives

To evaluate the efficacy and safety of triiodothyronine (T_3) as an accelerant, enhancer or augmentation agent to serotonin reuptake inhibitors in patients with major depressive disorder.

Searching

PubMed was searched for studies published in English after 1965. Search terms were reported, but search dates were not. The Cochrane Library was also searched. In addition, reference lists of relevant reports and articles identified as related articles were screened.

Study selection

Studies that evaluated triiodothyronine supplementation of serotonin reuptake inhibitors in patients with major depressive disorder were eligible for inclusion. The review classified studies as enhancement (triiodothyronine administered concurrently with serotonin reuptake inhibitors from the start of treatment) and augmentation (triiodothyronine administered after failure of a trial of standard antidepressants). The review assessed response and remission.

The review included randomised controlled trials and open-label studies. The duration of included interventions ranged from two to 14 weeks. Control treatments included placebo and other active treatments including lithium. All but one study involved only patients with non-psychotic major depressive disorder. All of the studies defined response as a reduction of 50 per cent or more in intention-to-treat scores on a depression rating scale (mostly the Hamilton Depression Rating Scale). Studies used different definitions of remission. Details of outcome definitions were reported.

The authors stated neither how papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality

The authors did not state that they assessed validity. They noted the level of blinding.

Data extraction

The authors stated neither how data were extracted for the review nor how many reviewers performed the data extraction. For each study, the number of completers and number analysed were reported as well as response and remission rates for each treatment group; p values were reported for controlled trials.

Methods of synthesis

The studies were grouped by type of treatment (enhancement or augmentation) and combined in a narrative synthesis.

Results of the review

Eight studies were included. These included five randomised controlled trials (n=472) and three open label studies (n approximately 56).

Enhancement (three randomised controlled trials)

Two (n=113 and n=57) of the three randomised controlled trials reported no significant difference in remission and response rates between triiodothyronine and placebo. One randomised controlled trial (n=124) reported significantly higher response (70 per cent versus 50 per cent, p=0.02) and remission rates (59 per cent versus 38 per cent, p=0.02) in the triiodothyronine group. One study reported higher adverse event rates (palpitations, sweating, nervousness and tremor) in triiodothyronine compared to placebo groups; the other two studies reported no difference between groups.

Augmentation (two randomised controlled trials and three open-label studies)
The three open-label augmentation studies (number of completers 11, 19 and 25) reported response rates ranging from 35 per cent to 49 per cent (reported as 48 per cent in the table) and remission rates ranging from 25 per cent to 36 per cent. One randomised controlled trial (n=142) reported no statistically significant difference in response or remission rates between lithium and triiodothyronine, but reported significantly higher rates of withdrawals due to adverse event rates in the lithium group (23 per cent versus 10 per cent, p=0.028). One randomised controlled trial (n=36) reported no significant difference in treatment effect between triiodothyronine, lithium, triiodothyronine plus lithium and placebo. Treatment groups were small (n=8 to 10).

Authors' conclusions

There was support for a conclusion that triiodothyronine enhanced and augmented the effects of serotonin reuptake inhibitors in patients with major depressive disorder, but there was no conclusive evidence. Further research was required.

CRD commentary

The review question was stated. Inclusion criteria were reported for participants and intervention (triiodothyronine supplementation of serotonin reuptake inhibitors), but some studies used antidepressants other than serotonin reuptake inhibitors. Inclusion criteria were not specified for study design or outcomes. Limiting the search to English-language studies listed in two databases plus references may have resulted in the omission of other relevant studies and raised the possibility of publication and language biases. As methods used to select studies and extract data were not described, it was unknown whether efforts were made to reduce reviewer errors and bias. Although some limitations of the included studies were mentioned, study validity was not formally assessed and so results from these studies and any synthesis may not be reliable. In view of the diversity among studies, a narrative synthesis was appropriate. The authors' conclusion about the lack of conclusive evidence appeared justified given the limitations of the evidence. However, the limited search, lack of reporting of review methods and lack of validity assessment mean that the conclusions may not be reliable.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that controlled trials were required to evaluate the effects of triiodothyronine supplementation of serotonin reuptake inhibitors in patients with major depressive disorder. Studies needed to determine the optimal timing, dose and duration of triiodothyronine supplementation, examine its efficacy compared to T_4 and examine clinical and thyroid function correlates of response. Clinicians needed to monitor potential adverse events.

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