The Use of Thyroid Supplements to Augment Antidepressant Medication

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Despite methodological flaws that limit conclusions, a considerable database documents the efficacy of triiodothyronine (T_3) as an augmentation strategy for response to various classes of antidepressants. One study suggests that T_3 and lithium are of comparable efficacy in antidepressant nonresponders. No clear biochemical or clinical predictors of preferential response to T_3 have been found. The role of T_3 augmentation requires further evaluation, especially with regard to dose and duration. *(J Clin Psychiatry 1998;59[suppl 5]:26–29)*

Clinical thyroid disease, both hyper- and hypothyroidism, is associated with psychiatric symptomatology.[1] In particular, hypothyroidism often presents with depressive symptomatology that frequently resolves after successful restoration of normal thyroid function.[2] These observations in patients with clinical thyroid disorders have provided the theoretical rationale and the clinical impetus for the use of thyroid hormones in the treatment of depressive disorders. This occurred despite the fact that most patients with primary major depression are euthyroid[3] and no specific abnormality of thyroid hormone levels has been identified in association with affective disorders.

Thyroid hormones have been used in several ways for the treatment of mood disorders. First, earlier studies[4,5] evaluated the efficacy of triiodothyronine (T_3) as monotherapy for the treatment of psychiatric disorders with prominent depressive symptomatology. Results from these studies were mixed and limited by numerous methodological flaws, particularly heterogenous samples and failure to adhere to acceptable clinical trial methodology. Second, thyroid hormones, particularly T_3, have been used to accelerate response to antidepressants.[6–8] These studies demonstrate a reduction in the lag in onset of therapeutic response to tricyclic antidepressants in depressed women; when T_3 was administered, using a randomized, double-blind, placebo-controlled design, at the outset of a tricyclic antidepressant trial, there was a significantly faster onset of therapeutic effect in depressed women. Although no significant T_3 versus placebo difference was observed in depressed men, their overall onset of antidepressant effect was comparable to that seen in the women who received T_3. These studies were carried out more than 25 years ago, and there are no modern published studies that confirm these earlier observations.[6–8] Third, thyroid hormones, particularly thyroxine (T_4), have been used to augment mood stabilizers in bipolar disorder, especially the rapid-cycling subtype. Last, thyroid hormones have been used as an adjunct to antidepressants to augment therapeutic response in antidepressant partial responders or nonresponders. This last application will form the focus of this report.

STUDIES OF T_3 AUGMENTATION OF ANTIDEPRESSANTS

The early studies of thyroid hormone augmentation of antidepressants ushered in the modern era of the use of thyroid hormones as psychotropic agents for the treatment of depression. Prior to this, hormones in general and thyroid hormones in particular had been used for a variety of psychiatric indications largely because of the limited therapeutic options available for these illnesses prior to the general availability of antipsychotics and antidepressants. To date, there have been 11 studies of the use of T_3 to augment therapeutic response in tricyclic nonresponders. Six of these studies[9–14] have been open and uncontrolled studies, one has been open and partially controlled,[15] and four have employed double-blind controlled designs.[16–19] Overall, these studies report that T_3 augmentation is effective in approximately 55% to 60% of patients who failed to respond to tricyclic antidepressants. All of these studies have involved tricyclic nonresponders, but there are also case reports of T_3 efficacy in the augmentation of both monoamine oxidase inhibitors[20] and serotonin selective reuptake inhibitors.[21] The dose range varies considerably, between 5 and 50 mg/day; there is, however, no evidence

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for a dose-response relationship for the efficacy of T_3 augmentation.

The data and conclusions from the open studies[9–14] have varied quite considerably. Response rates have varied from as low as 25% to almost 100%. This may be attributable to numerous factors, including the definition of treatment failure prior to receiving T_3. In several studies, patients who received T_3 augmentation had received inadequate antidepressant trials and, therefore, may not have been refractory to treatment. Another factor is the ascertainment of subjects included. For example, in the study by Thase et al.[14] in which one of the lowest response rates was recorded, patients included had highly refractory and recurrent illness. In one of the double-blind studies, Gitlin and collaborators[19] reported that T_3 was no more effective than placebo in augmentation of nonresponse to desipramine. However, Gitlin and coworkers' study involved 16 patients who received T_3 and placebo in a randomized, crossover controlled trial. The use of a crossover design is problematic in the evaluation of antidepressant treatments in general and augmentation strategies in particular. Although the results require further consideration, the methodological limitations in this study[19] preclude one from drawing firm conclusions that T_3 is no more effective than placebo. Furthermore, this study by Gitlin et al.[19] is contrary to the consistent finding observed in the open and double-blind trials of efficacy of T_3 augmentation. Moreover, Aronson and collaborators[22] performed a meta-analysis of all T_3 augmentation studies. They reported that, based on their meta-analysis, T_3 was more effective than placebo and that T_3 had a substantial effect in reducing severity of depression scores and therefore may have clinical utility as an agent to boost therapeutic response in antidepressant nonresponders.

In another of the double-blind studies, we[17] compared the use of T_3 with the use of thyroxine (T_4) in augmentation of antidepressant nonresponse. In this study, we observed that in a cohort of desipramine or imipramine nonresponders who were euthyroid and had a diagnosis of primary major depressive disorder, T_3 was significantly more effective than T_4 in augmenting antidepressant response over a 3-week treatment trial. There are numerous possible interpretations of this finding. Furthermore, the absence of a placebo control group limits the conclusions that can be drawn from this study.[17] However, our preliminary observation would suggest that in usual circumstances, T_3 rather than T_4 should be the preferred method of augmentation until such time as rigorously controlled studies would suggest otherwise. In another study that used T_4 to augment antidepressant response, Targum and collaborators[23] reported an antidepressant augmentation effect with T_4. However, five of the seven subjects who responded to T_4 had a diagnosis of subclinical hypothyroidism as evidenced by an enhanced thyrotropin (TSH) response to thyrotropin-releasing hormone. Because in most instances patients with major depression are euthyroid, these combined factors would suggest both that the efficacy of T_4 in the study by Targum et al.[23] was due to replacement therapy rather than to an intrinsic antidepressant augmentation effect and that this finding cannot be generalized to most depressed patients who are euthyroid.

In the most recent controlled trial of T_3 augmentation, we compared T_3 with lithium using a randomized, placebo-controlled design.[18] In 51 nonresponders to either desipramine or imipramine, we observed that both T_3 and lithium were significantly more effective than placebo but were not significantly different from one another. Although the sample was relatively modest in size, it is to date the largest controlled study of T_3 augmentation. Furthermore, it compares T_3 with lithium augmentation, which is generally regarded as the "gold standard" for augmentation strategies. Our study suggests that T_3 and lithium appear to be of comparable efficacy in augmentation of tricyclics. This study,[18] taken together with the recent meta-analysis,[22] would suggest that T_3 is an effective augmentation strategy, perhaps comparable in efficacy to the standard augmentation treatment, lithium.

In summary, there is a considerable database documenting the efficacy of T_3 augmentation in antidepressant nonresponders. Although there are clearly methodological limitations to these studies—particularly the preponderance of open trials—clinical experience, the collective conclusion from these studies, and the accompanying meta-analysis would strongly argue for the clinical efficacy of this strategy in the treatment of refractory depression.

MECHANISM OF ACTION

There have been considerable debate and speculation about the mechanism of action of T_3 augmentation in antidepressant nonresponders.[3] One of the common and first explanations offered is that thyroid hormones have important interactions with various neurotransmitters, particularly norepinephrine.[24] Although this is clearly a feasible hypothesis, it remains to be confirmed in systematic studies. The other possible explanation is that thyroid hormones act in augmenting antidepressant response by direct effect on the thyroid axis. Most depressed patients are euthyroid.[3] The possibility, therefore, that they act as replacement treatment for depressed patients with occult hypothyroidism probably applies to only a minority of subjects. T_3 appears to be effective in completely euthyroid subjects; in fact, in the majority of studies where T_3 augmentation has been evaluated,[9–19] patients were required to be euthyroid before being included in the study. An alternative hypothesis has been offered to suggest that T_3 acts by reducing thyroxine levels.[25] This hypothesis is based on the notion that brain utilization of thyroid hormone appears to differ from utilization by other tissues and that the two thyroid hormones, T_4 and T_3, may have different effects on brain

thyroid hormone levels.[25] This hypothesis requires further study. Therefore, at this stage, the mechanism of action of T_3 in antidepressant augmentation remains to be elucidated, but this does not detract from the data supporting the clinical efficacy of this hormone.

CLINICAL ISSUES

T_3 augmentation has been used to enhance antidepressant response with a variety of antidepressants. Although its success is best substantiated for the tricyclics,[9–19] there is also evidence for its efficacy with other classes of antidepressants[20] including the newer generation antidepressants such as the serotonin selective reuptake inhibitors.[21] There are no biochemical or clinical features of major depression that would suggest a preferential response to T_3 augmentation.[26] In particular, as previously mentioned, peripheral thyroid hormone levels prior to T_3 augmentation are of no clinical use in predicting response to T_3. Although, in a recent study,[27] we observed higher mean plasma T_4 levels in responders as compared with nonresponders to T_3, these differences, although significant, are of no clinical utility in prediction of augmentation response. It has been demonstrated that patients with major depression who have various degrees of subclinical hypothyroidism have a lower response rate to antidepressants.[28] It is entirely feasible that this group of patients would respond well, although, to date, they have generally been excluded from augmentation studies.[9–19]

As far as clinical variables are concerned, there is no conclusive evidence that particular clinical features or subtypes of depression preferentially respond to T_3 augmentation.[26] Therefore, the presence of psychomotor retardation does not predict response to T_3, nor does the presence or degree of severity of any other of the defining symptoms for major depression predict preferential response to this or any other augmentation strategy.[26] In particular, we have not been able to discern any biochemical or clinical feature that would distinguish a T_3, from a lithium responder, although there is a suggestion, from earlier case studies, that depressed patients who respond to T_3 may differ from those who respond to lithium.[29,30] Clearly, further studies are required to see if any clinical or biochemical variable may be of use in selecting an augmentation strategy. The identification of such predictors would greatly enhance the efficiency of antidepressant therapy, particularly in the refractory patient.

T_3, therefore, is one of the options that needs to be considered in the augmentation of various classes of antidepressants. With the exception of lithium, T_3 is one of the best and most extensively studied augmentation strategies. Although other augmentation strategies such as the use of buspirone and pindolol are gaining increased acceptance, the database for T_3 augmentation efficacy is still considerably larger. Although the efficacy and clinical utility of T_3

are still regarded with some skepticism, the data are clear that this intervention has substantial antidepressant augmenting effects and that it appears to be comparable in efficacy to the standard augmentation treatment, lithium. Its clinical utility, however, does require further evaluation.

Although there may be many advantages to the use of an augmentation strategy in the approach to the refractory patient, one of the major drawbacks is the lack of systematic, empirical data to support the efficacy of these augmentation strategies. Furthermore, with the exception of our own study,[18] which directly compared the efficacy of lithium to that of T_3, there are virtually no data on direct comparisons of the comparable efficacy of other augmentation strategies. For the same reasons, there are virtually no systematic data on clinical or biochemical predictors of one augmentation strategy as compared with another. Therefore, the decision to use one or another augmentation strategy is more dependent upon clinical experience or expert opinion than on systematic data from research studies. As a result, the attempt to develop an algorithm for the treatment-resistant patient becomes extremely difficult, particularly if this is to be based on systematic research studies. After a patient fails an antidepressant, there are very few data to guide the decision about whether to substitute with a second antidepressant or whether to use an augmentation treatment. Although clinical lore suggests that augmentation may be preferable in partial responders whereas substitution with a second antidepressant may be the better option in complete nonresponders, there is no empirical evidence to support this contention. In fact, in our own studies, we have observed that partial and complete responders are equally likely to respond to augmentation with either T_3 or lithium (Joffe RT, Levitt AJ. 1997. Unpublished data). Beyond that, if the decision is made to proceed with augmentation, there is no evidence to guide the decision about which augmentation strategy is preferable at which stage of treatment or which may be particularly useful in a particular patient group or subtype of depression. A concerted research effort will be required to carry out the necessary studies to provide these empirical data, which would then guide the development of a rational care map or algorithm for the treatment of the antidepressant nonresponder.

CONCLUSIONS

T_3 is an effective augmentation strategy for a variety of antidepressant classes and is comparable in efficacy to the standard augmentation treatment, lithium. There are no clear clinical or biochemical predictors to indicate which patients or subtypes of depression will preferentially respond to T_3. Furthermore, there are no clinical factors that would suggest where T_3 augmentation fits in the whole range of augmentation and other substitution options that are available in the approach to depressed patients who are

antidepressant nonresponders. Further systematic studies will provide important empirical information required to address these issues, leading to a rational and efficient approach to the refractory depressed patient.

In addition, there are several unresolved issues related to the clinical use of T_3 augmentation. First, the possibility of a relationship between dose of T_3 and clinical response requires evaluation. At present, no studies have directly addressed this, but in the studies to date,[9–19] the response rate has not differed substantially across a broad range of T_3 doses. Second, what constitutes an adequate duration of a T_3 trial remains to be determined. It is generally acknowledged that therapeutic response to T_3 is most likely to occur in the first 2 to 3 weeks of therapy. However, most studies to date, including the controlled trials, have been of short duration[9–19] and few trials have extended beyond a few weeks. Third, once a depressed patient responds to T_3 augmentation, there are no empirical data to indicate how long the T_3 should be maintained along with the antidepressant. It is common practice to continue T_3, or for that matter, any augmentation strategy, for as long as the antidepressant is required. However, this should be subject to rigorous evaluation using acceptable research methodology so as to ensure that the augmentation treatment is not used longer than necessary. Last, if T_3 is used for prolonged periods, extending over months or years, it would be important to document if there are long-term adverse effects. This is necessary to ensure that appropriate monitoring, if any is required, is carried out and that an adequate risk-benefit ratio for the use of T_3 augmentation can be calculated by both physician and patient.

Drug names: buspirone (BuSpar), desipramine (Norpramin and others), imipramine (Tofranil and others), levothyroxine (Synthroid and others), liothyronine (Cytomel), norepinephrine (Levophed), pindolol (Visken).

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DISCLOSURE OF OFF-LABEL USAGE

The following agent mentioned in this article is *not* indicated for treatment of depression: thyroid hormone.