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Special review article

# An examination of myth: A favorable cardiovascular risk-benefit analysis of high-dose thyroid for affective disorders

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ABSTRACT

*Introduction:* High dose thyroid (HDT) is included in major treatment guidelines for the treatment of bipolar disorders. Yet it is seldom used partly based on perceived cardiovascular risks. The cardiovascular risks of HDT are examined.

*Methods:* A literature search was conducted for the cardiovascular risks of HDT and for comparisons sake psychiatric medications. Case reports of atrial fibrillation (afib) associated with HDT are reported.

*Results:* While hyperthyroidism is a significant cardiovascular risk factor causing a 20% premature death rate, HDT treatment does not appear to be of significant cardiovascular risk. HDT differs from hyperthyroidism in significant ways. The sequela of hyperthyroidism are increasingly tied to autoimmune complications which are absent with HDT. Equating hyperthyroidism with HDT is incorrect. The five case reports of HDT treatment associated with afib were potentially caused by other factors. If HDT increases the risks of afib, monitoring for afib would minimizes the risk. Even in overt hyperthyroidism the risk of other arrhythmias are minimal. When compared to many psychiatric medications HDT is as safe or safer.

*Limitations:* There are no direct studies of cardiovascular risks of HDT for affective patients. High tolerance of a medication does not necessarily imply lack of risk. The five case reports were spontaneous, other cases may not have been reported.

*Conclusion:* The cardiovascular risks of HDT appear to be low. HDT is at least as safe as or safer than many psychiatric medications. It is effective and well tolerated.



**Contents**



*Abbreviations:* Afib, atrial fibrillation; BMI, body mass index; DTC, disseminated thyroid cancer; HAM-D, Hamilton Depression Rating Scale; HDT, high dose thyroid; MVA, motor vehicle accidents; OR, odds ratio; RR, relative risk; yo, years old

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## 1. Introduction

There are two major myths that prevent wide acceptance of high dose thyroid (HDT) for the treatment of affective disorders. The first myth is that HDT is a risk factor for developing osteoporosis, and the second myth is that HDT increases cardiovascular risk. A previously published review disproved the first myth (Kelly, 2014) and the present review addresses the myth that HDT poses a significant cardiovascular risk for affectively ill patients. This will be done in 4 steps. First, this review will demonstrate that the high circulating thyroid hormone levels resulting from HDT is fundamentally different than hyperthyroidism. Second, this paper will review the literature that directly examines the cardiovascular risks of HDT. Third, this paper, for comparison, will survey the risks posed by commonly used psychiatric medications to place the risks of HDT in a realistic, clinically oriented context. Fourth, this paper will discuss the inappropriate role of non-psychiatrists co-opting the decision process of psychiatric illness management, which is best performed by psychiatrists.

Clinically, the most significant road block preventing more acceptance of HDT treatment is disapproval from other specialists, chiefly endocrinologists. This is largely because endocrinologists and endocrine publications equate HDT with hyperthyroidism. Clinically, it is not unusual for endocrinologists to instruct patients to immediately stop HDT, disregarding the potential consequences or consideration of the patient's psychiatric history. This review will assert that psychiatrists should have primacy in making final treatment recommendations for psychiatric patients. Endocrinologists' disapproval of HDT as an affective illness treatment is puzzling considering their recognition and support for the use of HDT to prevent the reoccurrence of well differentiated thyroid cancer (DTC).

HDT is now recommended for the treatment of the bipolar disorders in two major treatment guidelines (Yatham et al., 2013; Crismon et al., 2007). The use of thyroid augmentation for major depression is well researched and has been found to have a significant benefit (Bauer and Whybrow, 2001). Extensive research has also shown that HDT is significantly helpful in preventing reoccurrences of stages 2, 3, and 4 DTC (Quan et al., 2002; Heemstra et al., 2006; Eftekhari et al., 2008). However, even though HDT is included in major treatment guidelines, most psychiatrists do not prescribe it, possibly because HDT is universally condemned. Numerous studies have linked thyroid disturbances and affective disorders (Chakrabarti, 2011).

In addition, this paper will discuss the first double blind placebo controlled study of HDT for bipolar disorder (Stamm et al., 2014). Five cases of atrial fibrillation (afib) associated with HDT are also reported and discussed.

## 2. Methods

Google and Google Scholar (which includes PubMed) were used to perform multiple searches with various keywords both individually and in combination: risks of, etiology of, cause of, HDT, supraphysiologic doses of thyroid, liothyronine (T3), levothyroxine (T4), thyroid stimulating hormone (TSH), TSH suppression, lithium, toxicity, tricyclic antidepressants, venlafaxine, selective serotonin reuptake inhibitors (SSRIs), neuroleptics, cardiovascular, cardiac, pulmonary hypertension, atrial fibrillation (afib), stroke, morbidity, mortality, bipolar, affective disorders, major depression, augmentation, thyroid cancer, autoimmune, hyperthyroidism, motor vehicle accidents and weight gain. Once key articles were identified, the citations of those papers were examined for relevancy using the PubMed "Related Citations" feature to search forward and backward for articles cited by the key article. In addition, the risks of psychiatric medications were also examined. Only statistically significant findings in the various studies are reported unless otherwise noted. All identified cases of afib associated with HDT from the author's clinic are reported. Approval for the study was obtained from the institutional review board of the Poudre Valley Health System.

### 2.1. Definition of terms

According to the joint task force of the American Thyroid Association and the American Association of Clinical Endocrinologists' management guidelines on hyperthyroidism treatment, thyrotoxicosis is defined as the presence of signs and symptoms of high circulating levels of thyroid hormone. Hyperthyroidism is defined as the overproduction of endogenous thyroid hormone with accompanying signs and symptoms of thyrotoxicosis. Both must be confirmed by laboratory studies. Hyperthyroidism is a subtype of thyrotoxicosis, while subclinical hyperthyroidism is a mild form of hyperthyroidism defined by TSH levels below normal with normal T3 and T4 levels. It may or may not be accompanied by thyrotoxic symptoms (Bahn et al., 2011). International authors agree with these definitions (Mansourian, 2010).

Other terminology used to describe the use of HDT to treat disease states appears to be a hodgepodge of terms that are not strictly defined, overlap, and or are defined differently in various studies. T3 doses of 50 mcg or less have been consistently regarded as augmentation in the psychiatric literature. "HDT" would then be defined as T3 doses above 50 mcg. The corresponding doses of T4 would be 200 mcg or less for augmentation and greater than 200 mcg for HDT. "TSH suppressive therapy" is defined as TSH levels below the accepted normal range for TSH or alternatively TSH levels below 0.1 u/ml. Three definitions of "superphysiologic" dosing are found in the literature: any alteration of thyroid hormone levels outside normal lab values, TSH levels below the normal range, or TSH levels of 0.1 u/ml even if T3 and T4 levels are normal. The use of "HDT" in this paper generally refers to doses of thyroid hormone greater than those typically used for augmentation. In this paper, the term "clinical experience" refers to the experience gained from more than 600 HDT trials. Two subsets of this experience has been previously published (Kelly and Lieberman, 2009a; Kelly and Lieberman, 2009b).

## 3. Results

### 3.1. Cardiovascular risks of hyperthyroidism

Hyperthyroidism is associated with a number of potentially lethal conditions such as structural changes in the heart, thromboembolic