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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

episodes and arrhythmias (Brandt et al., 2011). Hyperthyroidism has been linked to pulmonary hypertension (Vallabhajosula et al., 2011; Klein and Danzi, 2007). Overall the mortality of individuals with hyperthyroidism is 20% higher than the population (Fazio et al., 2004). Graves' disease is an autoimmune disorder and the most common cause of hyperthyroidism when in the setting of sufficient dietary iodine; it is triggered by autoimmune antibodies that mimic TSH. Graves' disease is linked with other autoimmune complications including pulmonary arterial hypertension, cardiac valve involvement, and specific cardiomyopathies (Biondi and Kahaly, 2010). Graves' disease is not limited to the thyroid gland; 90% of patients have one or more other pathologies such as orbitopathy (exophthalmos), dermopathy (pretibial myxedema), acropachy (Marie's disease), myxoid degeneration and cardiac valve prolapse (Biondi and Kahaly, 2010). Prospective studies have revealed a high prevalence of pulmonary arterial hypertension in patients with hyperthyroidism (40%) (Biondi and Kahaly, 2010). Afib is the most common cardiovascular sequelae of hyperthyroidism, but the reported rate of afib varies widely. Bondi's and Kahaly's 2010 review article reported that afib develops in 10–28% of patients compared with 0.5–9.0% of the general population (Biondi and Kahaly, 2010). Fazio described that afib affects 5–10% of overt hyperthyroid patients and often leads to the discovery of hyperthyroidism (Fazio et al., 2004). In the Danish National Registry, afib is most commonly associated with hyperthyroidism. This review reported that the prevalence of afib in hyperthyroid individuals was 13.8% compared to $<2\%$ of controls (Klein and Danzi, 2007).

The risk of afib is increased in hyperthyroid individuals with other risk factors including male sex, advanced age, a history of cardiac failure, diabetes, left ventricular hypertrophy, heart valve disease, ischemic heart disease, congestive heart failure, valvular heart disease, elevated systolic and diastolic blood pressures. Other cardiac arrhythmias, atrial flutter, ventricular tachycardia and paroxysmal supraventricular tachycardia are uncommon (Fadel et al., 2000). Heart failure occurs in between 6% and 16% of hyperthyroid patients (Biondi and Kahaly, 2010; Conradie et al., 2012).

Risk factors in the Danish National Registry for the development of afib in hyperthyroid individuals were male gender, ischemic heart disease, valvular heart disease and congestive heart failure (Klein and Danzi, 2007). Afib associated with hyperthyroidism is age dependent and is rare for those younger than 40. Over age 60, the rate is 25–40% (Fadel et al., 2000).

Toxic multinodular goiter, the second most common cause of hyperthyroidism in areas with adequate dietary iodine, is caused by autonomous thyroid nodules that are TSH independent. Patients with toxic multinodular goiter have an afib prevalence of 43%, an increased risk for atrial enlargement and an increased risk of cerebrovascular disease. A study of 3346 patients presenting with toxic multinodular goiter, Graves' disease or Hashimoto's thyroiditis who were followed for 20 years revealed an increased relative risk (RR) of 1.42 for the development of cardiovascular problems but no increased risk for mortality was found. Toxic multinodular goiter was found to increase the risk of cardiovascular disease, RR 1.50 and cerebrovascular disease in patients over age 65. It is hypothesized that the cardiovascular risks of hyperthyroidism stem from inflammation secondary to autoimmune risks and or radioiodine (Nyirenda et al., 2005).

Pulmonary hypertension has also been linked with hyperthyroidism (Klein and Danzi, 2007). Prospective studies have demonstrated a high prevalence of pulmonary arterial hypertension in patients with hyperthyroidism (40%). Carotid artery stiffness, a marker of subclinical atherosclerosis, has been associated with hyperthyroidism (Biondi and Kahaly, 2010).

In hyperthyroidism the risk of autoimmune mediated problems does not end with definitive treatment of the hyperthyroidism. Treating hyperthyroid patients with radioiodine doubles TSH receptor antibody levels in the first year and 60% of radioiodine patients still have elevated TSH receptor antibodies at the end of 5 years. Patients who undergo surgical thyroid removal or are treated with thyroid suppressive medication fared better; TSH-receptor antibodies levels gradually fell over 5 years, but 10% still had significant TSH-receptor antibody levels at 5 years (Laurberg et al., 2008). How other autoimmunities associated with hyperthyroidism fare after treatment is unknown but because there is a 20% risk of developing new or exacerbating Graves' orbitopathy after radioiodine treatment compared to only 5% after thyroid suppressive medication (Ponto et al., 2010; Laurberg et al., 2008), it is likely that the risks of other autoimmune problems associated with hyperthyroidism continue to be a risk after radioiodine treatment.

3.2. Cardiovascular risks of subclinical hyperthyroidism

Subclinical hyperthyroidism has been associated with a number of cardiac complications, including afib. A study of individuals over age 60 with subclinical hyperthyroidism who were followed for 10 years revealed a RR of 3.0. For individuals with subclinical hyperthyroidism not taking exogenous thyroid hormone, the RR was increased to 3.8 (Sawin et al., 1994).

Bernadette Biondi published an excellent discussion of the risks of subclinical hyperthyroidism in 2012. The commentary discussed all seven meta-analyses of cardiovascular risks associated with subclinical hyperthyroidism, with the most robust data coming, according to Dr. Biondi, from the two most recent meta-analysis were considered the most credible. They only included prospective studies, excluded patients who were taking thyroid medication, and used only second and third generation TSH measures (Biondi, 2012a). Dr. Bondi reported that Yang et al. showed the overall combined RR of cardiovascular disease for individuals with subclinical hyperthyroidism compared with the reference group was 1.19 and mortality showed a RR of 1.52, with an RR of 1.25 for all-cause mortality (Yang et al., 2012). Collet et al. performed age and sex adjusted analyses and found that subclinical hyperthyroidism was associated with an increased hazard ratios (HRs) for total mortality, coronary heart disease mortality, coronary heart disease events, and afib HRs of 1.24, 1.29, 1.21 and 1.68, respectively. Interestingly, the risks, except for that associated with stroke, increased with decreasing TSH levels (Collet et al., 2012).

Another study reported that a low TSH value (0.04–0.4 mU/l) did not increase cardiovascular risk. Cardiac risks associated with TSH levels were studied in a large population-based Scottish study involving 17,684 patients and 78,518 patient years. The median follow-up was 4.5 years, and the mean age was 60.5. The authors classified TSH values into four categories: high (>4.0 mU/l), normal (0.4–4.0 mU/l), low (0.04–0.4 mU/l), and suppressed (<0.04 mU/l). The high TSH category was associated with the largest HR for cardiovascular death (1.95), and the HR for death from arrhythmias was 1.80. There was no statistical difference between the low and normal TSH categories. In the suppressed TSH group, the HR for "cardiovascular/death" was 1.37 and the "dysrhythmia/death" HR was 1.60. The population contained a mixture of patients who were previously hyperthyroid; hypothyroid on replacement therapy; and had spontaneously high, normal, low, or suppressed TSH. It included a minority of patients who preferred and were given doses of T4 that resulted in low or suppressed TSH (Flynn et al., 2010).

3.3. Cardiovascular risks of HDT used in to treat DTC

HDT is recommended for this use in the expert guidelines task force of the American Thyroid Association for the treatment of well differentiated thyroid cancer (DTC). HDT has been shown to suppress the recurrence of stages II–IV DTC. There appears to be no benefit of HDT for stage I DTC (Cooper et al., 2009).

None of the DTC review papers evaluated in the review of osteoporosis risks reported increased cardiovascular morbidity or

mortality with HDT (Kelly et al., 2013). Three studies found no indication that HDT increased cardiovascular risks or premature death. A Finnish study that followed 2479 patients treated for DTC compared the causes of death to those of the general population. There was no significant difference between the DTC group compared to general public for the 16 year study period (Akslen et al., 1991). In a multi-institute registry study with a median of 3-year follow-up (range 0–14) for a total of 10,994 person-years, HDT treatment was shown to be beneficial to overall survival and disease specific survival for patients with stage II, III, and IV DTC ($n=1644$). There was no difference in the overall survival of stage I thyroid cancer patients treated with HDT ($n=681$) compared to other Stage I DTC patients who received replacement thyroid hormones ($n=611$). This is important because this is the only study that one can directly compared the two populations of DTC patients, that is patients treated with HDT and patients treated only with replacement doses. With the exception of HDT, the groups were treated the same. Notably, increased mortality was not observed in the HDT treated patients (Jonklaas et al., 2006).

A study of 504 Dutch patients followed for median of 9 years found no significant difference of cardiovascular or all causes death in individuals treated for DTC who did not have thyroid cancer recurrence (Links et al., 2005).

Only one prospective study of 524 Dutch patients being treated for DTC described increased cardiovascular deaths associated with TSH suppression. TSH levels were monitored and the median follow up time was 8.5 years. The authors reported a rate of 4.2% ($n=22$) cardiovascular related deaths with calculated HRs of 3.15 and 4.40 for cardiovascular death and all-cause mortality, respectively. The cardiovascular mortality HR of the DTC group was increased by 3.08 with every 10-fold decrease in TSH. However, this study incorrectly applied the use of HR; the appropriate control group would be DTC patients who received replacement levels of thyroid hormone not the general public. Furthermore, as the authors acknowledged, greater efforts were made to find the cause of death for the DTC group, where hospital records, medical records, autopsy reports and information from general practitioners was considered. The control group was essentially the general public. Another potential confounding factor was the large number of patients lost to follow up; the death of even a few more patients from either the treatment or control groups could have altered the outcome if these individuals had been included in the final analysis. Interestingly none of the patients with a known history of diabetes or heart disease in the DTC group died, yet the authors chose to adjust for these factors. This is counter intuitive to the notion that HDT increases the risks of cardiovascular mortality. Furthermore, important information needed to interpret the outcome is missing, such as the ages of the patients who died. While the authors reported the number of patients who died from DTC recurrence, they did not describe whether any of the patients who experienced cardiac death did so during a DTC recurrence. It is not unreasonable to suspect that patients weakened by DTC recurrence and associated treatments may be more vulnerable to other causes of death. The authors also did not report the number of patients who died from cardiovascular causes while their thyroid hormone medications had been completely stopped to check for DTC recurrence (Hesselink et al., 2013).

Only one paper by Abonowara et al. (2012) discussed whether the long term use of HDT to prevent recurrence of thyroid cancer increased the risk of afib. The study included 136 patients who were followed for an average 11 years. The mean TSH level was 0.17 mIU/L. A total of 14 patients were found to have afib: 2 with long-standing persistent afib and 12 with paroxysmal afib. The authors concluded that "TSH suppression in thyroid cancer is associated with a high prevalence (sic) of afib ($p<0.0001$)". However, careful examination of this paper reveals numerous mistakes that not only negate this conclusion but actually appear to contradict it. First, the study used the term prevalence when they should have used incidence. Second, they included a patient with pre-existing afib before HDT was started. Third, and most egregiously, the authors used a definition of afib that significantly differed than that used in the cited comparison paper. The authors, Abonowara et al. (2012) include in their count of afib 14 patients, 2 with persistent afib and 12 with paroxysmal afib but in the comparison paper, Go et al. defined afib as including only "Patients with nontransient atrial fibrillation." (Go et al., 2001). This would exclude the 12 patients with paroxysmal afib. If the one case of persistent afib that was present before the use of HDT and the paroxysmal afib cases were excluded, the incidence of afib for patients treated for HDT was only 0.74% ($n=1$). In comparison, the prevalence of afib in the cross-sectional study by Go et al. was just 0.95% (Go et al., 2001; Abonowara et al., 2012).

HDT may have some positive cardiac effects. Thyroid hormones have a pro-angiogenic effect and can stimulate arteriolar growth in a normal heart as well as after myocardial infarction (Biondi, 2012b).

Three factors may complicate the comparison of HDT use in affective disorders versus suppression of DTC recurrence. The first is that to check for DTC reoccurrence, all thyroid hormone treatment is abruptly stopped at least twice, each time typically for 1–3 weeks with the goal to get TSH to >30 μIU/ml. The acute withdraw of all thyroid hormone can have serious effects on multiple organs, including the brain and cardiovascular system. This can impair quality of life, be harmful to patients with preexisting cardiovascular disease, worsen lipid levels and exacerbate pre-existing psychiatric disorders. There is evidence that short term thyroid withdraw can have lasting cardiovascular effects, particularly in the elderly (Duntas and Biondi, 2007).

The second potential compounding factor is that anti-thyroglobulin antibodies occur in around 25% of thyroid cancer patients compared with 10% of the general public (Cooper et al., 2009). These antibodies persist in 72% of patients who undergo thyroid gland removal and radioiodine therapy (Pacini et al., 1988).

The third potential confounding factor is that used as part of the protocol for DTC treatment and hyperthyroid patients may increase the risks of cardiovascular and overall mortality (Biondi, 2012a). Four investigations described increases in all-cause mortality and cardiovascular mortality associated with radioiodine treatment, but other studies have not reached this conclusion (Biondi, 2012a). Radioiodine treatment may increase the risks of arrhythmias, atrial fibrillation, cerebrovascular disease, and heart failure, particularly in elderly patients with toxic multinodular goiter (Biondi, 2012a). Considering these three factors, it is possible that HDT is safer in affective patients than in those who are prescribed HDT to prevent the return of thyroid cancer or hyperthyroidism.

In hyperthyroidism the risk of autoimmune mediated problems does not end with definitive treatment of the hyperthyroidism. Treating hyperthyroid patients with radioiodine doubles TSH receptor antibody levels in the first year and 60% of radioiodine patients still have elevated TSH receptor antibodies at the end of 5 years. Patients who undergo surgical thyroid removal or are treated with thyroid suppressive medication fared better; TSH-receptor antibodies levels gradually fell over 5 years, but 10% still had significant TSH-receptor antibody levels at 5 years (Laurberg et al., 2008). How other autoimmunities associated with hyperthyroidism fare after treatment is unknown but because there is a 20% risk of developing new or exacerbating Graves' orbitopathy after radioiodine treatment compared to only 5% after thyroid suppressive medication (Ponto et al., 2010; Laurberg et al., 2008), it is likely that the risks of other autoimmune problems associated with hyperthyroidism continue to be a risk after radioiodine treatment.

3.4. Review of cardiovascular risks from psychiatric literature

No studies that directly examined the risks of HDT in psychiatric patients were identified. A psychiatric review examining the risks of T3 for the treatment of depression incorrectly equated HDT use with

hyperthyroidism and subclinical hyperthyroidism. The authors recommended that HDT be used with caution in those subjects with hypertension, tachycardia, and or hyperglycemia (Rosenthal et al., 2011).

In a 2001 review of HDT, Michael Bauer and Peter C. Whybrow stated, "However, there is no evidence from preliminary follow-up studies that the cardiovascular system is clinically impaired during supraphysiological T4 treatment in patients with affective disorders (unpublished data) (Bauer and Whybrow, 2001)."

3.5. Case reports of atrial fibrillation with HDT treatment

Since 2002, The Depression & Bipolar Clinic of Colorado has treated over 600 patients with HDT, with most cases overseen by the author. Five patients treated with HDT developed Afib. All the patients who developed afib had been treated with T3 and diagnosed with bipolar II or bipolar not otherwise specified (NOS). In the four cases where T3 was stopped, afib spontaneously remitted within 3–4 weeks. The first case was a 50 yo female who had a prior history of afib; treated with T3 for 10 months at a dose of 50 mcg. After stopping T3, she relapsed into a severe depression. After several unsuccessful treatment augmentations, she in consultation with her cardiologist resumed HDT and became euthymic. Over the subsequent 2 years her T3 dose was adjusted upward to almost double the dose on which she had previously developed afib without a reoccurrence of afib. The second case was a 35 yo male who developed afib after 3 months of treatment. His dose was 75 mcg per day. The patient reported that he developed afib after a day of heavy drinking (amount unknown), a large ingestion of methylphenidate (dose and source unknown), some caffeine use, self-described dehydration, and extensive sun exposure while attending a baseball double header. The third case was an 86 yo female who developed afib after 10 months of T3 treatment 50 mcg per day. After consultation with her primary care physician and her family, the patient elected to stay on HDT because of the previous severity of her depression. She has been prophylactically treated for clotting risks, and she has remained healthy without any complications associated with afib for 6.5 years. The fourth patient was a 55 yo female who developed afib after 8 years of treatment with a final T3 dose of 167.5 mcg daily. Addition trials of two other treatment agents failed to resolve her severe depression. After the return of severe depression including suicidal ideation, a 40 lb weight gain, restarting cigarettes and a work demotion that she directly attributed to the depression she resumed HDT. After 7 months the afib has not returned. The fifth case of was a 62 yo male treated for 8.5 years with T3 at a daily dose of 87.5 mcg who developed afib during a hospitalization for pneumonia, which is a known risk factor for a fib (Soto-Gomez et al., 2013). He did not have the afib at the time of admission. The afib spontaneously remitted after T3 was stopped and his pneumonia resolved. Severe depressive symptoms started to return after he was released from the hospital and HDT treatment was restarted. There has been no return of afib in the 8 months since reaching the previous HDT dose, and the patient is now euthymic.

3.6. Medical risks of common psychiatric medications

3.6.1. Lithium

There are three major ways that patients become toxic on lithium. The first is through an acute ingestion, accidental or a suicide attempt. The second is through long term iatrogenic, inappropriate lithium dosing and third is with concurrent use of medications that can raise lithium levels such as nonsteroidal antiinflammatory drugs, angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists (Cheng and Chong, 2013). Thiazide diuretics, by inducing sodium depletion, can lead to a 25% reduction of lithium clearance in just a week of therapy (Yip and Yeung, 2007). It is not unusual in clinical practice to find patients who start taking nonsteroidal antiinflammatory medications despite repeated warnings not to do so. Estimates of mortality due to lithium overdose range from 1% to 15% (Bailey and Mcguigan, 2000; Boeker et al., 2011). In patients suffering from severe lithium neurotoxicity, 92.9% of cases were attributed to chronic lithium poisoning. Chronic lithium poisoning carries a considerably higher risk of severe neurotoxicity than an acute lithium overdose, OR 6.20 (Oakley et al., 2001). In acute overdose one study estimated that 10% of survivors suffer permanent neurological sequelae after lithium toxicity (Boeker et al., 2011). Age plays an important role in the development of severe lithium neurotoxicity, with an adjusted odds ratio (OR) of 6.2 for individuals over 51 (Oakley et al., 2001).

Even minor disturbances in the hypothalamic-pituitary-thyroid axis have the potential to exacerbate the course of bipolar disorders. Studies have shown that lithium induces frank hypothyroidism in about 10% of individuals (range 0–47%) and induces subclinical hypothyroidism in about 25% (range 5–35%). Lithium concentrates in the thyroid gland where it retards iodine uptake and impairs iodotyrosine coupling and hormone secretion. Lithium also alters the structure of thyroglobulin and interferes with the conversion of T4 to T3 in the brain (Chakrabarti, 2011). Thyroid dysfunction significantly increases the risk for the development of lithium neurotoxicity (adjusted OR 9.3) (Oakley et al., 2001).

3.6.2. Tricyclics, SSRIs and MAOIs Antidepressants

It was not unusual to gain 1.3–2.9 pounds a month while taking tricyclic antidepressants; the overall average gain is 16 pounds, depending on which tricyclic was used. For this reason, patients often abruptly stop tricyclics because of weight gain (Berken et al., 1984). In addition, tricyclics have been associated with torsade de pointes and other arrhythmias (Vieweg and Wood, 2004). The risk of overdose with tricyclics is considerable. Before the introduction of selective SSRIs, tricyclic antidepressants were involved in 15–33% of fatal poisonings in the United Kingdom. Likewise in the U.S., tricyclics accounted for 37% of all poison-related admissions to intensive care. In general, tricyclic antidepressant use is associated with increased risk mortality from any cause, (HR 1.67). SSRI research has yielded conflicting results. In postmenopausal women, antidepressant use (primarily SSRIs) is not associated with coronary heart disease, but SSRIs are associated with increased stroke risk (HR 1.45), with an even higher risk of fatal stroke (HR 2.12). In patients taking SSRIs, all-cause mortality HR is 1.32. In addition, the published HR for sudden cardiac death in patients on SSRIs was 3.34. However, other studies have reported that SSRIs may decrease coronary artery disease (Narayan and Stein, 2009). Monoamine oxidase inhibitors also carry a plethora of risks due to food or drug interactions; many are potentially lethal. Severe serotonin syndrome mostly associated with monoamine oxidase inhibitors carries a high mortality rate (De-Yuan, 2009).

3.6.3. Antipsychotics

A significant risk of cardiac death was found for antipsychotics in a retrospective study of Tennessee Medicaid patients that included 481,744 patients with 1,282,896 patient years. With moderate antipsychotic doses, the sudden cardiac death rate was 2.39 greater than in non-users even when the findings were controlled for smoking and health risks associated with serious mental illness. This rate was only slightly reduced when schizophrenia was excluded. As a comparison current smokers had approximately twice the risk of sudden cardiac death compared to the general public (Ray et al., 2001).

Another large retrospective study (24,589 patient years) also found that antipsychotic use was a significant risk for sudden cardiac death. The incident rate ratios for specific drugs were: haloperidol, 1.61; thioridazine, 3.19; typical antipsychotics, 1.99; atypicals, 2.26; clozapine, 3.67; olanzapine, 2.04; quetiapine, 1.88; and risperidone, 2.91. These were only slightly decreased when schizophrenia was excluded. The incidence rate ratios for sudden death from atypical agents ranged from 1.59 to 2.86 for low to high doses. Past users of

antipsychotics did not have a significant risk of sudden cardiac death. The control group comprised other mentally ill individuals who were not taking antipsychotics. The authors corrected the results for medical confounding factors including smoking, other cardiovascular factors, somatic diseases, use of proarrhythmic medications, mood disorders, behavioral risk factors, substance abuse, poor self-care, and other effects of mental illness. They also excluded deaths from other causes and those that occurred during hospitalization or within 30 days of discharge (Ray et al., 2001).

Although rare, neuroleptic malignant syndrome has a high mortality rate (De-Yuan, 2009).

Individuals taking clozapine have a 1% risk of developing agranulocytosis during the first year of treatment (Package-Insert). One study reported that the mortality rate in clozapine users due to agranulocytosis was less than 1.2 per 10,000 (0.38% for all clozapine users). The incidence of myocarditis with clozaril ranges from 1 in 500 to 1 in 10,000. While rare, clozapine-related cardiomyopathy carries a 38% mortality rate (Tanner and Culling, 2003). Sedating psychotropic medications are associated with an increased risk of motor vehicle accidents (MVAs). High potency sleep medications (e.g., zolpidem, zopiclone, eszopiclone, and zaleplon) have an adjusted OR for MVAs of 2.1 and that for benzodiazepines is 2.09. Lower doses of antipsychotics carry an adjusted OR of 1.31 for MVAs; counterintuitively, the adjusted OR is lower for higher doses (0.92) (Chang et al., 2013a).

A British study revealed that in the first 4 weeks of benzodiazepine use, the incidence rate ratio for MVAs was 1.94. Over time, the incidence rate ratio increased to 2.38. In comparison, the respective incidence rate ratios for SSRIs and antihistamines were 1.16, and 1.21, while that for opioid use was 1.70–2.06 (Gibson et al., 2009). In a study of 64 patients, valproic acid use was associated with elevated serum amylase levels and pancreatitis in 19% and 1.5% of individuals, respectively. In another study of 10 patients on valproic acid who developed pancreatitis, 7 experienced a recurrence when rechallenged (Yazdani et al., 2002). Fatal hepatotoxicity from valproic acid ranges from 1 in 8312 to 1 in 15,517. In a more recent meta-analysis the younger the age the greater the risk. Poly pharmacy increases the risk (Bryant and Dreifuss, 1996).

3.6.4. Weight gain

Weight gain in itself is associated with significant mortality and morbidity, and many current psychiatric medications can and do cause weight gain. In the general male population younger than 50 yo, those with high body mass index (BMI) values had twice the risk of coronary heart disease compared with those with low BMIs. Similarly, the risk was increased 2.4-fold among obese women of the same age. Higher BMI values were associated with higher risks for sudden death in all age groups. The incidence of congestive heart failure in subjects younger than 50 increased 2.5–3 fold from the leanest to heaviest subjects. Women <70 years old with high BMI values had a four-fold higher stroke rate compared to the leanest group (Hubert et al., 1983). In particular, lithium-treated patients frequently gained 5% or more of their baseline weight (Fagiolini et al., 2002). In addition to cardiovascular risk, weight gain also increases the incidence and severity of sleep apnea. This is important given that the risk for obstructive sleep apnea (OSA) is already high in subjects with bipolar disorders, with estimates of 47% (Kelly et al., 2013; Soreca et al., 2012).

3.7. Is there a difference between hyperthyroidism and HDT treatment of affective disorders?

The main difference between HDT and hyperthyroidism is that the high circulating levels of thyroid hormones in subjects with Graves' hyperthyroidism are caused by autoimmune antibody that mimics TSH (Biondi and Kahaly, 2010). This is frequently accompanied by multiple autoimmune conditions, (Biondi, 2012b); conversely, other autoimmune diseases are associated with increase thyroid autoimmunity. For example, 27% of patients with rheumatoid arthritis also have autoimmune thyroid disease (Benvenga, 2013). Exophthalmos (Wall and Lahooti, 2010) and Graves' dermopathy (pretibial myxedema) (Topliss and Eastman, 2004) have definitively been shown to be caused by autoimmune processes. There is mounting evidence that many or even all of the sequelae previously attributed to high circulating levels of thyroid hormone in Graves' disease are in fact due to autoimmune antibodies (e.g., cardiovascular disease, pulmonary arterial hypertension, and myxomatous cardiac valve disease) (Biondi, 2012b). Furthermore, pulmonary hypertension linked to hyperthyroidism is also associated with other autoimmune diseases; personal or family history of autoimmune thyroid disease is reported in roughly half of the patients with pulmonary arterial hypertension (Klein and Danzi, 2007). Conversely, there is no suspicion that HDT is associated with autoimmune problems. Patients suffering from affective disorders respond to HDT differently than subjects without affective or thyroid abnormalities. A study that compared the effects of HDT treatment in a group of refractory bipolar depressed and major depressed patients with a matched control group of non-affectively ill volunteers was conducted. Both groups were started at a dose of 100 mcg a day that was titrated to 500 mcg a day (if tolerated) over a 4-week period. This dose was maintained for 4 more weeks. In the refractory depressed group the Hamilton depression rating scale (HAM-D) score decreased from 27.0 to 10.7, while the control group's score increased from 0.9 to 5.2. Thyrotoxic symptoms caused 38% of the control group to discontinue T4 while none of the T4 augmentation group halted treatment. There were no differences in thyroid hormone levels of both groups at the start of the study. TSH was equally suppression in both groups at the end of the study. The control group had T3 and T4 levels were significantly higher than the affective group after the intervention (Bauer et al., 2002).

There is now evidence that blood thyroid levels of subjects with affective disorders do not accurately reflect the more important intercellular thyroid levels. This could potentially be the biggest difference between HDT and hyperthyroidism. It was previously believed that T3/T4 transportation was achieved through passive diffusion into cells. However, this process is energy dependent and requires active transportation, and T4 is more energy dependent than T3. However, the pituitary uses a different and far less energy dependent mechanism to move T3/T4 across the cell membrane. This discrepancy between pituitary cells and the rest of the body can lead to “false normal” thyroid blood levels when the rest of the body is actually in a state of cellular hypothyroidism. Bipolar disorders and major depression have been identified as diseases in which this discrepancy is present (Holtorf, 2014).

3.8. Benefits of HDT for affective disorders

A review of the benefits of HDT was previously reported (Kelly, 2014). Subsequently a new prospective double blind placebo controlled study has been reported. This was carried out to assess the utility of HDT for bipolar I disorder. It failed to find significant effects compared to placebo. Sub analyses revealed female subjects did show statistically significant improvement. Men initially experienced significant improvements but an unexpected placebo response erased the significance. There are a number of concerns with this study. Firstly, steady state levels could not have been achieved by the end of the study; the treatment period was just 6 weeks and the T4 dose did not reach the goal of 300 mg until the third week. Given that T4 has a half-life of approximately 7 days, the subjects did not have time to reach full blood levels. Moreover, a fixed dose of 300 mcg is lower than doses found in most case series. Flexible

dosing could have yielded better results. Secondly, the authors chose the lesser studied T4 despite the plethora of factors that can adversely affect T4 blood levels (Stamm et al., 2014).

4. Discussion

There have been two major objections to the use of HDT to treat affective disorders. However, a careful examination of the literature reveals that these objections turn out to be myths. The first myth, that HDT poses a risk of osteoporosis, was disproven in an earlier review (Kelly, 2014).

4.1. What differentiates HDT from hyperthyroidism?

Hyperthyroidism causes 20% more premature death in affected subjects than in the population at large (Fazio et al., 2004). Yet neither the literature describing the use of HDT for affective disorder or DTC nor clinical experience show any indication of this whole sale increase in the rate of death found with hyperthyroidism despite the fact that HDT treatment continues for decades.

When the risks HDT were directly studied in the three papers discussed above (four if you include the corrected paper) indicate that HDT used to prevent thyroid cancer recurrence does not increase cardiovascular risk or cause premature death (Jonklaas et al., 2006; Links et al., 2005; Akslen et al., 1991). There are a larger number of studies implicating cardiovascular complications associated with radioiodine treatment than there are for HDT (Biondi, 2012a).

Two studies purported that long term HDT may be associated with some degree of cardiac risk (Abonowara et al., 2012; Hesselink et al., 2013). As discussed above, there were numerous problems with the Abonowara et al. study. In the context of these issues, it would appear that HDT did not increase the risk for developing afib in thyroid cancer patients. The Hesselink et al. paper posited that HDT used to prevent the reoccurrence of thyroid cancer increased mortality, but they failed to consider other factors such as the risks involved with abruptly stopping T4 which is part of the protocol to assess for DTC reoccurrence. The biggest objection to both studies is that considerably more effort was made in obtaining data from the treatment group than the control group, thus rendering the comparisons invalid. Both papers compounded this error by incorrectly applying statistical methods. The fallacy of comparing prevalence rates in general populations and study groups was illustrated by published research conducted by the author. Previously, the only estimate of the prevalence of OSA in those suffering from a bipolar disorder was 3.3% based on information from a large Veterans Administration database. When patients were actively screened, the point prevalence of OSA was found to be at least 21% and perhaps as high as 47% (Kelly et al., 2013).

The question arises of why there is such discordance between the risks of hyperthyroidism and HDT. It was previously posited that the causes of morbidity and mortality associated with hyperthyroidism were due to high circulating levels of thyroid hormones. This is likely due to the fact that hyperthyroidism is usually recognized based on symptoms caused by high circulating levels of thyroid hormone. On the other hand, the lack of signs and symptoms of thyrotoxicity in patients with affective disorders who receive HDT treatment would seem to contradict this. In addition, there seems to be little or no relationship between thyroid hormone blood levels and hyperthyroidism symptom severity (Trzepacz et al., 1989). The biggest difference between HDT treatments and hyperthyroidism is that the latter is mediated by an autoimmune process. The root cause of Graves' hyperthyroidism is the production of an autoimmune antibody that stimulates the TSH receptor. A growing body of evidence indicates that the risks of medical complications of hyperthyroidism are caused by accompanying autoimmunities (Kalra and Khandelwal, 2011; Klein and Danzi, 2007; Yanai-Landau et al., 1995). In fact the sequela of medical problems associated with hyperthyroidism and high circulating thyroid hormone levels have never been more than a correlation. Multiple studies have discussed the correct dosing of thyroid hormones or TSH levels following hyperthyroid treatment. Due to the persistence of autoantibodies the results are not relevant to potential risks associated with HDT in subjects with affective disorders.

The myth that HDT carries the same risk as hyperthyroidism stems from the correlation between hyperthyroidism and high circulating thyroid hormone levels being assigned the status of cause and effect. Clearly the lack of cardiovascular and osteoporosis risks (Kelly, 2014) when HDT is used to prevent reoccurrence of thyroid cancer shows that this is not a cause and effect relationship. This inaccuracy has been promulgated by the chronic misuse of terminology (i.e. calling all suppressed TSHs or elevations of thyroid hormones hyperthyroidism). In the literature and in discussion with other clinicians, there is at best confusion about the difference between HDT and hyperthyroidism. At worst there is remarkably resolute conviction that there is no difference. To sum, the use of HDT is not equivalent to hyperthyroidism. By definition HDT treatments cannot cause hyperthyroidism, which is the result of overproduction of endogenous thyroid hormone accompanied by thyrotoxic symptoms and is confirmed by laboratory studies. The definition of thyrotoxicity is high circulating thyroid hormone levels with clinical signs and symptoms of excess thyroid hormone confirmed by elevated thyroid laboratory values (Bahn et al., 2011). The presence of signs or symptoms of thyrotoxicity when using HDT for affective treatment would warrant dosage reduction. Clinically HDT suppresses TSH levels and often results in elevations of T3 and or T4; however, without actual thyrotoxic signs or symptoms, this would not be considered evidence of thyrotoxicity.

The medical literature reveals a nearly complete lack of differentiation between HDT and hyperthyroidism (including subclinical hyperthyroidism). For example despite the correct use of the term subclinical thyrotoxicosis, the *Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer* cite papers that either refer to hyperthyroidism or do not support the guidelines' assertion that HDT is a risk (Cooper et al., 2009). When discussing the risks of HDT the guidelines state that "Adverse effects of TSH suppression may include the known consequences of subclinical thyrotoxicosis." However the only citation referred to was actually a study of subclinical hyperthyroidism ($>96\%$ of subjects were not taking exogenous thyroid hormone) (Sawin et al., 1994). The paper cited by the guidelines to warn of the risks of HDT causing osteoporosis does not support this assertion that it does cause osteoporosis. The article referred to concluded that "The evidence that exogenous (thyroid) is a risk factor for osteoporosis is therefore inconclusive (Toft, 2001)." Curiously the guideline taskforce failed to consider the extensive literature that directly examined the risks of external HDT (Cooper et al., 2009). The failure to keep in mind that high circulating thyroid hormone levels and the associated sequelae of hyperthyroidism are a correlation and disregard of appropriate terminology helped create and maintain the myth that HDT carries the same risks as HDT. Furthermore the myth has been perpetuated by ignoring a large body of direct research as presented in this paper and other review papers (Kelly, 2014).

There is clear experimental evidence that HDT and hyperthyroidism should not be equated. The treatment of affective disorders with HDT has profoundly different effects than those associated with hyperthyroidism. As discussed above, a group of affectively ill individuals tolerated 400 mcg of T4 with no drop outs in the treatment group, had a substantial decrease in the mean HAM-D score, and the mean blood levels of T3 and T4 significantly lower compared to that of the control group. Conversely, 38% of subjects in the control dropped out of the study due to side effects and their HAM-D scores increased (Bauer et al., 2002). Furthermore, there is evidence that HDT treatment corrects an abnormal physiologic state. An 18-fluoro-deoxyglucose

positron emission tomography study demonstrated that treatment of refractory bipolar depressed female subjects with 400 mcg of T4 resulted in the normalization of abnormal brain metabolism, particularly in the prefrontal and limbic brain areas. Further, none of these subjects dropped out due to side effects (Bauer et al., 2002). Conversely, thyroid cancer survivors treated with HDT often do not tolerate TSH suppressive doses that can impair psychological, social and physical functioning, especially in very low TSH ranges (Biondi and Cooper, 2010).

It is difficult to draw firm conclusions from the five case reports. Whether or not HDT is used, there would be a certain percentage of patients who spontaneously develop afib as happens in the general population. In four of five cases there were plausible alternative risk factors for afib including advanced age (Heeringa et al., 2006), drug/alcohol abuse (Schelleman et al., 2012), pneumonia (Soto-Gomez et al., 2013) and a history of afib. However, that the afib stopped within 3–4 weeks in all four cases for which HDT was stopped indicates that HDT may have been a contributing factor. That afib did not return when rechallenged with T3 in two individuals weaken this association, especially because one of the cases eventually reached a far higher dose of T3 than previously used and still did not experience an afib recurrence.

Even if the risk of afib is increased with HDT, it should not be considered a major risk. The risk can be minimized by monitoring patients. This can easily be accomplished with a pulse oximeter with a wave form that facilitates monitoring for an irregularly irregular heart rhythm, the hallmark of afib. In hyperthyroidism, afib spontaneously remits after treatment depending on age and the length of time that afib was present (Fazio et al., 2004, Biondi and Kahaly, 2010). The risks of other arrhythmias (e.g., atrial flutter, ventricular tachycardia and paroxysmal supraventricular tachycardia) are uncommon even in hyperthyroid subjects (Fadel et al., 2000). The absence of autoimmune damage to the cardiovascular system associated with hyperthyroidism may predict lower risks of arrhythmias with HDT. The observations of no increase in sudden cardiac death rate or mortality in HDT studies would suggest that the risk of ventricular fibrillation is minimal or absent.

Who should determine what medications psychiatric patients should take? The final arbiter is of course the patient. If we consult other specialties we should only ask what risks are involved for a proposed treatment course. Only psychiatrists who have a complete understanding of the risks of psychiatric illnesses, the risks/benefits of psychiatric treatments, the potential risks of alternative medications and the risks of not fully treating a psychiatric illness should make final treatment recommendations. We must not accept encroachment from other specialties regarding treatment recommendations for psychiatric patients. While we certainly should and need their considered opinion to inform us of risks related to the specialist's area of expertise, we should not abdicate our responsibilities and physicians who are not psychiatrists should not accept the responsibilities of making treatment recommendations concerning complex psychiatric conditions.

5. Limitations

No studies have directly assessed the cardiovascular risks of HDT in psychiatry patients. The morbidities and mortalities associated with affective disorders makes it difficult to separately assess the morbidity and mortality of medications used to treat these conditions. While the research indicates that HDT seems to be at least as safe as or safer than many of our psychiatric medications, specific medical problems and advanced age may preclude the use of HDT. The five case reports are spontaneous, and other cases may have gone unreported to the author. “Clinical experience” is used several times in this review. Even when the clinical experience is based on large number of patients, as in this review, it is a low level of evidence most useful when it supports formal studies. This shortcoming is mitigated by the fact that much of this experience has been systematically evaluated and published by the author. The assessment of the medical risks of psychiatric medications was a survey rather than a full review. The various definitions denoting the use of higher doses of thyroid hormone; TSH suppressive therapy, superphysiologic, and HDT each have slightly different meanings and are used in different contexts. The use of the term HDT is for convenience and to help delineate the differences when used for psychiatric treatments.

6. Conclusion

This is the second of two review papers debunking the myth that HDT carries the same risks as hyperthyroidism. Clearly this is not true. While the previous review dealt with the myth that HDT is a risk factor for osteoporosis, the present findings demonstrate that HDT does not carry the same cardiovascular risks as hyperthyroidism. Moreover the published evidence supports that HDT is at least as safe as or safer than other psychiatric medications. Furthermore, HDT treatment for affective disorders is well tolerated, efficacious and is at least as safe as other psychiatric medications. It is certainly safer than not fully controlling bipolar disorder. The use of any medication to treat affective disorders requires a careful risk-benefit analysis.

Refractory major depression and bipolar disorders are great burdens to patients, their families and society at large. Individuals with bipolar disorder die 10–11 years earlier than those without affective disorders (Leboyer et al., 2012) while the risk of premature death with breast cancer is less than ½ of that (Chang et al., 2013b). Bluntly, too many of our patients are suffering and dying prematurely to ignore a medication that has the potential to be of great benefit. HDT is well tolerated and has been shown to be effective for both bipolar disorders and refractory major depression. Although the only double blind placebo controlled research failed to show benefit from HDT at least in in males, the multiple problems with the research make it difficult to reach any conclusions, and the findings should not be a deterrent to the further investigation or use of HDT, which certainly deserves more attention from the research community.

The evidence cited in this review provides further proof that psychiatric treatment decisions should not be guided by other specialists who lack the requisite knowledge of the morbidities and mortality of psychiatric illnesses and do not understand the risks and benefits of alternative treatments. The myths surrounding HDT should not be a deterrent.

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Conflict of interest

None.

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