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Review

A favorable risk-benefit analysis of high dose thyroid for treatment of bipolar disorders with regard to osteoporosis

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ABSTRACT

High dose thyroid hormone has been in use since the 1930s for the treatment of affective disorders. Despite numerous papers showing benefit, the lack of negative trials and its inclusion in multiple treatment guidelines, high dose thyroid has yet to find wide spread use. The major objection to the use of high dose thyroid is the myth that it causes osteoporosis. This paper reviews the literature surrounding the use of high dose thyroid, both in endocrinology and in psychiatry. High dose thyroid does not appear to be a significant risk factor for osteoporosis while other widely employed psychiatric medications do pose a risk. Psychiatrists are uniquely qualified to do the risk-benefit analyses of high dose thyroid for the treatment of the bipolar I, bipolar II and bipolar NOS. Other specialties do not have the requisite knowledge of the risks of alterative medications or of the mortality and morbidity of the bipolar disorders to do a full risk benefit analysis.

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1. Introduction

Thyroid augmentation and high dose thyroid (HDT) can be an invaluable tool for stabilizing bipolar disorders. It is recommended in at least 4 treatment guidelines (Sachs et al., 2000; Yatham et al., 2013; Crismon et al., 2007; Hirschfeld, 2002). There are no negative trials of HDT for bipolar disorder and most augmentation trials for affective disorders are favorable. Despite this the use of HDT appears to be sparse based on the lack of published research and lectures discussing its use at the American Psychiatric Association's annual meetings (2012, 2013). The reluctance to use HDT may be based on false beliefs equating HDT with hyperthyroidism. For example, with few exceptions, the literature covering HDT includes caveats on the risks of hyperthyroidism. Any elevation of thyroid laboratory levels is often labeled as "hyperthyroidism" without regard to the presence or absence of

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thyrotoxic symptoms or the source of the high circulating levels of thyroid hormone. This could explain the confusion regarding the risks of hyperthyroidism and HDT, which in turn can result in conflict between psychiatrists and the rest of the medical community. Liothyronine (T3) and levothyroxine (T4) have long been recognized as being helpful treatments for affective disorders (Chakrabarti, 2011). The use of HDT hormone in psychiatry began in the 1930s when Norwegian physicians treated "periodic catatonia" using "hypermetabolic" doses of desiccated sheep thyroid gland. Since then numerous studies, discussed below, have provided evidence that support thyroid treatment for bipolar disorders (Bauer et al., 2003). With the recent inclusion of HDT in the Canadian treatment guidelines for bipolar II disorder, the use of HDT is becoming more widely recognized (Yatham et al., 2009).

The use of high-dose thyroid for the treatment of bipolar disorder has never been endorsed by endocrinologists and is considered dangerous (Rosenthal et al., 2011). For example, one expert states, "the use of thyroxine in euthyroid patients with a psychiatric illness should be regarded as controversial and potentially hazardous." Clinically, endocrinologists equate treatment with HDT with hyperthyroidism and do not perform a risk benefit analysis when advising patients on the use of HDT for psychiatric reasons.

Most studies of hyperthyroidism have reported a 12–20% reduction in bone mineral density (BMD) in hyperthyroid subjects (Lakatos, 2003). This risk of osteoporosis appears to be the main objection. Indeed, osteoporosis has profound implications for both society and individuals. The cost of osteoporosis in the United States was estimated to be between $13.7 billion and $20.3 billion in 2005 (Dempster, 2011). Osteoporosis is the major risk factor for fractures of the hip, spine, wrist, and other bones. Hip fractures alone increase the mortality risk by 10–20% within the first year of the fracture and confer a 2.5-fold increased risk for future fractures. One-third of patients who experience a hip fracture are admitted to a long-term care, and most patients do not regain their prefracture level of independence. Nevertheless, HDT is recommended by endocrinologists for non-psychiatric reasons. In patients with well differentiated thyroid cancer (DTC), HDT is routinely used post thyroidectomy to suppress DTC recurrence. The potential deleterious effect of thyroid hormone therapy on bone has been debated for the last two decades (Lakatos, 2003). The risk of osteoporosis from HDT in psychiatry has been considered before but the authors of that study failed to examine the bipolar literature or relevant non-psychiatric literature (Rosenthal et al., 2011). The objective of this paper was to examine the risks and benefits of HDT for patients with bipolar disorder with special regard to osteoporosis.

2. Methods

Google and Google Scholar (which includes PubMed) were used to perform multiple searches which employed 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 suppressive doses, osteoporosis, bipolar, affective disorders, major depression, augmentation, thyroid cancer, autoimmune, TSH receptors, fall risk, hyperthyroid and hyperthyroidism. Once key articles were identified the citations of those papers were examined for relevancy using the PubMed "Related Citations" feature. In addition, the risk of osteoporosis and fall risks from psychiatric medications were examined. The medical risks of bipolar disorders were examined.

Approval for the study was obtained from the institutional review board of the Poudre Valley Health System.

2.1. Definition of terms

According to a joint task force of the American Thyroid Association and the American Association of Clinical Endocrinologists' management guidelines on the treatment of hyperthyroidism, thyrotoxicosis is defined as the signs and symptoms of high circulating levels of thyroid hormone and hyperthyroidism is defined by the overproduction of endogenous thyroid hormone with accompanying signs and symptoms of thyrotoxicosis. Both must be confirmed by laboratory studies (Bahn et al., 2011). Hyperthyroidism is a subset of thyrotoxicosis (Bahn et al., 2011). Other international authors agree with these definitions (Mansourian, 2010). Other terminology used to describe the use of thyroid hormone to treat disease states appears to be a hodgepodge mixture of terms that are not strictly defined, overlap and or are defined differently in various studies. Doses of T3 of 50 mcg or less have been consistently regarded as the augmentation in psychiatric practice. "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 would be considered high dose. "Thyroid stimulating hormone (TSH) suppressive therapy" is defined by TSH levels below the accepted normal range for TSH or alternatively TSH levels below 0.1 u/ml. Three definition of "super physiologic" dosing is found in the literature: any alteration of thyroid hormone levels outside normal lab values, TSH levels below the normal range, or TSH levels <0.1 u/ml even if T3 and T4 levels are normal. High dose thyroid will be used in this paper and generally refers to doses of thyroid hormone greater than doses typically used for augmentation.

3. Results

There is a general agreement in the literature that HDT does not pose a risk for decreasing BMD in men or premenopausal women. The literature regarding postmenopausal women is mixed, with most studies showing no significant decrease in BMD and the rest reporting variability in the sites where the decreases in BMD were found.

3.1. Literature review: endocrine

HDT is routinely used in post-surgical treatment of DTC to suppress reoccurrence of the cancer (Quan et al., 2002). There is a large body of evidence supporting the safety and efficacy of this practice. A 2002 review article of 11 articles that studied patients with DTC found no significant change in BMD for men or premenopausal women. Findings for postmenopausal women lack consistency with two of the most well-designed studies from this review reporting opposing results. The study that showed a decrease in BMD was performed in China. The review article noted that the women in the Chinese study had low calcium intake. The subjects in the British study that did not show lower BMD had a much higher calcium intake (Quan et al., 2002). A 2006 review of 21 studies of the effects of HDT on patients with DTC treated with TSH suppressive doses of T4 found that in the eight studies that included men, two studies found decreased BMD, but six did not. In one of the studies that did find a decrease in men, only one of the three assessed sites showed a decreased BMD. In 17 studies of premenopausal women, five reported a decrease in BMD, and 12 studies showed no significant change in BMI. Sixteen studies addressed postmenopausal women; 4 showed significant decreases in BMD, while 12 studies did not (Heemstra et al., 2006). There have been three studies published since the last review paper. A 2008 cross sectional study of 66 patients (11 men, 22 premenopausal and 33 postmenopausal women) being treated for