Journal of Affective Disorders 116 (2009) 222–226

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Brief report

The use of triiodothyronine as an augmentation agent in treatment-resistant bipolar II and bipolar disorder NOS

Tammas Kelly [a,*], Daniel Z. Lieberman [b]

[a] The Depression & Bipolar Clinic of Colorado, 315 West Oak Street, Fort Collins, Colorado 80525, USA
[b] Department of Psychiatry and Behavioral Sciences, George Washington University School of Medicine and Health Sciences, 2150 Pennsylvania Ave. NW Washington, DC 20037 USA

ARTICLE INFO

Article history:
Received 12 July 2008
Received in revised form 3 December 2008
Accepted 9 December 2008
Available online 11 February 2009

Keywords:
Bipolar disorder
Manic depressive illness
Bipolar II treatment resistant depression
Bipolar disorder NOS

ABSTRACT

Background: Thyroid hormone plays a role in both serotonin and catecholamine functions in the brain, and has been linked to abnormal mood states in bipolar disorder. Unlike most studies which have included only patients with bipolar I, this study evaluated triiodothyronine (T3) as an augmentation agent for treatment-resistant depression in patients with bipolar II and bipolar disorder NOS.

Methods: This study was a retrospective chart review of patients treated in a private clinic between 2002 and 2006. The charts of 125 patients with bipolar II disorder and 34 patients with bipolar disorder NOS were reviewed.

Results: Patients had been unsuccessfully treated with an average of 14 other medications before starting T3. At an average dose of 90.4 mcg (range 13 mcg–188 mcg) the medication was well tolerated. None of the patients experienced a switch into hypomania, and only 16 discontinued due to side effects. Improvement was experienced by 84%, and 33% experienced full remission.

Limitations: The limitations are those associated with the retrospective chart review design.

Conclusions: A high percentage of bipolar II and bipolar NOS patients with treatment resistant depression improved on T3. Despite the use of higher than usual doses in many of the patients, the medication was well tolerated. Augmentation with supraphysiologic doses of T3 should be considered in cases of treatment resistant bipolar depression.

1. Introduction

Sir William Osler in *The Principles And Practice Of Medicine* noted that Caleb Hillier Parry was the first to connect thyroid abnormalities with psychiatric disorders (Osler, 1901). Most studies concerning thyroid hormones in depression are more than twenty years old, some of them having good methodological designs but few participants (Bahls and de Carvalho, 2004). The recently completed STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study was one of the largest studies to evaluate thyroid hormone in depression. Patients with major depressive disorder who had experienced inadequate benefits or drug intolerance in at least two previous drug trials were offered augmentation with triiodothyronine (T3). The dose was limited to 50 mcg, and 25% experienced remission.

Thyroid hormone plays a role in both serotonin and catecholamine function in the brain. Plasma serotonin levels have been found to be positively correlated to T3 concentrations (Cleare et al., 1995), and a hypothesized mechanism of this effect is the interaction between thyroid hormones and serotonergic auto-receptors. Thyroid hormones given to euthyroid animals, and those with induced hypothyroidism, caused a desensitization of the 5HT1A inhibitory auto-receptors, and increased serotonin in the cortex (Heal and Smith, 1998). Similarly, thyroid hormones have been found to influence the activity of beta-adrenergic post-synaptic receptors in which hypothyroid states can cause a functional decrease in noradrenergic neurotransmission (Hendrick et al., 1998).

* Corresponding author. Tel.: +1 970 484 5625 (Office).
E-mail address: TamKellyNews@comcast.net (T. Kelly).

0165-0327/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.jad.2008.12.010

Thyroid abnormalities have also been linked to abnormal mood states in bipolar disorder. Thyroid abnormalities have been associated with rapid-cycling (Cowdry et al., 1983; Bartalena et al., 1990; Oomen et al., 1996), mixed states (Chang et al., 1998), and slower treatment response (Cole et al., 2002).

There are no double-blind studies reporting the use of thyroid hormone in bipolar patients (Sachs and Thase, 2000). In an open-label trial, 10 of 11 rapid cycling bipolar patients with depression at baseline and five of seven patients with mania at baseline responded to supraphysiologic doses of levothyroxin (T4) added to their mood-stabilizing treatment regimens. (Bauer and Whybrow, 1990). Clinical response of patients was independent of initial thyroid status, and the effect was lost when the dose was reduced below supraphysiologic levels.

Most studies of thyroid hormone augmentation in bipolar disorder have included only patients with bipolar I disorder. Much less is known about bipolar II disorder and its treatment. In this study we performed a chart review of 159 patients with bipolar II or bipolar NOS disorders who suffered from refractory depression, and received augmentation with triiodothyronine (T3).

2. Methods

The charts of patients treated with T3 in a private clinic during the period of 2002–2006 were reviewed. The data were collected during the course of routine clinical practice by the lead author. The data were abstracted from the patient charts without identifying information. Patients were included in the analysis if they had a primary diagnosis of bipolar II or bipolar disorder NOS current episode depressed based on clinical examination, according to DSM-IV criteria, and had failed to attain stabilization with medications taken before T3. The diagnosis of bipolar disorder NOS was based on meeting full DSM-IV criteria for bipolar II disorder except the required duration was reduced from four days to two (Akiskal, 2007).

Demographic data and history of previous medication trials were recorded, as well as T3 dosage and duration of treatment. Efficacy was assessed with the Clinical Global Impression-Improvement (CGI-S) score, which is a 7-point scale ranging from 1 = very much improved to 7 = very much worse. The CGI-I scores were assigned by the prescribing clinician at the time of treatment. The assessment was based on both changes in mood and changes in stability and cycling. Additionally, remission was documented in the chart based on a Global Assessment of Functioning Score of 80 and above for at least two of the last visits. Pearson's correlation was used to explore the relationship between clinical improvement and the following variables: the duration of treatment with T3, the dose of T3, and the number of prior medication trials. Student's t-test was used to evaluate gender differences. Approval for the study was obtained from the institutional review board of the Poudre Valley Health System.

As with previous studies of T3 in the treatment of mood disorders, T3 was used as an augmentation agent. Dosing of T3 started at 25 mcg and was adjusted every 2 to 3 weeks in 12.5 to 25 mcg increments as clinically indicated until the maximum response was achieved or the patient was unable to tolerate the dose. If response was lost, this process was repeated with dose increases of 12.5 mcg until response was once again maximized. Mild tremor or heat intolerance were the only acceptable hyperthyroid symptoms, otherwise, if symptoms of hyperthyroidism appeared the dose was reduced.

Table 1
Clinical and demographic characteristics of study patients.

Age (years)	45.5 (SD = 13.2), range 16–84
Dose (mcg)	90.4 (SD = 37.4), range 13–188
Months of triiodothyronine use	20.3 (SD = 9.7), range 0.3–66.6
Previous medication trials	14.0 (SD = 8.8), range 1–43
Female	62.5%
Discontinued due to side effects	10.0%
Became hypomanic	0%
Became more depressed	1.9%

Table 2
Improvement on triiodothyronine augmentation.

Diagnosis	*N*	*N* improved	% improved	Mean CGI-I (SD)	% remission
Bipolar II	125	106	84%	1.9 (1.2)	32%
Bipolar NOS	34	29	85%	1.8 (1.2)	38%

3. Results

The charts of 159 patients who met the inclusion criteria were reviewed. As shown in Table 1, the majority of patients were female. Patients had been tried on an average of 14.0 medications, exclusive of present medications, prior to being started on T3. Very few patients experienced worsening depression, and none experienced a switch into hypomania on T3. A high percentage of patients experienced improvement on T3, and approximately one third went into remission (Table 2).

There were no gender differences in the average dose T3 (86.5 mcg for men and 92.7 mcg for women, $P = .31$), or in the magnitude of improvement as measured by the CGI-I (2.03 for men and 2.16 for women $P = .51$). Improvement was positively correlated with both the duration of treatment and the dose of T3. A significant negative correlation was found between improvement and the number of previous medication trials (Table 3). Four patients switched to T4, primarily for cost reasons, and experienced no loss of efficacy. One patient who also switched to T4 for cost reasons experienced a return of symptoms, which resolved with the reintroduction of T3.

The most common treatment-emergent adverse effect was tremor, which generally responded well to a dose reduction. A

Table 3
Correlation between clinical variables.

	R	*P*
Age and CGI-I	−.06	*NS*
Months taken and CGI-I	.55	<.01
Dose and CGI-I	.40	<.01
Previous medication trials and CGI-I	−.25	<.01

total of 16 (10%) patients discontinued T3 due to adverse effects. Bone loss was not systematically assessed, however three cases of osteoporosis were identified in patients. All of them were female, and all of them had the following risk factors for osteoporosis: a family history of osteoporosis, a greater than 10 pack-year history of smoking, an extensive history of serotonin reuptake inhibitor (SSRI) exposure, a long history of reduced activity associated with chronic symptoms of depression, and a greater than 10 year history of bipolar II disorder spent almost entirely in the depressive phase.

One of the three patients who developed osteoporosis was a 42-year-old woman who suffered from hyperparathyroidism. She had taken T3 for 11 months before osteoporosis was discovered, with a maximum dose of 125 mcg. The second patient was a 47-year-old woman who took T3 for 13 months with a maximum dose of 90 mcg, and had a history of exposure to carbamazepine and valproic acid. The third patient was a 54-year-old woman who took a maximum dose of 75 mcg with a length of exposure of 16 months. One of the three women discontinued T3 due to concerns about bone loss, one continued at a reduced dose, and the patient who suffered from hyperparathyroidism continued because the mood stabilization benefits outweighed the risk of continued bone loss. She initiated treatment with alendronate approximately 4 months ago, no follow-up bone scan has been performed at this time.

One patient, a 52-year-old woman with a history of atrial fibrillation, developed a recurrence of atrial fibrillation at a dose of 125 mcg. The atrial fibrillation terminated with medical intervention that included a reduction of the T3 dose. When the dose was reduced her depression became so severe that her cardiologist modified her anti-arrhythmia treatment so that she could return to her previous dose of T3. Her depression went back into remission after resuming the full dose of T3, and she has not experienced a return of atrial fibrillation.

4. Discussion

Thyroid augmentation is a commonly recommended treatment strategy for non-responsive bipolar mood episodes. The Expert Consensus Guidelines (Sachs et al., 2000) reported that experts frequently considered including thyroid hormone as an option in refractory bipolar disorder. Thyroid hormone was recommended for both rapid and non-rapid cycling patients for the treatment of acute depression, and the prevention of recurrent episodes of both depression and mania in rapid cycling patients. T3 was preferred over T4, and replacement rather than hypermetabolic doses were preferred for acute depression. The Texas Medication Algorithm Project for bipolar disorder also recommends thyroid hormone as an augmentation strategy for partially responsive or nonresponsive bipolar depression (Suppes et al., 2005). The guidelines recommend a target dose of between 25–50 mcg per day, and a maximum dose of 160 mcg per day (Crismon et al., 2007).

Despite the general agreement that thyroid hormone is an effective treatment, very little data has been published on its use. The current retrospective chart review is the largest sample of DSM-IV diagnosed bipolar patients to be assessed. The results support the clinical utility of a full range of T3 augmentation including high dose T3. More than 80% of the patients responded to T3, and approximately one third experienced remission. These findings are particularly significant in this sample of patients who demonstrated a high degree of treatment resistance. Prior to initiating T3, patients had failed to adequately respond to an average of 14 other medications used to treat their bipolar disorder. Not surprisingly, a larger number of failed trials in the past was correlated with a less favorable response to T3, however most patients experienced substantial symptom improvement.

Unlike most trials of thyroid hormone, which have been performed with patients diagnosed with bipolar I disorder or major depressive disorder, the current study evaluated patients with bipolar II disorder and bipolar disorder NOS. There is substantially greater diagnostic heterogeneity in these groups, especially in the NOS category. Well-characterized patient samples are easier to obtain using the bipolar I criteria, however from a clinical perspective, a better understanding of the pathophysiology and treatment of bipolar II and NOS is needed.

Bipolar II disorder may be the most prevalent type of bipolar disorder, particularly if the requirement for the length of hypomania is shortened to two days (Vieta and Suppes, 2008). It is probably underdiagnosed (Akiskal et al., 2006), and the failure to identify the less severe manifestations of elevated mood characteristic of hypomania can lead to misdiagnosis of bipolar II patients as unipolar. One study found that only 9% of bipolar II patients were accurately diagnosed (Vieta and Suppes, 2008). Additionally, brief hypomanic episodes lasting fewer than four days may be more common than those that meet the DSM-IV duration criteria (Benazzi and Akiskal, 2003), which was why patients with shorter episodes were included under a NOS diagnostic category. These patients, however, can be difficult to diagnose, which may account for the low number of patients with bipolar NOS in this sample.

The medication was generally well-tolerated. The standard clinical strategy of titrating the dose based on efficacy and tolerability helped to minimize the discontinuation rate. Nevertheless, the discontinuation rate of only 10% was notable given that the average dose was 90.6 mcg, and that over 80% of the patients tolerated titration to the point of clinical response. This dose was almost twice as high as the maximum allowable dose in the STAR*D major depressive disorder trial. Some studies have found significantly larger discontinuation rates with thyroid augmentation (Bauer et al., 2002) and while others have not (Łojko and Rybakowski, 2007; Bauer and Whybrow, 1990). Łojko and Rybakowski (2007), for example, started subjects on 100 mcg of thyroxine daily without titration, and reported that it was well tolerated with only a single subject complaining of tachycardia. It is unclear whether differences in patient samples may account for the variation in the literature or if other factors are at play, but overall it appears that patients with affective disorders tolerate high doses of thyroid with minimal rates of discontinuation.

One of the concerns associated with the use of thyroid hormone is the risk of bone loss (Vestergaard and Mosekilde, 2003), however a number of studies have begun to question the validity of this putative relationship (Karga et al., 2004). One study that looked specifically at patients with mood

disorders who were receiving maintenance treatment with supraphysiological doses of T4 found no significant difference between normally expected bone loss and actual bone loss over a period of 33.6 months (Bauer et al., 2004).

Although systematic screening for osteoporosis was not performed, three cases of osteoporosis were identified during the course of treatment. It is not clear that the T3 was a contributing factor. The prevalence of osteoporosis in women ages 40–49 is 4%, and ages 50–59 is 25.9% (Melton et al., 2005). All three women also had independent risk factors including a family history of osteoporosis (Soroko et al., 1994), a history of smoking (Eskandari et al., 2007), SSRI use (Haney et al., 2007), and reduced activity associated with chronic depression. One of the patients who developed osteoporosis also had a history of exposure to carbamazepine and valproic acid, which have been associated with bone loss (Misra et al., 2004). One patient suffered from hyperparathyroidism. Two of the three women continued to take thyroid hormone following diagnosis of osteoporosis because of the mood stabilization benefit experienced after having failed to respond adequately to numerous other medications.

Another important potential side effect of treatment with thyroid hormone, atrial fibrillation, was experienced by one patient who had a history of this condition. The atrial fibrillation was treated by the patient's cardiologist, and in consultation with him, she elected to continue taking T3 because of a favorable response.

There is some evidence to suggest that depressed patients are less likely to experience adverse effects from supraphysiological doses of thyroid hormones compared to healthy controls. In an eight-week, open label study utilizing T4 the rate of discontinuation due to side effects in the control group was 38% compared to 0% for the patients (Bauer et al., 2002). Interestingly, although the serum concentrations of thyroid hormones rose significantly in both groups, concentrations of free T3 and free T4 were significantly higher in the controls compared to the depressed patients.

Serum thyroid hormone levels were not obtained by the treating clinician. As noted above, dosing was guided by tolerability and response. It is possible, that serum levels of thyroid hormones are not well correlated with levels in the brain in patients with depression. The brain controls its own thyroid hormone economy through specific deiodination enzymes (Leonard and Koehrle, 2000), and one hypothesis is that depressed patients have a “central” thyroid deficit (Bauer et al., 2005).

The thyroid hormone-binding protein transthyretin may be required to transfer thyroid hormone across the blood-brain barrier, and is the main binding protein for thyroid hormone in the CNS. Mean cerebrospinal fluid transthyretin levels have been found to be significantly lower in depressed patients compared to normal comparison subjects (Sullivan et al., 1999). Reduced levels of transthyretin in the brain might disrupt thyroid hormone levels inside the blood-brain barrier, despite adequate, or even elevated, serum thyroid hormone levels. These considerations tend to support a strategy of titration based on clinical response rather than titration to a specific serum level of T3, T4, or thyroid stimulating hormone.

There is little evidence to suggest the superiority of either T3 or T4 in the treatment of bipolar depression. There are no studies that directly compare the two. However T3 offers some advantages. Unlike T4, T3 does not need to be taken on an empty stomach (Singh and Hershman, 2003), which may raise adherence issues in patients with mental illness. T3 has an oral bioavailability of 95% (American Society of Health-System Pharmacists, 2007b) while the oral bioavailability of T4 is erratic at 40% to 80% (American Society of Health-System Pharmacists, 2007a).

Another advantage of T3 is that it has a substantially shorter half-life than T4. The half life of T4 is about 7 days which makes it more difficult to titrate. T3, by contrast, has a half life of about 2 days, and therefore can be titrated more rapidly. The onset of activity of T3 is also rapid, occurring within a few hours. A disadvantage of T3 is that it costs substantially more than T4, and five patients in this study had to be switched to T4 due to cost. All but one of these patients maintained an adequate response on T4. The patient who experienced a relapse responded to the reintroduction of T3.

The results of this study should be interpreted with caution. The analysis is limited by its open, uncontrolled, retrospective design, and clinical response was assessed by the treating physician. Patients were on numerous other medications during the treatment period with thyroid hormone, and the concomitant medications underwent adjustment as clinically indicated. Nevertheless, these patients had failed to respond to an average of 14 previous medication trials prior to starting T3, so it is less likely that the concomitant medications accounted for the entirety of the improvement.

There are numerous physiologic changes that take place in depression that suggest an important role of thyroid hormone in the pathophysiology of depression, and may explain why high dose thyroid is an effective augmentation treatment. While the efficacy of T3 for the treatment of non-responsive bipolar depression remains to be established in larger, controlled trials, these naturalistic data suggest effectiveness as an augmenting agent. A large proportion of patients responded to treatment, and the discontinuation rate was only 10%. Higher doses than are typically seen in clinical practice were used, and the medication was well tolerated. While the risks have not yet been fully delineated the risk/benefit analysis appears to be favorable. The current state of the evidence indicates that the risk for osteoporosis of supraphysiologic doses of thyroid hormone may be comparable to typically used doses of carbamazepine, valproic acid and the SSRIs. Despite the limitations of retrospective trials, the data suggest that augmentation with T3 at relatively high doses may be a good option for patients who have not responded to first line therapies for bipolar depression.

Role of funding source

This is entirely self funded with no external support of any kind.

Conflict of interest

Tammas F. Kelly has received honoraria from GlaxoSmithKline, and AstraZeneca. Daniel Z. Lieberman has received grant support from AstraZeneca, Comentis, Eli Lilly, Epix, McNeil, Ono, Predix, Sanofi Aventis, Wyeth, and The Dalio Family Foundation, and has received honoraria from GlaxoSmithKline.

Acknowledgement

I wish to thank Lanny Douglas Nurse Practitioner for freeing up time for me to write, Drs. Larry Denmark, and Jim

Phelps for their encouragement in writing the paper and finally to Charles Nemeroff, M.D., Ph.D. who encouraged me to go beyond the traditional 50 mcg of T3 that has helped so many of my patients.

References

Akiskal, H.S., 2007. The emergence of the bipolar spectrum:validation along clinical-epidemiologic and familial-genetic lines. Psychopharmacol. Bull. 40, 99–115.

Akiskal, H.S., Akiskal, K.K., Lancrenon, S., Hantouche, E.G., Fraud, J.P., Gury, C., Allilaire, J.F., 2006. Validating the bipolar spectrum in the French National EPIDEP Study: overview of the phenomenology and relative prevalence of its clinical prototypes. J. Affect. Disord. 96, 197–205.

American Society of Health-System Pharmacists, 2007a. Levothyroxine sodium In AHFS Drug InformationBethesda, MD, pp. 3242–3245.

American Society of Health-System Pharmacists, 2007b. Liothyronine sodium In AHFS Drug InformationBethesda, MD, pp. 3246–3247.

Bahls, S.C., de Carvalho, G.A., 2004. The relation between thyroid function and depression: a review. Rev. Bras. Psiquiatr. 26, 41–49.

Bartalena, L., Pellegrini, L., Meschi, M., Antonangeli, L., Bogazzi, F., Dell'Osso, L., Pinchera, A., Placidi, G.F., 1990. Evaluation of thyroid function in patients with rapid-cycling and non-rapid-cycling bipolar disorder. Psychiatry Res. 34, 13–17.

Bauer, M.S., Whybrow, P.C., 1990. Rapid cycling bipolar affective disorder. II. Treatment of refractory rapid cycling with high-dose levothyroxine: a preliminary study. Arch. Gen. Psychiatry 47, 435–440.

Bauer, M., Baur, H., Berghofer, A., Strohle, A., Hellweg, R., Muller-Oerlinghausen, B., Baumgartner, A., 2002. Effects of supraphysiological thyroxine administration in healthy controls and patients with depressive disorders. J. Affect. Disord. 68, 285–294.

Bauer, M., Fairbanks, L., Berghofer, A., Hierholzer, J., Bschor, T., Baethge, C., Rasgon, N., Sasse, J., Whybrow, P.C., 2004. Bone mineral density during maintenance treatment with supraphysiological doses of levothyroxine in affective disorders: a longitudinal study. J. Affect. Disord. 83, 183–190.

Bauer, M., London, E.D., Rasgon, N., Berman, S.M., Frye, M.A., Altshuler, L.L., Mandelkern, M.A., Bramen, J., Voytek, B., Woods, R., Mazziotta, J.C., Whybrow, P.C., 2005. Supraphysiological doses of levothyroxine alter regional cerebral metabolism and improve mood in bipolar depression. Mol. Psychiatry 10, 456–469.

Benazzi, F., Akiskal, H.S., 2003. Refining the evaluation of bipolar II: beyond the strict SCID-CV guidelines for hypomania. J. Affect. Disord. 73, 33–38.

Chang, K.D., Keck, P.E., Stanton, S.P., McElroy, S.L., Strakowski, S.M., Geracioti, T.D., 1998. Differences in thyroid function between bipolar manic and mixed states. Biol. Psychiatry 43, 730–733.

Cleare, A.J., McGregor, A., O'Keane, V., 1995. Neuroendocrine evidence for an association between hypothyroidism, reduced central 5-HT activity and depression. Clin. Endocrinol. (Oxf.) 43, 713–719.

Cole, D.P., Thase, M.E., Mallinger, A.G., Soares, J.C., Luther, J.F., Kupfer, D.J., Frank, E., 2002. Slower treatment response in bipolar depression predicted by lower pretreatment thyroid function. Am. J. Psychiatry 159, 116–121.

Cowdry, R.W., Wehr, T.A., Zis, A.P., Goodwin, F.K., 1983. Thyroid abnormalities associated with rapid-cycling bipolar illness. Arch. Gen. Psychiatry 40, 414–420.

Crismon, M.L., Argo, T.R., Bendele, S.D., Suppes, T., 2007. Texas Medication Algorithm Project Procdural Manual, Bipolar Disorder Algorithms, Texas Department of State Health Services.

Eskandari, F., Martinez, P.E., Torvik, S., Phillips, T.M., Sternberg, E.M., Mistry, S., Ronsaville, D., Wesley, R., Toomey, C., Sebring, N.G., Reynolds, J.C., Blackman, M.R., Calis, K.A., Gold, P.W., Cizza, G., 2007. Low bone mass in premenopausal women with depression. Arch. Intern. Med. 167, 2329–2336.

Haney, E.M., Chan, B.K., Diem, S.J., Ensrud, K.E., Cauley, J.A., Barrett-Connor, E., Orwoll, E., Bliziotes, M.M., 2007. Association of low bone mineral density with selective serotonin reuptake inhibitor use by older men. Arch. Intern. Med. 167, 1246–1251.

Heal, D.J., Smith, S.L., 1998. The effects of acute and repeated administration of T3 to mice on 5-HT1 and 5-HT2 function in the brain and its influence on the actions of repeated eletroconvulsive shock. Neuropharmacology 27, 1239–1248.

Hendrick, V., Altshuler, L., Whybrow, P., 1998. Psychoneuroendocrinology of mood disorders. The hypothalamic-pituitary-thyroid axis. Psychiatr. Clin. North Am. 21, 277–292.

Karga, H., Papapetrou, P.D., Korakovouni, A., Papandroulaki, F., Polymeris, A., Pampouras, G., 2004. Bone mineral density in hyperthyroidism. Clin. Endocrinol. (Oxf.) 61, 466–472.

Leonard, J.L., Koehrle, J., 2000. Intracellular pathways of iodothyronine metabolism, In: Braverman, L.E., Utiger, R.D. (Eds.), The Thyroid. A Fundamental and Clinical Text, 8th ed. Williams & Wilkins, Philadelphia, pp. 136–171.

Łojko, D., Rybakowski, J., 2007. L-thyroxine augmentation of serotonergic antidepressants in female patients with refractory depression. J. Affect. Disord. 103 (1), 253–256 (November).

Melton, L.J., III, Chrischilles, E.A., Cooper, C., Lane, A.W. and Riggs, B.L. (2005) How many women have osteoporosis? JBMR Anniversary Classic. JBMR, Volume 7, Number 9, 1992 J Bone Miner Res, 20, 886–92.

Misra, M., Papakostas, G.I., Klibanski, A., 2004. Effects of psychiatric disorders and psychotropic medications on prolactin and bone metabolism. J. Clin. Psychiatry 65, 1607–1618 (quiz 1590, 1760–1.).

Oomen, H.A., Schipperijn, A.J., Drexhage, H.A., 1996. The prevalence of affective disorder and in particular of a rapid cycling of bipolar disorder in patients with abnormal thyroid function tests. Clin. Endocrinol. (Oxf.) 45, 215–223.

Osler, W., 1901. The Principles and Practice of Medicine. D. Appleton and Company, New York, NY.

Sachs, G.S., Thase, M.E., 2000. Bipolar disorder therapeutics: maintenance treatment. Biol. Psychiatry 48, 573–581.

Sachs, G.S., Printz, D.J., Kahn, D.A., Carpenter, D., Docherty, J.P., 2000. The expert consensus guideline series: medication treatment of bipolar disorder. Postgrad. Med. 1–104 (Spec No).

Singh, N., Hershman, J.M., 2003. Interference with the absorption of levothyroxine. Curr. Opin. Endocrinol. Diabetes 10, 347–352.

Soroko, S.B., Barrett-Connor, E., Edelstein, S.L., Kritz-Silverstein, D., 1994. Family history of osteoporosis and bone mineral density at the axial skeleton: the Rancho Bernardo Study. J. Bone Miner. Res. 9, 761–769.

Sullivan, G.M., Hatterer, J.A., Herbert, J., Chen, X., Roose, S.P., Attia, E., Mann, J.J., Marangell, L.B., Goetz, R.R., Gorman, J.M., 1999. Low levels of transthyretin in the CSF of depressed patients. Am. J. Psychiatry 156, 710–715.

Suppes, T., Dennehy, E.B., Hirschfeld, R.M., Altshuler, L.L., Bowden, C.L., Calabrese, J.R., Crismon, M.L., Ketter, T.A., Sachs, G.S., Swann, A.C., 2005. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. J. Clin. Psychiatry 66, 870–886.

Vestergaard, P., Mosekilde, L., 2003. Hyperthyroidism, bone mineral, and fracture risk—a meta-analysis. Thyroid 13, 585–593.

Vieta, E., Suppes, T., 2008. Bipolar II disorder: arguments for and against a distinct diagnostic entity. Bipolar Disord. 10, 163–178.