Original Article

ADVERSE EVENT REPORTING IN PATIENTS TREATED WITH THYROID HORMONE EXTRACT

Rupendra T. Shrestha, MD[1]; Alan Malabanan, MD, FACE, CCD[2]; Bryan R. Haugen, MD[3]; Elliott G. Levy, MD[4]; James V. Hennessey, MD[2]

ABSTRACT

Objective: Thyroid hormone extract is used for the treatment of thyroid disorders, but limited data exist on adverse events commonly noted by the physicians associated with this use. The purpose of this survey was to report adverse events observed by expert physicians managing patients treated for thyroid disease with thyroid hormones.

Methods: Members of the American Thyroid Association, The Endocrine Society, and the American Association of Clinical Endocrinologists developed a survey instrument modeled on the U.S. Food and Drug Administration (FDA)'s reported adverse events for levothyroxine that would effectively assess the clinical experience of frequent prescribers of thyroid hormone. Survey links were emailed to physicians, and the websites of each society provided links to the data collection form.

Results: A total of 174 reports of adverse events occurring in patients on thyroid hormone extract were received. Ninety-one of these reports were accompanied by alterations in thyrotropin values and were further analyzed. Of these, 62 (68%) subjects had developed new symptoms associated with altered thyroid-stimulating hormone (TSH). A majority of TSH changes and symptoms described were consistent with thyrotoxicosis (65%), and 2 patients had developed arrhythmias. Reporters noted difficulty in dose adjustment by primary care providers due to confusion in interpreting thyroid function test results while on thyroid extract, which often necessitated subspecialty referrals.

Conclusion: These adverse event reports should stimulate consideration by the FDA to regulate and monitor thyroid hormone extract use and consider standardizing these extracts to meet current standards of manufacture, hormone content, availability, and shelf-life, like the rigor with which preparations such as levothyroxine are monitored. **(Endocr Pract. 2017;23:566-575)**

Abbreviations:
AE = adverse event; **ATA** = American Thyroid Association; **FDA** = Food and Drug Administration; **LT3** = liothyronine; **LT4** = levothyroxine; **PTF** = Pharmacovigilance Task Force; **T3** = triiodothyronine; **TSH** = thyroid-stimulating hormone

INTRODUCTION

Oral thyroid hormone extract use for the treatment of hypothyroidism has been described since the 1890s in the English literature but dates as far back as the sixth century CE in Chinese writings (1,2). Prior to the development of radioimmune assays to measure both serum thyroxine (T4) and serum triiodothyronine (T3) levels in the early 1970s (3), extract doses were titrated based on a clinical assessment of wellbeing and avoidance of the signs of overt hyperthyroidism. Both T4 and T3 have been measured in those ingesting thyroid extracts or liothyronine (LT3), and supraphysiologic T3 levels have been documented following absorption (3). Due to these nonphysiologic fluctua-

Submitted for publication September 27, 2016
Accepted for publication December 18, 2016
From the [1]Division of Endocrinology, Diabetes and Metabolism, University of Minnesota, Minneapolis, Minnesota, [2]Harvard Medical School, Division of Endocrinology, Diabetes and Metabolism, Beth Israel Deaconess Medical Center, Boston, Massachusetts, [3]Division of Endocrinology, Metabolism & Diabetes, University of Colorado Denver, Aurora, Colorado, and [4]Division of Endocrinology, University of Miami, Miller School of Medicine, Miami, Florida.
Address correspondence to Dr. James V. Hennessey, Division of Endocrinology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, GZ-6, Boston, MA 02215.
E-mail: Jhenness@bidmc.harvard.edu
Published as a Rapid Electronic Article in Press at http://www.endocrinepractice.org on February 22, 2017. DOI: 10.4158/EP161584.OR

tions in T3, several authors have long advocated removal of thyroid extract from the market (4,5). While there are no available data on annual number of prescriptions written for thyroid hormone extract, levothyroxine (LT4) accounts for most thyroid direct therapies. Data published in 2014 showed that 119.5 million prescriptions out of 131 million (92%) total prescriptions for thyroid therapies were written for LT4, leaving less than 11.5 million prescriptions estimated for thyroid hormone extract or other therapies such as LT3 (6). Thyroid hormone extract remains an unapproved product by the U.S. Food and Drug Administration (FDA) (7). Further, current clinical practice guidelines for the treatment of hypothyroidism do not support the use of thyroid extract (8-10), and in some recommendations, the use of extract is actively discouraged (11). Despite these warnings, the product continues to be favored by some physicians and patients. Currently, U.S. physicians have a choice of two thyroid extract preparations. Each 65-mg (1 grain) tablet of contemporarily available thyroid extract product provides 38 μg of T4 and 9 μg of T3, per the manufacturer's label (12,13).

Although some claim that the thyroid extract is superior to LT4 products in the treatment of both hypothyroidism and its "sub-laboratory" forms (14), several experimental protocols of such combination therapy have failed to substantiate objective advantages of extract products (15-18). Some advocate the use of thyroid hormone extracts as an alternative to the use of LT4 and LT3 combination therapy (19,20) for patients with hypothyroidism. However, the ratio of T4 to T3 in thyroid extract products once absorbed differs from that of endogenous normal human thyroid output (10). In the first prospective, randomized, double-blind, crossover study of clinical outcomes of 70 adults with primary hypothyroidism randomized to thyroid extract or LT4, no objective difference in symptoms or neurocognitive function was observed. However, nearly half of the participants reported a preference for the time they were on extract (21).

The safety and adverse outcomes while using thyroid hormone extract and issues that prescribers are faced with when managing patients on thyroid hormone extract have not been well described in the recent literature. This report describes adverse outcomes reported by endocrinologists and frequent prescribers of thyroid hormone extract products collected by the American Thyroid Association (ATA)-appointed Pharmacovigilance Task Force (PTF).

METHODS

The PTF was created to assess potential adverse events (AEs) attributable to the use of thyroid hormone products. It used a survey tool that was created to gather data similar to that used by the FDA to change policy for LT4 (22,23). Members of the ATA, the American Association of Clinical Endocrinologists (AACE), and the Endocrine Society (TES) collaborated to survey the experience of physicians caring for patients with thyroid disease on LT3, thyroid extract, or LT4 therapy. The result of reports received from physicians after prescribing thyroid extract is being reported here; the reports received regarding LT4 use have been previously summarized (24), and the reports received concerning LT3 use will not be further analyzed due to the low number of validated responses.

Following the development of a satisfactory questionnaire (Appendix A), the PTF contracted with Intertwine Healthcare Solutions (Baltimore) to distribute email surveys. The email invited recipients to participate in a survey regarding possible adverse events or product availability problems related to thyroid hormone medications. Recipients were made aware of the Thyroid Pharmacovigilance website, and a personal link was provided to access the survey. Although LT4 was the primary focus of this project, opportunities to share clinical data on LT3 and thyroid extract (thyroid USP) were available on the website. A total of 30,000 emails inviting participation were sent between December 2005 and May 2006. An additional 5,000 emails were sent to physicians who had been identified by the vendor as having prescribed thyroid extract between 7 and 1,253 times in the previous year. A final mass emailing was sent in September 2006 to 8,167 clinical members of the AACE, ATA, and TES to document further incidents. In addition, the websites of each society contained information about the project, and links were provided to report cases. The database was closed on December 1, 2007. The current report describes the AEs reported by physicians caring for individuals using thyroid hormone extracts. Further details of the method of data collection have been described previously (24).

RESULTS

Of the total 1,536 survey responses received, the majority (971 of 1,536 [63%]) reported no AEs. Since the physicians who responded to these surveys could have been members of all three organizations and had received multiple requests to respond, calculation of an accurate response rate was not possible.

A total of 565 completed AE reports (37% of total responses) were further reviewed. Of these, 335 (59%) reported on events occurring in LT4-treated patients, 174 (31%) reports were on thyroid hormone extract users, and 51 (9%) reported adverse experiences with LT3. Of the 51 AEs reported for LT3, only 11 patients were on it as sole treatment for their thyroid disorder, and among these 11 reports, 6 of the AEs indicated that there had been recent dose adjustments, which would account for the symptoms and altered thyroid function assessments. Because of the paucity of reports, the data on LT3 were not further analyzed.

A total of 174 reports received were focused on AEs observed by physicians caring for patients on thyroid hormone extract. After elimination of reports related to

noncompliance with thyroid USP ingestion (n = 11); erroneous reporting (n = 4); interfering medication use (n = 4); pregnancy (n = 3); recent changes in thyroid extract dosing, defined as change of dose of thyroid hormone extract since the prior clinical assessment (n = 55); and the reporting of symptoms only associated with an unchanged TSH value (n = 6), 91 reports of AEs remained (Fig. 1).

Validated Response From the Survey

Table 1 summarizes survey responses of the 91 reports. The majority (84 of 91 [92%]) of reports were completed by an endocrinologist, and nonendocrinologist physicians (MD or DO) accounted for the remaining 8% (7 of 91) reports.

Medication Compliance and Indications for Treatment

Compliance with the thyroid extract treatment was confirmed by the reporting physician based on verbal report of the patient in 76 of 91 (84%) cases and by pharmacy records or both verbal and pill count in 15 of 91 (16%) cases. Thyroid extract therapy was being administered for the indications of hypothyroidism in 87 of the 91 patients (96%), thyroid cancer in 3 of 91 (3%), and goiter or nodule suppression in the remaining 1 of 91 (1%) reports. Therefore, biochemical euthyroidism would have been expected in 96% or more of the reports, and TSH suppression of some degree would have been expected in the remaining cases.

Description of AEs

Of the 91 completed reports on compliant individuals on stable doses of thyroid USP, the AE was due to new or unexpected symptoms in 15 (16%), a TSH change alone in 14 (15%), or both in 62 (68%). Symptoms assessed are listed in Appendix A and include both typical thyrotoxic symptoms (e.g., weight loss, nervousness, difficulty sleeping, palpitations, and tiredness) and typical hypothyroid symptoms (e.g., weight gain, constipation, menstrual irregularity, dry skin, fatigue, and hair loss). Most of the symptoms (59 of 91 [65%]) were consistent with thyrotoxicosis, whereas arrhythmias were documented in 2 cases and 5% (5 of 91) of cases had symptoms typical of hypothyroidism.

Thyroid Function Tests Reported

The TSH distribution from suppressed to elevated levels found during the survey is described in Figure 2. Prior to the reported AE, TSH values were within the normal range (0.5 to 5 mU/L) in 46 of 91 (51%) of the reports, were suppressed below normal in 43 of 91 (47%), and exceeded the upper limit of the reference range in 2 of 91 (2%) reports. At the time of the reported AE, 83 of 91 (91%) TSH values were below normal, with 29 of 91 (32%) levels suppressed but detectable, and the majority, 54 of 91 (59%), being frankly undetectable. While 33 (36%) of subjects had TSH values less than 0.1 mU/L prior to the reported event, 54 (59%) were undetectable at the time of the reported AE. As noted above, prior to the time of the AE, 2% of TSH values were greater than normal, while the reported AE values documented that 6 (7%) of the TSH values were between 5.1 and 10 mU/L, and 2% of TSH values were greater than 10 mU/L. The overall trend in TSH change at the time of the reported event was a substantial increase in the number of subjects demonstrating evidence of excess thyroid hormone (83 of 91) exposure, a rate that nearly doubled.

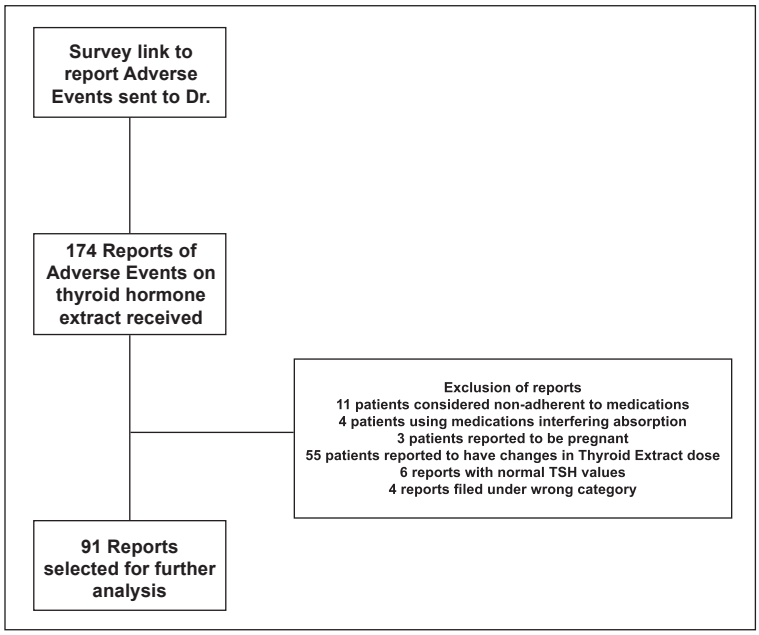

Fig. 1. Number of validated responses during the survey on thyroid hormone extract. *TSH* = thyroid-stimulating hormone.

Table 1
Summary of Response to the Survey Questions on Thyroid Hormone Extract

1. The reason you suspect an adverse reaction to thyroid hormone extract is based upon:	
	n (%)
Both	62 (68)
New symptom	15 (16)
TSH change	14 (15)
2. Is your patient compliant with taking thyroid pill? (only those answering yes included)	
Compliance confirmed	**n (%)**
Verbally	76 (84)
Pill count/pharmacy record	0
Both	15 (16)
3. Symptoms documented were:	
Symptom	**Count (%)**
Hyperthyroid	59 (65)
Hypothyroid	5 (5)
Not specified	15 (16)
Others: palpitation, menstrual irregularities, constipation, sleep issues, hair loss	12 (13)
4. The results of the most recent TSH was:	
TSH range	**Count (%)**
<0.1	54 (59)
0.1-0.4	29 (32)
0.5-1.9	0
2-5	0
5-10	6 (7)
>10	2 (2)
5. The results of the last TSH on record was:	
TSH range	**Count (%)**
<0.1	33 (36)
0.1-0.4	10 (11)
0.5-1.9	30 (33)
2-5	16 (18)
5-10	1 (1)
>10	1 (1)
6. Your patient is taking thyroid hormone for:	
Condition	**Count (%)**
Goiter or nodule	1 (1)
Hypothyroidism	87 (96)
Thyroid cancer	3 (3)
Abbreviation: TSH = thyroid-stimulating hormone.	

Clinical Commentary Reported

Free text comments were made by 23 physicians during the survey. The most common reason cited for discontinuing the drug was an inability to dose the drug based on symptoms and TSH values (7 of 23 comments). Nine of these 23 physicians stated that the drug was initially prescribed by a different provider. Arrhythmias were documented in 2 patients. Samples of such comments are listed in Table 2.

DISCUSSION

This survey of thyroid extract therapy documents 91 validated reports of AEs accompanied by objective changes in the thyroid function that were associated with the use of stable doses of thyroid extracts in compliant subjects in the U.S. It should be emphasized that nearly one-third of the reports received had been excluded (55 of 174 [32%]) from analysis, as the subjects had undergone dose adjustments between the two assessment occasions. Compared to a rate of only 8.9% reporting unstable LT4 dosing during the same study period (24), this higher frequency of dosing adjustments in those treated with extract is of concern and might possibly be due to the dosing variation in pursuit of nonspecific symptoms. The majority of clinical symptoms reported were consistent with being the consequence of an excess of thyroid hormone action. It is noteworthy that more than half of the patients had undetectable TSH, and most patients (91%) had suppressed TSH values at the time of AE reporting. In contrast, data obtained from reports of subjects on LT4 in the same survey showed a much lower rate of suppressed TSH (16%) with larger proportion of normal TSH range (79%), with similar proportions of hypothyroid and thyroid cancer indications (24). These data support a significant risk of thyroid hormone overdosage when using extract and document the occurrence of clinical problems that may be explained by an inability of prescribing physicians to reliably titrate extract doses or might be the result of the ingestion of superpotent extract preparations during ongoing care. We have no evidence that the potency of thyroid hormone extract preparations varies with currently available products nor that any such variability played any role in the events reported here. The FDA has chosen not to regulate or actively monitor the hormone content of contemporary products (personal communication, Kristofer Baumgartner, Center for Drug Evaluation and Research Trade Press Office, FDA; February 2, 2015).

The narrative comments document unique clinical consequences associated with the use of extract products. The comments provided in this report identify two potentially serious consequences of suboptimal thyroid extract therapy, such as atrial fibrillation and a malignant arrhythmia in subjects exposed to excess thyroid extract treatment. Several comments note a referral had been made to endo-

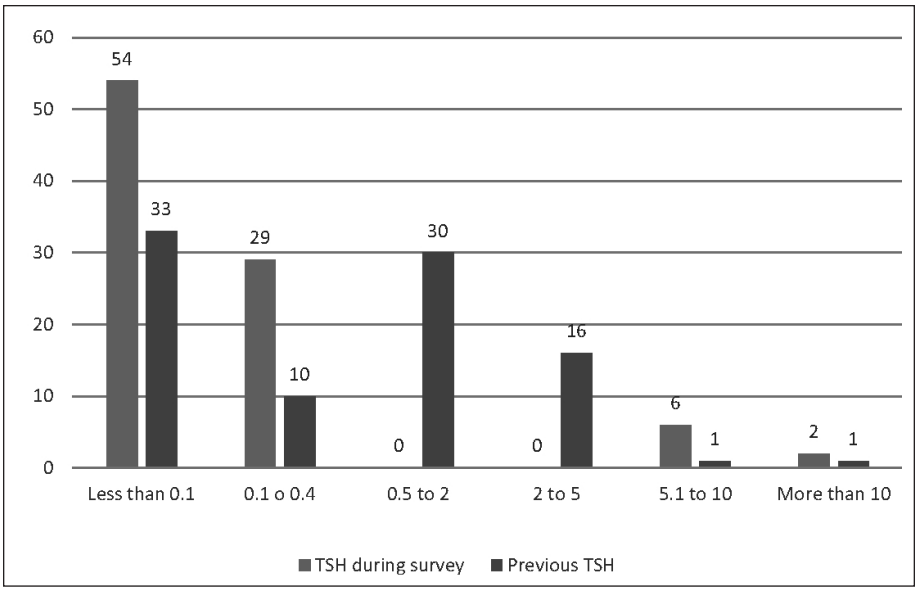

Fig. 2. Observed thyroid-stimulating hormone (TSH) values before and in conjunction with the adverse event report.

crinology experts after thyroid function tests could not be interpreted by a general practitioner. Although serious AE data were not available for this subgroup, the most frequent clinical impact of these events was the time and expense of lost productivity, travel for additional testing, and follow-up care that was associated with such incidents. This testing could include measuring T3, which is now considered a low-value test (25).

This study is not without limitations. Although the study instrument was created using the type of clinical data utilized by the FDA to make regulatory decisions, all surveys are subject to recall biases. The data provided by the reporting physicians could not be verified independently. There may also have been selection bias, as the most dramatic cases seen would have been preferentially put forward as AEs. However, since the reporting was voluntary and provided by busy practitioners, the frequency of AEs was likely underreported. No clear inference as to the relative frequency of AEs can be made. However, among AEs noted on LT4, nearly 200 otherwise unexplained events were evident against a background of about 120 million annual prescriptions for LT4 written in the U.S., while 91 similarly validated AEs were reported in the same survey from among the 11.5 million or less extract prescriptions generated in the U.S. during the same period (6). Lastly, incomplete data entry in some instances limited the clarity of interpretation. Despite these limitations, this analysis provides insight into the clinical dilemma physicians face daily when encountering patients using current forms of thyroid hormone extract.

Our survey design did not facilitate the collection of information to quantify the additional costs involved in assessing and managing the incident cases reported. As outlined above, at least, repeat thyroid function tests and an endocrine consultation was necessary in most cases. Our report on these aspects is also limited, as the frequency with which extract-treated patients sought or were referred for endocrine consultation and the full impact of any additional costs accrued in this process could not be calculated. Although 3 patients were reported to be pregnant in this survey, further data on the circumstances and outcomes are not available in this vulnerable group.

These data show that the frequency of dose adjustments in thyroid hormone extract users appears to be much more common when compared to rates observed in those treated with LT4 (24). Further, most symptoms encountered in those using extract were consistent with exposure to excessive thyroid hormone use. Further studies are required to compare the AEs of extract preparations with those of LT4 and assess the cost of these events to justify the continued use of FDA-unapproved extract preparations.

CONCLUSION

Although the manufacturers of thyroid hormone extract have made great strides to standardize the LT4 and LT3 content of their products, the preparations remain unregulated by the FDA. The responses documented in this survey raise clinical concerns. It is important to provide a broader understanding of issues that may arise from use of the thyroid extract products among physicians, pharmacists, and patients to achieve optimal treatment for hypothyroidism. Clinicians prescribing thyroid hormone extract preparations should be reminded that these products are not harmless, as many "natural" remedies are assumed to be by a portion of the lay public. Preferably, patients and primary care physicians desiring natural holistic solutions should be made aware of these results and be familiar with

Table 2
Sample of Comments Made by the Physicians Who Reported the Adverse Events

	Prescriber's comments on thyroid hormone extract use
1.	I never prescribe thyroid extract but I see new patients (to me) who are taking it. This is one such patient. I insist on changing them to brand levothyroxine. I refuse to prescribe thyroid extract.
2.	Gentleman has a history of malignant arrhythmia but is "doctor-shopping" to ensure that he finds a doctor that will give him this particular preparation. He states that he would rather die than stop using this preparation. He brings stacks of literature…
3.	I have had several patients with problems with thyroid extract. They are referred to me because of abnormal labs while on extract that don't make sense to the primary doctor.
4.	I see this problem in the majority of patients who are taking desiccated thyroid. It is a dangerous preparation and should be withdrawn from the market. This has been a well-documented problem for several years, and FDA failure to remove this product.
5.	Patient was clearly experiencing variable thyroid levels due to unreliable product, there were no conflicting medications or circumstances. Thyroid extract causing variable thyroid hormone levels is one of my best referral sources; it is a consistent source of problems.
6.	"…this has happened to at least 20 patients. In other cases, again at least 20, the TSH went DOWN from 2-5 to <1."

Abbreviations: FDA = Food and Drug Administration; TSH = thyroid-stimulating hormone.

evidence-based clinical practice guidelines which discourage extract use (9-11). Finally, these issues should raise adequate concern to include consideration by the FDA to regulate and oversee the standardized forms of thyroid extract to meet current standards of manufacture, hormone content, bioavailability, and shelf-life, similar to the rigor with which preparations such as LT4 are monitored.

ACKNOWLEDGMENT

The study was supported by the American Thyroid Association. The Pharmacovigilance committee was chaired by Drs. Haugen and Levy by providing tele-conferencing support. The ATA, TES, and AACE provided for the distribution and collection of the data by the vendors. Other members of the task force were: Nicholas J. Sarlis, MBBS, MD, PhD; Matthew D. Ringel, MD; Irwin L. Klein, MD; Ernie Richardson, MD; Paul S. Jellinger, MD; James V. Hennessey, MD; Jeffrey R. Garber, MD; Ruth M. Belin, MD; Eric Alvarez, MD; and Andrea T. Adamus, MD. The authors are solely responsible for data analysis, manuscript preparation, and approval and did not receive any input from the ATA, TES, or AACE. No commercial support was obtained in the survey design, data collection, data analysis, or manuscript preparation. We thank Bobbi Smith and Teresa Ronk of the ATA staff for their patience and hard work in pulling together the data from these surveys.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

Appendix A: Outline of Questionnaire

1. The reason you suspect an adverse reaction to thyroid hormone is based upon:
   New Symptoms:
   Hyperthyroid symptoms –
   Hypothyroid symptoms –
   Palpitations –
   Tiredness –
   Difficulty sleeping –
   Nervousness –
   Weight loss –
   Weight gain –
   Dry skin –
   Constipation –
   Hair loss –
   Menstrual irregularities –
   Change in TSH despite no change in dosage –
   Both –

2. Is your patient compliant with taking thyroid pills?
   Yes, I have asked the patient who says that pills are NOT or rarely missed –
   Yes, Verified by pill count/pharmacy records –
   Yes, I both asked the patient AND verified pill count/records –
   No –

3. Has your patient been started on any of these medications since the last TSH? (These medications can inhibit absorption or metabolism)
   Select more than one as appropriate:
   Bile and acid binding resin (absorption) –
   Calcium (absorption) –
   Multivitamins (absorption) –
   Estrogen (BCP/HRT) –
   Iron (absorption) –
   Sucralfate (absorption) –
   Phenytoin (metabolism) –
   Rifampin (metabolism) –
   Not applicable –

4. The medication (affecting absorption) is taken:
   At the same time as the LT4 –
   At least 4 hours apart from the LT4 –
   Don't know –

5. Is your patient pregnant?
   Yes –
   No, verbal confirmation (or male) –
   No, negative pregnancy test –

6. Your patient is taking thyroid hormone for:
   Goiter or nodules –
   Hypothyroidism –
   Thyroid Cancer –

7. The results of the most recent TSH was:
   Less than 0.1 –
   0.1 – 0.4 –
   0.5 – 1.9 –
   2 – 4.9 –
   5 – 9.9 –
   More than 10

8. The results of the last TSH on record was:
   Less than 0.1 –
   0.1 – 0.4 –
   0.5 – 1.9 –
   2 – 4.9 –
   5 – 9.9 –
   More than 10 –

9. Was the dose stable between the TSH measurements?
   No, not stable –
   Yes, stable –

10. Was your patient given a different type of thyroid hormone tablet than you previously prescribed?
   Change from brand to generic –
   Change from generic to brand v
   Change from one brand to another –
   Change from one generic to another generic –
   No change –

11. If the type of thyroid hormone was changed, it was changed by:
   Not applicable -–
   Pharmacy with knowledge –
   Pharmacy without your knowledge –
   You/your office –

12. Did this change in the type of thyroid hormone result in any serious adverse events?
   Yes:
   Urgent Clinic Visit –
   Hospitalization –
   Missed work –
   Emergency Room Visit –
   Other (expand in comments below) –
   No –

13. Do you protect your prescriptions (do not substitute, dispense as written, etc.)?
   Yes –
   No –

13. Additional Comments on adverse event: (enter free text comments)

14. The person completing this form: (enter free text)

15. Your area of the country: (enter free text)

Thank you for your participation. If we have any questions, may we contact you by your email address?

Yes –

No –

Appendix B: E-mail Invitation to Participate in the Collection of Data on the Pharmacovigilance Survey

From: "admin@thyroid.org" <thyroid_pcv@jangomail.com>
Date: Thu, 20 Oct 2005 12:41:02 +0000
Subject: American Thyroid Association - Pharmacovigilance Survey

Dear Doctor, MD,

You are invited to participate in an important survey regarding possible adverse events or product availability problems related to thyroid hormone medications. The ATA has developed a Thyroid Pharmacovigilance web site: http://www.thyroidpharmacovigilance.org/?uid=718bd1fd6955edd5f0246188c919ee49 to collect data and information from physicians, health care providers, pharmacists and patients. A few minutes of your time will greatly enhance the results of the survey. If you have had no adverse experience related to thyroid hormone medications it will take less than a minute to respond.

Levothyroxine (LT4) is the most commonly used medication for thyroid disease and the primary focus of this project, although data on Liothyronine (T3) and thyroid extract (thyroid USP) will also be gathered on this web site. Please access the website now using your personal web link: <http://www.thyroidpharmacovigilance.org/?uid=718bd1fd6955edd5f0246188c919ee49>

Thank you.

The American Thyroid Association
** You have received this mailing as a member or associate of the American Thyroid Association. If you feel you have received the message in error, please contact the ATA at admin@thyroid.org, or at 703 998-8890.

REFERENCES

1. **Slater S.** The discovery of thyroid replacement therapy. Part 3: a complete transformation. *J R Soc Med*. 2011;104:100-106.
2. **Slater S.** The discovery of thyroid replacement therapy. Part 1: in the beginning. *J R Soc Med*. 2011;104:15-18.
3. **Surks MI, Schadlow AR, Oppenheimer JH.** A new radioimmunoassay for plasma L-triiodothyronine: measurements in thyroid disease and in patients maintained on hormonal replacement. *J Clin Invest*. 1972;51:3104-3113.
4. **Jackson IM, Cobb WE.** Why does anyone still use desiccated thyroid USP? *Am J Med*. 1978;64:284-288.
5. **Smith SR.** Desiccated thyroid preparations. Obsolete therapy. *Arch Intern Med*. 1984;144:926-927.
6. **Aitken M, Kleinrock M, Lyle J, Nass D, Caskey L.** Medicines use and spending shift. QuintilesIMS 2014. Available at: http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/medicines-use-in-the-us-2014. Accessed March 15, 2017.
7. **Hennessey JV.** Historical and current perspective in the use of thyroid extracts for the treatment of hypothyroidism. *Endocr Pract*. 2015;21:1161-1170.
8. **Garber JR, Cobin RH, Gharib H, et al.** Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract*. 2012;18:988-1028.
9. **Jonklaas J, Bianco AC, Bauer AJ, et al.** Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. *Thyroid*. 2014;24:1670-1751.
10. **Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP.** 2012 ETA guidelines: the use of L-T4 + L-T3 in the treatment of hypothyroidism. *Eur Thyroid J*. 2012;1:55-71.
11. **Stagnaro-Green A, Abalovich M, Alexander E, et al.** Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid*. 2011;21:1081-1125.
12. Armour Thyroid (thyroid): drug summary. PDR. Available at: http://www.pdr.net/drug-summary/armour-thyroid?druglabelid=2466. Accessed March 15, 2017.
13. Nature-Throid (thyroid): full prescribing information. Available at: http://www.pdr.net/full-prescribing-information/Nature-Throid-thyroid-496. Accessed March 15, 2017.

14. **Gaby AR.** Sub-laboratory hypothyroidism and the empirical use of armour thyroid. *Altern Med Rev*. 2004;9:157-179.
15. **Siegmund W, Spieker K, Weike AI, et al.** Replacement therapy with levothyroxine plus triiodothyronine (bioavailable molar ratio 14:1) is not superior to thyroxine alone to improve well-being and cognitive performance in hypothyroidism. *Clin Endocrinol (Oxf)*. 2004;60:750-757.
16. **Escobar-Morreale HF, Botella-Carretero JI, Gómez-Bueno M, Galán JM, Barrios V, Sancho J.** Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone. *Ann Intern Med*. 2005;142: 412-424.
17. **Grozinsky-Glasberg S, Fraser A, Nahshoni E, Weizman A, Leibovici L.** Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab*. 2006;91:2592-2599.
18. **Ma C, Xie J, Huang X, et al.** Thyroxine alone or thyroxine plus triiodothyronine replacement therapy for hypothyroidism. *Nucl Med Commun*. 2009;30:586-593.
19. **Lichten EM.** Synthetic thyroxine vs dessicated thyroid. *JAMA*. 2004;291:1445; author reply 1445.
20. **Jellinger PS.** Acquired hypothyroidism after switching from thyroid USP to levothyroxine. *Clin Cornerstone*. 2005;7(suppl 2):S22-S24.
21. **Hoang TD, Olsen CH, Mai VQ, Clyde PW, Shakir MK.** Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study. *J Clin Endocrinol Metab*. 2013;98:1982-1990.
22. **Hennessey JV.** Levothyroxine a new drug? Since when? How could that be? *Thyroid*. 2003;13:279-282.
23. U.S. Department of Health and Human Services, U.S. Food and Drug Administration. Orange Book: approved drug products with therapeutic equivalence evaluations. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/. Accessed March 22, 2017.
24. **Hennessey JV, Malabanan AO, Haugen BR, Levy EG.** Adverse event reporting in patients treated with levothyroxine: results of the pharmacovigilance task force survey of the American Thyroid Association, American Association of Clinical Endocrinologists, and the Endocrine Society. *Endocr Pract*. 2010;16:357-370.
25. **Reid RO, Rabideau B, Sood N.** Low-value health care services in a commercially insured population. *JAMA Intern Med*. 2016;176:1567-1571.