Letter to the Editor

To the Editor:

AUTHOR RESPONSE TO DR. PEPPER

We thank Dr. Pepper for writing regarding our report "Adverse Event Reporting in Patients Treated with Thyroid Hormone Extract" that was published in the Vol. 23 No. 5 issue of *Endocrine Practice*.

The author indicated that the increased adverse events (AEs) in the thyroid extract (TE) group was based on the calculation of incidence using national prescription rates. However, in the initial paragraph of our discussion, we pointed out that 32% (55/174) of the AE reports received concerning patients on TE were excluded because the doses had been recently adjusted due to a lack of thyroid function test normalization (unstable dosing) (1). In the same survey, only 8.9% of AEs in the levothyroxine (LT4) group resulted from doses that needed adjustment (2). As the difference in these rates was statistically significant ($P<.01$), we concluded that those treated (primarily by nonendocrinologists according to the reporters) with TE were more prone to unstable dosing. Among many possible explanations for this difference, the lack of regulation (TE is neither Food & Drug Administration [FDA] approved nor regulated) may be playing a role.

While preparing the manuscript, we called the major manufacturers of TE to request precise information on the annual volume of use for their respective preparations. They declined to provide this information and indicated that such reports were not available. Therefore, the most accurate estimations that could be obtained were reports of the numbers of prescriptions that were filled as cited. Given this limitation, we clearly stated, "No clear inference as to the relative frequency of AEs can be made" (1). This was not the main conclusion of our report.

The author suggests that the goals of quality control for TE have been met based on the manufacturer's own statement. We did acknowledge that the manufacturers are taking great strides toward standardizing the products of LT4 and liothyronine (LT3) in the first line of our conclusion (1), but unlike LT4 preparations that are NDA (New Drug Application) and ANDA (Abbreviated New Drug Application) approved and monitored by FDA, TE products have not been subjected to such standardization and oversight. The U.S. Pharmacopeia monograph designation of TE represents a minimal quality standard, but independent verification of thyroid hormone content in these products has not been conducted by the FDA (3).

We performed a rigorous PubMed search at the time of manuscript preparation to include all relevant, peer-reviewed studies on this topic. Based on the comment that we did not cite the author's paper, we performed further PubMed, Web of Science, and Scientific Journal Ranking searches and were still unable to find that study. We thank the lead author for the PDF link to access and review their paper (https://www.jscimedcentral.com/Endocrinology/endocrinology-2-1055.pdf). We also appreciate the author's sharing of a 2% rate of AEs (as unusual as the AEs noted were and the apparent threefold higher rate than on LT4) while treated with TE after declared as failed on LT4 therapy based on symptoms. However, we have some concerns regarding this study: (*1*) There are some methodologic issues in using a discrete variable as a continuous measure to generate mean and statistical significance using this unique scoring system. In this study, discrete variables (the numerical satisfaction score: 1-3 as less preferred and 4 or 5 as preferred) were used to calculate means and *P* values. (*2*) Significant proportions of subjects in both groups did not have normal thyroid-stimulating hormone (TSH) values, presumably at the time that LT4 was declared to have failed (6.5% elevated and 35% suppressed TSH) and again when surveyed for satisfaction on TE (10% elevated and 40% suppressed TSH). (*3*) It is unclear how to interpret the reported thyroid function values and the clinical satisfaction observed, especially the calculated thyroxine/triiodothyronine (T4/T3) ratios, where T4/T3 was the same for the LT4-treated subjects as measured in ambulatory controls without thyroid disease but lower in those on TE due to higher T3 levels. (*4*) Finally, selection bias was introduced by only including those dissatisfied with LT4 treatment.

See accompanying article, p. 230.

With these explanations, we believe that most of the reader's concerns have been allayed and that all the points that were raised were appropriately addressed in various sections of our report.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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REFERENCES

1. **Shrestha RT, Malabanan A, Haugen BR, Levy EG, Hennessey JV.** Adverse event reporting in patients treated with thyroid hormone extract. *Endocr Pract*. 2017;23:566-575.
2. **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.
3. **Hennessey JV.** Historical and current perspectives in the use of thyroid extracts for the treatment of hypothyroidism. *Endocr Pract*. 2015;21:1161-1170.